Original article

# Multicentre study of abdominal aortic aneurysm measurement and enlargement

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**Background:** No effective treatment is currently available to prevent progression of small and medium-sized abdominal aortic aneurysms (AAAs). Identification of drugs with sufficient promise to justify large expensive randomized trials remains challenging. One potentially useful strategy is to look for associations between commonly used drugs and AAA enlargement in appropriately adjusted observational studies.

**Methods:** Potential AAA measurements were identified from abdominal imaging reports in the electronic data files of three medical centres from 1995 to 2010. AAA measurements were extracted manually and patients with an aneurysm of 3 cm or larger, who had at least two measurements over an interval of at least 6 months, were identified. Other data were obtained from the electronic data files (demographics, co-morbidities, smoking status, drug use) to conduct a propensity analysis of the associations of drugs and other factors with AAA enlargement.

**Results:** From 52 962 abdominal imaging studies, 5362 patients with an AAA of 3 cm or more were identified, of whom 2428 had at least two measurements over at least 6 months. Mean AAA follow-up was 3·4 years and the mean AAA enlargement rate was 2·0 mm per year. Propensity analysis demonstrated no significant association of AAA enlargement with statins, beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. Diabetes was associated with a reduction in AAA enlargement of 1·2 mm per year ($P = 0·008$), and chronic obstructive pulmonary disease was associated with increased enlargement (0·5 mm per year; $P = 0·050$). Moderate AAA measurement variation and substantial terminal digit preference were also observed, but the digit preference became less pronounced after 2000.

**Conclusion:** This study confirms the negative association of diabetes with AAA progression. There was no evidence that commonly used cardiovascular drugs affect AAA enlargement.

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## Introduction

Large randomized trials have demonstrated that one-time ultrasound screening decreases mortality from abdominal aortic aneurysm (AAA) and all causes, in selected high-risk populations[1]. Based on these studies and resulting recommendations from the US Preventive Services Task Force[2] and other groups, ultrasound screening for AAA has become widespread. Screening, together with incidental imaging findings, results in the discovery of many AAAs, most of them smaller than 5·5 cm, the diameter threshold for elective repair established by randomized trials[3]. This presents an opportunity to intervene with treatments to inhibit aneurysm progression, but unfortunately no such treatments are available; these individuals are currently managed with imaging surveillance alone[4]. Few treatments to slow AAA enlargement have been tested adequately. Identification of drugs with sufficient promise to justify large expensive randomized trials is challenging, partly because positive animal studies have not been predictive of success in humans. An alternative strategy is to look for associations between commonly used drugs and aneurysm enlargement rates in appropriately adjusted observational studies. A variety of drugs have been proposed as potentially effective at reducing AAA enlargement, including statins, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs)[5]. This approach has been limited by a scarcity of data sets that contain both sufficient numbers of AAA

measurements and the necessary information on drugs and confounders.

In the present study, AAA measurements were extracted from a large, comprehensive electronic medical record system, along with information on drug use and other factors. These data were used to assess AAA measurement variability and enlargement patterns, and the association of patient factors and several classes of drugs with AAA enlargement. AAA enlargement was selected as the outcome of interest because it represents disease progression, is strongly associated with rupture, is the main determinant of AAA repair and is the only one potentially modifiable by drugs. It is the usual primary outcome of randomized trials of medical therapy for AAA.

## Methods

Electronic data files were searched from the US Department of Veterans Affairs (VA) medical centres in Minneapolis, Seattle and West Los Angeles. The study was approved by the institutional review boards of all three centres.

Abdominal CT and ultrasound reports from 1995 to 2009 were identified using Current Procedural Terminology (CPT®) codes (74150, 74160, 74170–74175, 76700–76705, 76770–76775). Because some studies (such as 'CT of the abdomen and pelvis') had no CPT® code, studies without CPT® codes were also included if the procedure name contained 'abdom' plus a term indicating CT or ultrasonography (CT, US, U/S, ultrasound, echo). Using a trial-and-error approach with sample sets, a strategy to identify AAA measurements was developed from the text of the radiology reports (clinical history, body of report and impression), whereby reports were included if they contained: (a) 'AAA' or 'aneu', or (b) 'aort' within 60 characters of 'mm', 'cm', 'millimeters' or 'centimeters', and not 'velocit' (used in flow studies of occlusive disease). For individual patients with tests that met either of these criteria, all other abdominal CT or ultrasound reports from any of the three study centres were included, as well as abdominal CT or ultrasound reports from other VA medical centres throughout the nation if these outside reports themselves met criterion (a) or (b) above.

### Data extraction

Research technicians reviewed each report and recorded maximum infrarenal aortic diameter in any cross-sectional plane, as reported by the radiologist, and any indication of aortic repair or rupture, using an application developed by the investigators that presented each report with key terms highlighted, and provided spaces to enter the desired information (*Fig. 1*). Each report was reviewed by two technicians who were unaware of each other's findings, and who could also submit a question. Discrepancies between the two technicians' reports and all questions were resolved by one of the authors.

AAA was defined as an infrarenal aortic diameter of 3·0 cm or larger. For each individual, imaging studies from before the first report of AAA and those done after AAA repair were excluded. AAA repair was identified from the radiology reports and from the electronic records using CPT® (0078T–0081T, 34800–34805, 34825–34832, 35081–35103, 75952 or 75953) and ICD-9 (38.14, 38.44, 39.71) procedure codes. One of the authors resolved discrepancies between administrative evidence of repair or rupture and subsequent extracted reports, and instances of a large (1 cm) decrease in AAA diameter without reported repair.

Other data on study patients, such as demographics, visits and hospital admissions, distance from residence to the medical centre, diagnoses and medications were obtained from VA databases. The diagnosis of diabetes was determined by ICD-9 diagnosis code or use of drugs to treat diabetes. Blood pressure measurements and dates were extracted for use as a time-varying co-variable. Smoking status (never, ever, current or unknown) at the time of each measurement was determined from a variety of data sources: attendance at a smoking cessation clinic, ICD-9 diagnosis codes 305.1X or V15.82, prescriptions for smoking cessation aids, data collected on patients having procedures for the National VA Surgical Quality Improvement Program, and the VA tobacco use clinical reminder field, which was searched for common text strings. All prescription data were collected on the drugs of interest. Drug use was defined as receipt of a VA prescription for a drug in that class during the study.

### Analysis

For the AAA enlargement analyses, all individuals with at least two measurements of an unrepaired AAA at least 6 months apart were included. The first infrarenal aortic diameter of 3·0 cm or larger after 1994 and all subsequent aortic diameter measurements before abdominal aortic surgery or AAA rupture were included until the end of the study in 2010. Multiple measurements made within 30 days for a given patient were replaced with their mean, entered at the date of the last measurement. A correction term derived from the study data was used to make CT measurements comparable with ultrasound measurements.

The Akaike and Bayesian information criteria (AIC and BIC respectively) were used to compare goodness-of-fit

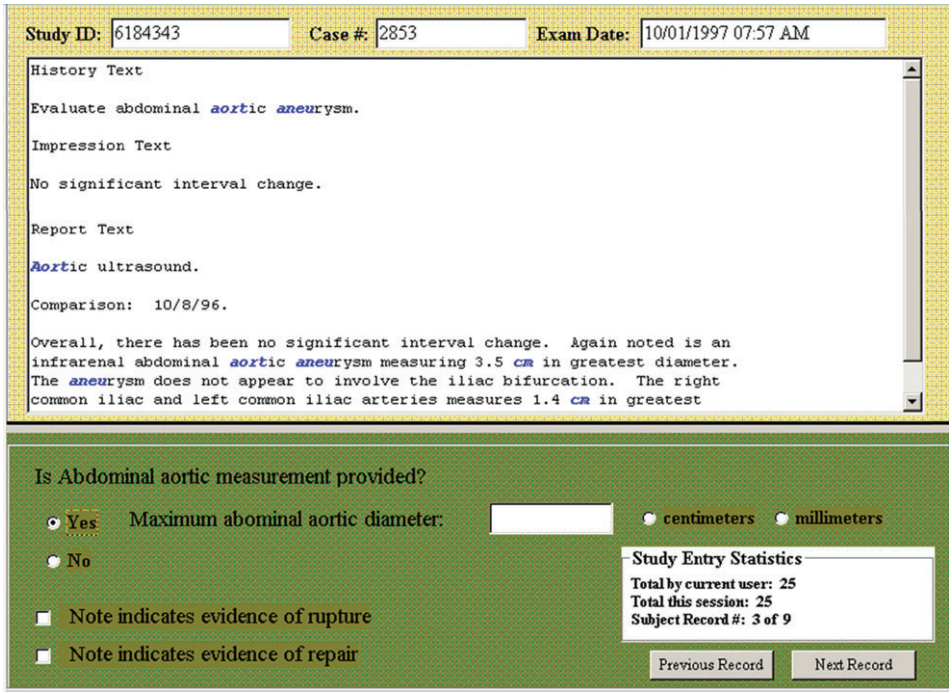


**Fig. 1** Data extraction application developed by the authors

of several patterns of AAA enlargement, including linear, exponential, logistic and Gompertz models[6].

Individual drugs within a class were converted to an equivalent dose of a class archetype. For each interval, the proportion of time with medication and the total number of milligrams taken were calculated, for use as co-variables in the propensity models (*Appendix S1*, supporting information).

For each factor examined, a propensity score was constructed for the likelihood of having the factor given the other co-variables. The other co-variables included demographics, diagnoses, smoking status, drug use and dose, and healthcare utilization (*Appendix S1*, supporting information). A generalized linear mixed model with logistic link was used to construct the longitudinal propensity model.

Nearest-neighbour matching based on propensity score was used for each factor to create matched data sets for the final mixed models. The matched models were also adjusted for baseline AAA diameter and any co-variables that were not balanced (*Appendix S2*, supporting information). All the matchings were done using MatchIt[7] and the mixed modelling was performed using Zelig (http://GKing.harvard.edu/zelig)[8]. Missing values were imputed using a Bayesian bootstrap method (*Appendix S2*, supporting information).

To plan the appropriate sample size for the study, an absolute reduction of 1·2 mm per year was used as the minimum important difference in AAA expansion rate that would justify drug therapy, based on a survey of physicians[9]. Using data from the Aneurysm Detection and Management (ADAM) trial[10], the standard deviation of change in AAA measurement from first to last measurement was estimated to be 5·8 mm. To have 90 per cent power to detect a mean change in AAA diameter of 1·2 mm per year from each drug with $\alpha = 0{\cdot}05$, discounted for presumably unbalanced propensity strata, at least 2000 individuals were needed. Data were therefore collected from three VA medical centres.

## Results

From 180 404 abdominal imaging reports on 83 226 patients between 1995 and 2009 at the three VA medical centres, the search identified 19 597 patients with at least one study meeting the search criteria. All 52 962 abdominal radiology studies on these patients were obtained for manual extraction. The two reviewers disagreed or had questions in 6·0 per cent of instances, and these were resolved by a third reviewer. This extraction process identified 23 432 studies with an AAA of 3 cm or more. To assess the sensitivity of the search, 4638 of the abdominal imaging studies that did not meet the search criteria were also reviewed (3·6 per cent). This identified 19 studies with an AAA diameter of at least 3 cm, implying that the search

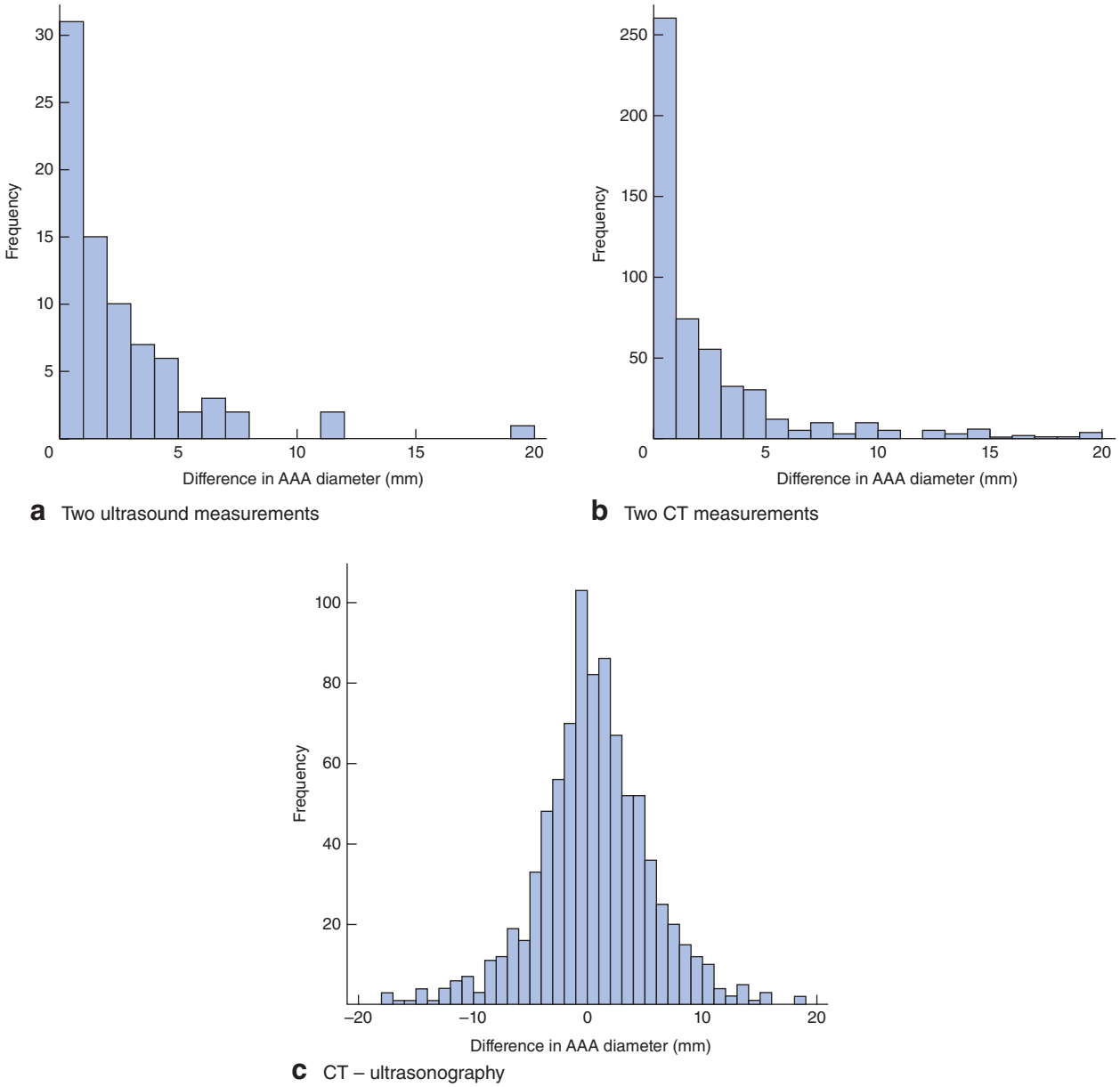


**Fig. 2** Differences between two abdominal aortic aneurysm (AAA) measurements done within 30 days, by type of test. **a** Two ultrasound measurements in 81 individuals; mean(s.d.) difference 3·7(7·0) mm. **b** Two CT measurements in 524 individuals; mean(s.d.) difference 3·0(4·5) mm. **c** CT *versus* ultrasound measurements in 887 individuals; mean difference (CT – ultrasonography) 0·9 mm; mean(s.d.) absolute difference 4·1(6·1) mm

missed 522 AAA measurements, and indicating that the sensitivity of the search to identify measurements of AAA diameter 3 cm or greater was 97·8 per cent. As finding one AAA measurement resulted in inclusion of all other imaging on that patient, it is unlikely that a patient with more than one AAA measurement was missed.

Some 5362 individuals with an unrepaired AAA were identified. This group was used to examine the agreement of reported measurements. There were 81 instances of an individual having two ultrasound measurements of aortic diameter within 30 days (*Fig. 2a*). The mean(s.d.) difference between the two measurements was 3·7(7·0) mm. Of 524 instances of two CT measurements within 30 days, the mean difference was 3·0(4·5) mm (*Fig. 2b*). There were 887 instances of an individual having ultrasonography and CT within 30 days, with a mean difference between the two

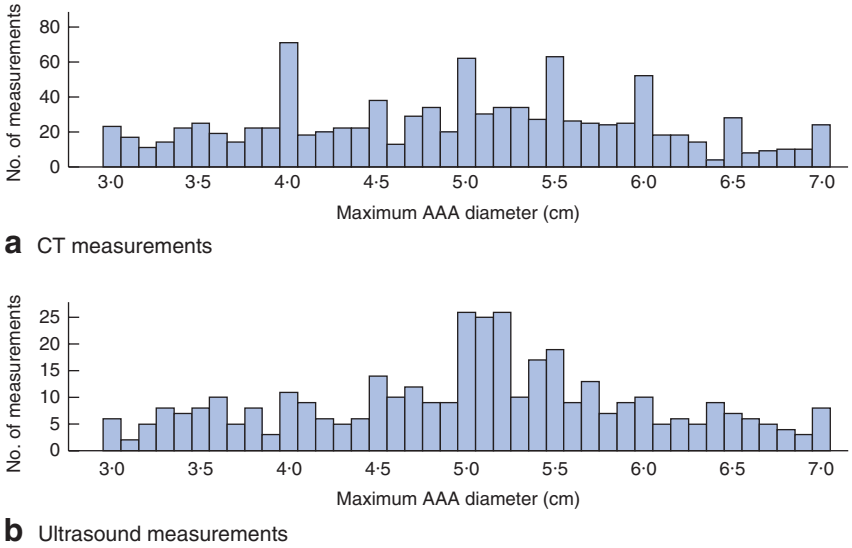


**Fig. 3** Frequency distribution of abdominal aortic aneurysm (AAA) diameter among **a** 1021 CT measurements and **b** 382 ultrasound measurements. Extreme values are not shown for ease of display

measurements of 4·1(6·1) mm (*Fig. 2c*). The mean group difference was 0·9 mm larger for CT than for ultrasound imaging. Limiting these comparisons to measurements after 1 January 2000 did not result in substantial differences (*Figs S1–S3*, supporting information). The CT measurements show marked rounding to the half-centimetre ($P < 0·001$) (*Fig. 3*), but this rounding became significantly less pronounced after 2000 ($P < 0·001$) (*Figs S4* and *S5*, supporting information).

There were 2428 patients with an AAA who had at least two measurements over at least 6 months; this group was used to conduct the analyses of AAA enlargement. These individuals had a mean follow-up of 3·4 years (maximum 14·4 years) with median follow-up of 2·7 (i.q.r. 1·4–4·7) years, and a total of 11 879 measurements (mean 4·9, median 4·0 per patient). Of these 2428 individuals, 484 had all of their measurements by ultrasound imaging, 539 had all of their measurements by CT, and the remainder had measurements by both examinations. Their mean age was 71·2 years, and 99·0 per cent were men (*Table 1*). Some 26·3 per cent were identified as current smokers at study entry, 3·7 per cent had never smoked, and smoking status was unknown for 23·5 per cent. Statins, beta-blockers and ACE inhibitors were each received by about 40 per cent of the individuals at some time during the study, whereas ARBs were received by only 4·7 per cent. AAA rupture was identified in 57 patients in the follow-up group, of whom 30 had an aortic diameter of 5·5 cm or larger a week or more before rupture.

The AIC and BIC for the various models of AAA enlargement were: linear 6767·4 and 6802·2, exponential 6343·9 and 6378·6, logistic 6293·0 and 6333·5, and Gompertz 7944·3 and 7984·9, with lower numbers signifying better fit. These data most closely fitted the logistic model, but the linear model produced sufficiently similar results. Because of its simplicity, it was used for subsequent analyses. Using

**Table 1** Characteristics of 2428 individuals with an abdominal aortic aneurysm of 3 cm or more followed for at least 6 months

| | No. of individuals* ($n = 2428$) |
|---|---|
| Age (years)† | 71·2(7·9) |
| Sex ratio (M : F) | 2403 : 25 |
| Smoking status | |
| Current smoker | 639 (26·3) |
| Never smoked | 91 (3·8) |
| Unknown | 570 (23·5) |
| No. of AAA measurements† | 4·9(3·6) |
| AAA diameter at first measurement (cm)† | 4·0(0·8) |
| AAA diameter at last measurement (cm)† | 4·6(1·2) |
| Co-morbidities | |
| Coronary artery disease | 894 (36·8) |
| Cerebrovascular disease | 290 (11·9) |
| Peripheral vascular disease | 352 (14·5) |
| Hypertension | 1368 (56·3) |
| Diabetes | 263 (10·8) |
| Chronic obstructive pulmonary disease | 671 (27·6) |
| Depression | 323 (13·3) |
| Renal failure | 157 (6·5) |
| Any drug use | |
| Statins | 1013 (41·7) |
| Beta-blockers | 992 (40·9) |
| Angiotensin-converting enzyme inhibitors | 994 (40·9) |
| Angiotensin II receptor blockers | 115 (4·7) |

*With percentages in parentheses unless indicated otherwise; †values are mean(s.d.). Data are for characteristics at baseline, except drug use which is at any time during the study. AAA, abdominal aortic aneurysm.

**Table 2** Propensity analysis of factors potentially affecting abdominal aortic aneurysm enlargement rate

| | No. of matched pairs | Enlargement rate without factor (mm/year) | Change in rate with factor (mm/year) | *P* |
|---|---|---|---|---|
| Age > 72 years* | 459 | 2·1 | 0·0 (–0·7, 0·7) | 0·934 |
| After 2000 | 310 | 1·9 | –1·1 (–2·0, –0·2) | 0·016 |
| Current smoking | 639 | 2·1 | – 0·2 (–0·6, 0·2) | 0·358 |
| After 2000 | 461 | 2·0 | –0·2 (–0·7, 0·2) | 0·338 |
| Coronary artery disease | 894 | 2·1 | –0·3 (–0·8, 0·2) | 0·198 |
| After 2000 | 561 | 2·1 | –0·5 (–1·2, 0·2) | 0·154 |
| Chronic obstructive pulmonary disease | 671 | 1·7 | 0·5 (0·0, 1·0) | 0·050 |
| After 2000 | 430 | 1·7 | 0·7 (–0·1, 1·6) | 0·109 |
| Diabetes | 263 | 2·4 | –1·2 (–2·0, –0·3) | 0·008 |
| After 2000 | 185 | 2·1 | –1·1 (–2·0, –0·2) | 0·020 |
| Statins | 1013 | 2·1 | 0·1 (–0·2, 0·5) | 0·510 |
| After 2000 | 538 | 1·8 | 0·4 (0·3, 1·1) | 0·290 |
| Beta-blockers | 828 | 2·1 | –0·5 (–1·2, 0·3) | 0·242 |
| After 2000 | 605 | 2·0 | 0·0 (–0·6, 0·6) | 0·997 |
| Angiotensin-converting enzyme inhibitors | 994 | 2·0 | 0·1 (–0·3, 0·4) | 0·656 |
| After 2000 | 669 | 2·0 | 0·1 (–0·4, 0·7) | 0·613 |
| Angiotensin II receptor blockers | 115 | 1·8 | –0·2 (–1·3, 0·9) | 0·608 |
| After 2000 | 107 | 1·8 | 0·1 (–1·3, 1·1) | 0·823 |

Values in parentheses are 95 per cent c.i. *Age at first measurement; other factors could be present at any time during follow-up. After 2000 refers to measurements after 1 January 2000.

the linear model, the mean AAA enlargement rate for the follow-up group was 2·0 (95 per cent c.i. 1·9 to 2·3) mm per year.

*Table 2* shows the results of the propensity analysis. Any use of each of the four classes of drug (statins, beta-blockers, ACE inhibitors, ARBs) was associated with a small change in AAA enlargement of 0·5 mm per year or less that was not statistically significant. Current smoking also had no statistically significant association with AAA enlargement, although chronic obstructive pulmonary disease was associated with more rapid enlargement of 0·5 mm per year ($P = 0·050$). Diabetes was associated with a decrease in AAA enlargement of 1·2 mm per year ($P = 0·008$). Because of changes in practice over time, the analysis was repeated, limited to measurements since 1 January 2000, with no important differences. The association of current smoking with AAA enlargement remained non-significant in models that placed all those with unknown smoking status into the current smoking group, or alternatively into the not currently smoking group.

Possible associations of any use of statins, beta-blockers and ACE inhibitors up to the time of each measurement with AAA enlargement from the first measurement to the measurement in question, and from the immediately preceding measurement to the measurement in question, were also examined, but none was found to be statistically significant.

## Discussion

In this study of 2428 individuals with an AAA followed up for a mean of 3·4 years, there was no reduction in AAA enlargement rate associated with use of statins, beta-blockers, ACE inhibitors or ARBs. The 95 per cent confidence intervals exclude the prespecified minimum important difference of 1·2 mm per year in AAA enlargement rate for all drugs, except the less frequently used ARBs. These findings are similar to those reported by an adjusted meta-analysis[11] of previous studies of AAA enlargement and to a recent analysis of ADAM trial data[12], both of which reported no significant drug associations. Of the drugs studied, randomized trials are available only for the beta-blocker propranolol, and the three trials[13–15] that have been reported all had high rates of drug discontinuation and found non-significant reductions in AAA enlargement.

The AAA enlargement rate of 2·0 mm per year observed in this study was similar to the rate of 2·2 mm per year in the meta-analysis[11]; the latter value falls within the 95 per cent c.i. of the present study. Unlike the meta-analysis and the ADAM study, the present study did not find a significant association between current smoking and AAA enlargement. The only factors associated with AAA enlargement in this study were chronic obstructive pulmonary disease and diabetes.

The reduction in AAA enlargement rate by diabetes was 1·2 mm per year, compared with 1·1 mm per year in the ADAM data[12] and 0·5 mm per year in the meta-analysis[11]. The negative association between diabetes and AAA was first described in the ADAM screening study and subsequently confirmed by a variety of studies of AAA diagnosed through screening or clinical events[16]. Although the negative association between diabetes and AAA now

seems convincing, the mechanism remains unexplained. It is nevertheless strong evidence that AAA is not a manifestation of atherosclerosis[16], which may help explain the lack of associations with AAA progression by drugs that are effective against atherosclerosis.

In this study, CT measurements were a mean of 0·9 mm larger than ultrasound measurements done within 30 days. This is similar to the difference observed in the ADAM study[17], in which local CT measurements were an average of 1·2 mm larger than ultrasound measurements done within 30 days[17]. The slightly larger readings by CT may reflect the ability of CT to identify the maximum cross-sectional diameter in any plane, whereas ultrasound imaging usually measures only the anterior–posterior diameter.

The measurement variability observed in this study for CT compared with ultrasound is similar to the ADAM study comparison of ultrasound with central CT reading[17]. The variability between unblinded measurements of two separate CT images in this study was similar to that seen for the local *versus* blinded central readings of the same CT image in the ADAM study. The rounding to the half-centimetre seen in the CT measurements, termed terminal digit preference, was described previously in the ADAM study[17], and in the present study was seen to improve from 2000, possibly influenced by the ADAM study report.

This study has several potential limitations. First, it relies on observational rather than randomized data, which could affect the observed drug associations. The findings of no drug associations could represent residual confounding by drug indication (such as occlusive vascular disease and hypertension), although every effort was made to account for this in the analysis. Had there been evidence of reduced AAA enlargement associated with one or more of the study drugs, development of a randomized trial was planned.

Second, use of VA pharmacy data may have failed to reflect the medications taken by these individuals, owing to either non-adherence to prescribed medications or use of prescriptions from sources other than VA. However, available data do not support these concerns. Wannemacher and colleagues[18] calculated adherence (defined as mean percentage of time with drug) for the year 1998 in a VA region to be 93 per cent for beta-blockers and 95 per cent for ACE inhibitors. Piette and Heisler[19] found that cost-related medication non-adherence was lower among VA patients than among other groups. The use of VA pharmacy refill data as a measure of adherence has been validated by comparison with clinical drug effects[20]. A 1997 systematic review[21] noted that 98–100 per cent of VA pharmacy users reported no non-VA pharmacy use.

Third, drug indications may have changed during the study, such as increased use of the study drugs for coronary disease and heart failure in the 1990s. However, limiting the analyses to data collected after 2000 did not result in substantial changes to the findings.

Fourth, routine clinically reported measurements of AAA diameter were relied on, rather than measurements done for research, which resulted in suboptimal accuracy as evidenced by the substantial terminal digit preference noted above. The large numbers of patients and long duration of follow-up should minimize the impact of minor measurement inaccuracy.

Finally, administrative data were used for identification of co-variables, which entails some inaccuracy, particularly in the ability to identify baseline smoking status in older records. This may partially explain why no association between current smoking and AAA enlargement was detected, although models that placed all those with unknown smoking status into the current smoking group or into the not currently smoking group obtained the same result. Another possible reason for no association between current smoking and AAA enlargement was that there were few never smokers, so comparison was largely with former smokers, which may result in less of a difference.

Consistent with previous studies, diabetes was associated with slower AAA enlargement, whereas use of statins, beta-blockers, ACE inhibitors or ARBs was not. Based on these findings, the expense of a large randomized trial of these drugs to reduce AAA enlargement is difficult to justify.

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## Supporting information

Additional supporting information may be found in the online version of this article:

**Appendix S1** Co-variables (Word document)

**Appendix S2** Statistical methods (Word document)

**Fig. S1** Differences between two ultrasound measurements of abdominal aortic aneurysm done within 30 days: **a** before and **b** after 1 January 2000 (Word document)

**Fig. S2** Differences between two CT measurements of abdominal aortic aneurysm done within 30 days: **a** before and **b** after 1 January 2000 (Word document)

**Fig. S3** Differences between CT and ultrasound measurements of abdominal aortic aneurysm done within 30 days: **a** before and **b** after 1 January 2000 (Word document)

**Fig. S4** Frequency distribution of ultrasound measurements of abdominal aortic aneurysm diameter before and after 1 January 2000 (Word document)

**Fig. S5** Frequency distribution of CT measurements of abdominal aortic aneurysm diameter before and after 1 January 2000 (Word document)