An evaluation of the effect of an angiotensin-converting enzyme inhibitor on the growth rate of small abdominal aortic aneurysms: a randomised placebo-controlled trial (AARDVARK)

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Scientific summary

The AARDVARK trial

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Scientific summary

Background

An abdominal aortic aneurysm (AAA) is a ballooning of the infrarenal aorta to either 1.5 times its normal anteroposterior (AP) diameter or an absolute value of ≥ 3 cm. Small AAAs can be defined as those between 3.0 cm and 5.4 cm in diameter. These small AAAs have a low risk of rupture, and operation to repair small AAAs is fatal in approximately 2–3% of patients. Small AAAs are generally managed by optimising cardiovascular health and placing the patient on a surveillance programme to measure the AAA diameter at regular intervals. Once AAAs reach 5.5 cm (or if initially detected at a larger size) they are often repaired as the risk of rupture rises exponentially above this size. If rupture does occur, one-third of patients die without reaching hospital and repair is performed in fewer than half of those reaching hospital alive, of whom 30–35% die within 30 days, leading to an overall mortality rate from rupture of ≥ 80%. Although recent reports have suggested that the incidence of aneurysms appears to be in decline, AAA remains a significant health risk in the older population, with around 4000 deaths each year in England and Wales attributed to AAA rupture.

Except when they rupture, most small AAAs are asymptomatic and so, until recently, they were detected as an incidental finding on clinical examination or various types of imaging performed for other purposes. However, in the UK, the NHS Abdominal Aortic Aneurysm Screening Programme was introduced in 2009 and so many more small AAAs are now being detected early. The programme has been very successful and screened its millionth man in autumn 2015. There is an opportunity to reduce the number of patients needing AAA repair if we can slow or prevent AAA growth in this growing cohort of patients.

Although data on the effects of angiotensin-converting enzyme inhibitors (ACE-Is) in this context are not consistent, ACE-Is have been associated with a reduced incidence of AAA rupture in analysis of administrative databases. Previous trials of other drugs that may slow AAA growth have been hindered by poor patient compliance. Therefore, this pilot trial was undertaken to assess whether or not an ACE-I could potentially slow AAA growth and be well tolerated in doing so. We are unaware of other completed randomised controlled trials designed to examine the efficacy of ACE-Is or angiotensin receptor blockers (ARBs) in limiting or inhibiting AAA progression, although two trials of the impact of ARBs on the growth rate of AAAs are in progress.

Objectives

Primary

- To investigate in a three-arm, randomised, placebo-controlled pilot trial the hypothesis that the ACE-I perindopril (Coversyl arginine, Servier) reduces the growth rate of small AAAs.

Secondary

- To evaluate any blood pressure (BP)-independent effects of perindopril on the growth rate of small AAAs.
- To determine differences in AAA rupture rate and/or time taken to reach an AAA diameter of 5.5 cm and/or referral for surgical intervention among the three randomised groups.
- To evaluate how well perindopril is tolerated as measured by compliance, adverse events (AEs) and quality of life.
- To compare the repeatability of ultrasound measurements of internal and external small AAA diameters.

Pending the results of this pilot trial, our objective was to conduct a larger definitive trial to investigate whether an ACE-I can reduce the rate of AAA-related mortality, rupture or surgery.

Methods

This randomised, single-blind (so classified because trial medications were not identical, but neither the investigators nor the trial participants at each site were aware of their treatment allocations), placebo-controlled study was performed at 14 sites in England. Participants were randomised to receive perindopril (10 mg of arginine salt daily), placebo (primary comparison) or amlodipine (5 mg daily) (secondary comparison). The perindopril and amlodipine doses used were estimated to have similar effects on BP reduction and hence a secondary comparison assessed whether or not any benefits of perindopril were independent of a reduction in BP.

Men and women aged at least 55 years with an AAA of 3.0–5.4 cm in AP diameter (internal or external) and a systolic BP (SBP) of < 150 mmHg were invited to participate in the study. Patients who were already required to take either an ACE-I or a calcium channel blocker (CCB) (with the exception of 5 mg of amlodipine) or an ARB were excluded. Those with known renal artery stenosis (> 50%), a serum creatinine level of > 180 µmol/l, any clinically significant medical condition that, in the opinion of the investigator, might interfere with the study results and/or reduce life expectancy to < 2 years, or a known allergy or sensitivity to perindopril or amlodipine were also excluded.

Suitable subjects with SBP < 150 mmHg who wished to participate in the trial were given either 5 mg of amlodipine daily (if not already on a CCB) or 1.5 mg of slow-release indapamide daily and were asked to return for screening at 6 weeks. At this point they could be included in the trial if their SBP was < 150 mmHg.

Eligible subjects were randomised to the three groups using a 1 : 1 : 1 ratio and were stratified by centre and into one of two ranges of baseline aneurysm size: 3.00–4.50 cm and 4.51–5.40 cm.

Patients were followed up every 3–6 months over 2 years. At each visit, three BP recordings were taken in the sitting position using a validated semiautomated device after at least 10 minutes' rest. The mean of the second and third readings was used in the analyses. Smoking was not permitted during the 30 minutes before BP measurement.

Ultrasound AAA diameter measurements were taken at each visit. For all patients the maximum internal and external AP AAA diameters were measured from ultrasound images of the AAA in the transverse and longitudinal planes. A scanning protocol was provided to all participating sites in an attempt to optimise the consistency and accuracy of the ultrasound measurements made across the 11 scanning sites that serviced the 14 collaborating hospitals.

Quality assurance (QA) scanning events were organised to ensure consistency between observers and between measurements by the same observers (inter- and intraobserver variability). The specific aims of the QA events were to ensure the reliability of the results in terms of inter- and intra-observer variability and evaluate, which was the most accurate and repeatable AAA measurement. In addition, the quality of the ultrasound images and the ultrasound measurement data were assessed centrally to ensure a reliable standard of ultrasound scanning across the 11 scanning sites and to highlight any errors. Representative ultrasound images from all sites were assessed for quality by a single experienced vascular scientist.

Blood tests for concentrations of creatinine and electrolytes were carried out at screening and 3, 12 and 24 months (in keeping with best recommended practice for the management of hypertension with ACE-Is).

Patient compliance with trial investigational medicinal products was assessed using pill counts and potential side effects of drug treatments were monitored.

Based on the inclusion of 225 patients with a baseline AAA diameter of ≤ 5.4 cm and an estimated AAA growth rate (data from the UK Small Aneurysm Trial) of 2.6 mm per year, the trial had 90% power at the 5% level to detect a 38% reduction in growth rate associated with randomisation to the ACE-I group compared with the placebo group. The detectable reduction in growth rates with 80% and 70% power were 31% and 28%, respectively. On the assumption that the effects on aneurysm progression are specific to ACE-I rather than to lowering of BP, the trial was powered to detect a smaller difference in growth rate (< 20%) by comparing the ACE-I group with the other two groups. These calculations allowed for a 10% attrition rate, defined as withdrawal of subjects who did not have more than baseline measurements of their AAA diameter, thereby preventing the possibility of any direct measurement of AAA growth over time.

It was anticipated that the AAA growth rate in those randomised to amlodipine would allow evaluation of the extent to which any potential ACE-I effect on AAA growth rate compared with placebo was attributable to a reduction in BP.

Patients were to be censored at the time of death, referral for AAA repair or AAA rupture should they occur, or in the absence of these events, at the end of the trial.

The primary outcome measure was growth in AAA diameter using external measurements in the longitudinal plane, estimated using multilevel modelling. Secondary outcome measures included AAA rupture, AAA repair, modelling of the time taken for the AAA to reach the threshold for intervention (5.5 cm) or referral for surgery, tolerance of study medication (measured by compliance, AEs and quality of life) and a comparison of the repeatability of measures of internal and external AAA diameter.

Results

Between September 2011 and April 2013, 227 patients were randomised ($n = 75$ perindopril, $n = 73$ amlodipine, $n = 79$ placebo). Because of the large number of patients who were ineligible (mainly because they were already taking an ACE-I), a recruitment extension of 6 months and the addition of nine extra research sites was required.

The recruitment target was met by April 2013. Trial follow-up was completed in April 2015, with 70% of patients completing all trial visits and an attrition rate of 6%. Groups were well matched at baseline for standard demographic parameters.

Based on the QA scanning events, the measurement of maximum aortic diameter in the longitudinal plane was more repeatable than the measurement of the diameter in the transverse plane. For the maximum aortic diameter measured in the longitudinal plane, the intraobserver repeatability was similar for internal and external measurements, but interobserver variability was better for external measurements. Therefore, as most sites used more than one observer, external measurements in the longitudinal plane were selected for monitoring AAA growth. Further support for this decision arose from comparisons of measurement variability [standard deviations (SDs) between internal and external measures shown at most time points in the trial].

Mean differences (SD) in SBP from baseline to 24 months in the perindopril, amlodipine and placebo groups were –5.0 (16.3) mmHg, –2.8 (11.7) mmHg and +2.5 (16.5) mmHg, respectively.

Compliance measured by pill counts was good throughout the trial (> 80% at all visit time points). There were no significant safety concerns associated with any of the three allocated trial drugs. Six patients withdrew because of AEs attributed to the study medications ($n = 2$ perindopril, $n = 4$ amlodipine). No patients ruptured their AAA and 27 patients underwent elective surgery during the trial period ($n = 9$ placebo, $n = 10$ perindopril, $n = 8$ amlodipine).

Multilevel modelling was used to determine the maximum likelihood estimates for AAA diameter growth. There were no significant differences in the estimated annual diameter growth rate among the three randomised groups [1.68 (standard error 0.02) mm, 1.77 (0.02) mm and 1.81 (0.02) mm in the placebo, perindopril and amlodipine groups, respectively]. Similarly, the differences in the slope of modelled growth over time were not significant between perindopril and placebo ($p = 0.78$) or between perindopril and amlodipine ($p = 0.89$). The difference in the slope of modelled growth between the perindopril group and the placebo and amlodipine groups combined was also not significant ($p = 0.92$). These results were essentially unchanged after adjustment for potential confounders including smoking, diabetes and statin use. Similarly, there were no differences between the groups in time to AAA referral for repair and/or time to reach an AAA diameter of 5.5 cm.

Conclusions

This study is, to our knowledge, unique in having evaluated the effect of an ACE-I on the growth rate of small AAAs in a randomised placebo-controlled trial. The ACE-I perindopril was well tolerated in this trial, with good compliance rates, and there were similar numbers of AEs in all three groups.

However, we were unable to demonstrate any significant impact of perindopril compared with placebo or the CCB amlodipine on the growth rate of small AAAs over a 2-year period. The growth rates observed in the trial were slower than expected, which may reflect specific characteristics of the included population (e.g. SBP had to be < 150 mmHg at baseline). With the observed growth rate of 1.7 mm per year, 190 patients per group would have been needed to detect a 1 mm per year reduction in growth with a power of 90%. The sample evaluated ($n = 227$) generated 51% power to detect a 1-mm difference in growth (between two groups) and 85% power to detect a difference of 1.5 mm (close to the annual growth rate observed). However, the estimated difference in annual growth between the perindopril and placebo groups was 0.08 mm with 95% confidence interval of –0.50 mm to 0.65 mm. This statistically excludes a likely reduction of 1 mm per year with perindopril administration.

A significant BP reduction was apparent in both the perindopril group and the amlodipine group. The doses of perindopril and amlodipine chosen for the trial were expected to cause similar BP reductions but this was not realised. At 3 months BP reduction with perindopril was significantly greater than that with amlodipine ($p = 0.002$). With similar withdrawal rates observed in all three treatment groups and no differences in relation to compliance, the reasons for the difference in BP reduction between the perindopril group and the amlodipine group remain unclear.

According to the QA repeatability studies, measurements in the longitudinal plane were more repeatable than transverse measurements. However, overall, the measurement variability in the trial as reflected by SDs was greater than anticipated, adding uncertainty to the interpretation of the results.

Implications for health care

Despite some earlier evidence which suggests that the rupture rates of AAAs may be lower in patients taking ACE-Is, this trial found no evidence that patients with small AAAs should be prescribed an ACE-I to slow AAA growth. The QA studies undertaken as well as the comparison of various aspects of the variability of internal and external measurements provide support for the use of external rather than internal AAA diameter measurements taken in the longitudinal plane.

The following research recommendations are made as a consequence of the conduct and findings of the trial:

- Further work relating to the data already collected in the trial:
  - A multivariate analysis of determinants of AAA growth in the trial.
  - Potential differences were observed between the three treatment groups in relation to the numbers of patients whose AAA grew at a fast rate during the trial (as defined by a growth rate of > 5 mm per year). However, formal analyses are still required.
  - An evaluation of the incremental predictive power of baseline and changing central BP and BP variability on AAA growth rates.
- Further work potentially arising from the trial:
  - An evaluation of currently available data regarding AAA growth rates in those with SBP < 150 mmHg and ≥ 150 mmHg to investigate whether growth rates could be critically affected by this systolic threshold or other systolic and diastolic thresholds.
  - An evaluation of whether the BP-lowering effect of perindopril and amlodipine is affected by the presence or absence of an AAA.
  - The strong protective effect of type 2 diabetes on the development of AAAs observed in large observational databases merits further investigation.
  - A large measurement variability study to optimise training and standardisation.
  - A trial to evaluate the impact of ACE-Is on the rupture of larger AAAs.

Trial registration

This trial is registered as ISRCTN51383267.

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