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Abstract

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)

Gaia Kiru,[1]* Colin Bicknell,[2] Emanuela Falaschetti,[1] Janet Powell[2] and Neil Poulter[1] on behalf of the AARDVARK collaborators

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Background: Although data are inconsistent, angiotensin-converting enzyme inhibitors (ACE-Is) have been associated with a reduced incidence of abdominal aortic aneurysm (AAA) rupture in analysis of administrative databases.

Objectives: (1) To investigate whether or not the ACE-I perindopril (Coversyl arginine, Servier) reduces small AAA growth rate and (2) to evaluate blood pressure (BP)-independent effects of perindopril on small AAA growth and to compare the repeatability of measurement of internal and external aneurysm diameters.

Design: A three-arm, multicentre, single-blind, randomised placebo-controlled trial.

Setting: Fourteen hospitals in England.

Participants: Men or women aged ≥ 55 years with an AAA of 3.0–5.4 cm in diameter by internal or external measurement according to ultrasonography and who met the trial eligibility criteria.

Interventions: Patients were randomised to receive 10 mg of perindopril arginine daily, 5 mg of the calcium channel blocker amlodipine daily or placebo daily.

Main outcome measures: The primary outcome was AAA diameter growth using external measurements in the longitudinal plane, which in-trial studies suggested was the preferred measure. 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, adverse events and quality of life) and a comparison of the repeatability of measures of internal and external AAA diameter. Patients were followed up every 3–6 months over 2 years.

Results: In total, 227 patients were recruited and randomised into the three groups, which were generally well matched at baseline. Multilevel modelling was used to determine the maximum likelihood estimates for AAA diameter growth. No significant differences in the estimates of annual growth were apparent [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, no significant differences in the slopes of modelled growth over time were apparent between perindopril and placebo ($p = 0.78$) or between perindopril and amlodipine ($p = 0.89$). The results were essentially unaffected by adjustment for potential confounders. Compliance, measured by pill counts, was good throughout (> 80% at all visit time points). There were no significant in-trial safety concerns. Six patients withdrew because of adverse events attributed to the study

medications ($n = 2$ perindopril, $n = 4$ amlodipine). No patients ruptured their AAA and 27 underwent elective surgery during the trial ($n = 9$ placebo, $n = 10$ perindopril, $n = 8$ amlodipine).

Conclusions: We were unable to demonstrate a significant impact of perindopril compared with placebo or amlodipine on small AAA growth over a 2-year period. Furthermore, there were no differences in the times to reach a diameter of 5.5 cm or undergo surgery among the three groups. Perindopril and amlodipine were well tolerated by this population. External AAA measurements were found to be more repeatable than internal measurements. The observed AAA growth measurement variability was greater than that expected pre trial. This, combined with slower than expected mean growth rates, resulted in our having limited power to detect small differences between growth rates and hence this adds uncertainty to the interpretation of the results. Several further analyses are planned including a multivariate analysis of determinants of AAA growth, an evaluation of the possible differential effect of perindopril on fast AAA growth and an investigation into the roles of central BP and BP variability on AAA growth.

Trial registration: Current Controlled Trials ISRCTN51383267.

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List of abbreviations

AAA	abdominal aortic aneurysm
AARDVARK	Aortic Aneurysmal Regression of Dilation: Value of ACE-inhibition on RisK
ACE-I	angiotensin-converting enzyme inhibitor
AE	adverse event
AP	anteroposterior
ARB	angiotensin receptor blocker
BP	blood pressure
CCB	calcium channel blocker
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CT	computerised tomography
DBP	diastolic blood pressure
DSMC	Data Safety Monitoring Committee
EQ-5D	European Quality of Life-5 Dimensions
EVAR	endovascular aneurysm repair
GP	general practitioner
HR	hazard ratio
HTA	Health Technology Assessment
ICCH	International Centre for Circulatory Health
ICF	informed consent form
ICTU	Imperial Clinical Trials Unit
IMP	investigational medicinal product
ITI	inner to inner
ITT	intention to treat
MASS	Multicentre Aneurysm Screening Study
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
NAAASP	NHS Abdominal Aortic Aneurysm Screening Programme
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OTO	outer to outer
PI	principal investigator
PIC	patient identification centre
PIS	patient information sheet
QA	quality assurance
RAS	renin–angiotensin system
RCT	randomised controlled trial
REC	Research Ethics Committee
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
TMG	Trial Management Group
TSC	Trial Steering Committee
UKHPS	UK Heart Protection Study
UKSAT	UK Small Aneurysm Trial

Plain English summary

An abdominal aortic aneurysm (AAA) is a swelling of the main blood vessel (the aorta) in the body. Large AAAs may burst, and this is usually fatal.

When an AAA is small (< 5.5 cm across), changes in size can be monitored safely using ultrasound scanning. Larger aneurysms need surgery before they burst. No drug treatments are currently available that slow AAA growth, avoid surgery or stop them from bursting.

Some studies have suggested that drugs called angiotensin-converting enzyme inhibitors (ACE-Is), which are usually used to treat high blood pressure, may reduce the risk of AAAs bursting. This trial investigated whether or not an ACE-I called perindopril reduced the growth of small AAAs.

A group of 227 patients with small AAAs from 14 hospitals in England took part in the trial. Patients were randomly allocated to receive perindopril or another drug used to treat blood pressure called amlodipine or a placebo (dummy) pill. To see whether perindopril slowed AAA growth more than blood pressure lowering with an ordinary tablet (amlodipine) or placebo, each patient had their AAA measured every 3–6 months for 2 years.

At the end of the trial we found that, on average, perindopril was about the same as amlodipine and placebo in terms of affecting AAA growth. However, the AAAs in the trial grew more slowly than expected and the accuracy of ultrasound scanning was less than expected, both of which may have reduced our ability to detect small differences between groups if they were present.

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.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research (NIHR). The NIHR Biomedical Research Centre based at Imperial College NHS Trust supported the trial. Servier provided perindopril at no charge.

Chapter 1 Background and rationale

Introduction

An abdominal aortic aneurysm (AAA) is a ballooning of the infrarenal aorta to either 1.5 times its normal anteroposterior (AP) diameter or to an absolute value of ≥ 3 cm.[1] 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, whereas the operation to repair them is fatal in approximately 2–3% of patients.[2] 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, the results of emergency aneurysm repair are not good, with only about 40% of patients surviving. Without repair few survive, so that overall the survival of AAA rupture is probably $< 20\%$. Although recent reports have suggested that the incidence of aneurysms appears to be in decline,[3,4] AAA remains a significant health risk in the older population, with around 4000 deaths each year in England and Wales attributed to AAA rupture.[5]

Except when they rupture, most AAAs are usually asymptomatic and so, until recently, they were detected as an incidental finding on clinical examination or ultrasonography, abdominal computerised tomography (CT) or magnetic resonance imaging performed for other purposes. However, in the UK, the NHS Abdominal Aortic Aneurysm Screening Programme (NAAASP) 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 AAA growth can be slowed or prevented 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.[6] Previous trials of some other drugs to slow AAA growth have been hindered by poor patient compliance.[7] Therefore, this pilot trial was undertaken to assess whether or not ACE-Is could potentially slow AAA growth and are well tolerated in doing so. We are unaware of any other completed randomised controlled trials (RCTs) 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 of AAAs are in progress.

Risk factors

A wide variety of risk factors have been attributed to the formation and progression of AAAs. The single most important risk factor for AAAs has consistently been found to be smoking,[8–10] although other risk factors including male sex, age, high blood pressure (BP) [particularly raised diastolic BP (DBP)] and family history of AAA are frequently linked with the aetiology of AAA.[11] Low prevalence rates have been observed among African[12] and Asian[13] men compared with Caucasian men. Several studies have also found a strong coexistence of localised and generalised atherosclerosis and AAA,[14,15] an underlying disturbed connective tissue metabolism[16] and an increased risk for AAA with increasing alcohol consumption.[17]

There are many genetic syndromes that are associated with aortic aneurysmal disease affecting patients often at a very early age, including Marfan syndrome, Ehlers–Danlos syndrome, Loeys–Dietz syndrome and familial thoracic aortic aneurysms and dissections.[18]

The NHS Abdominal Aortic Aneurysm Screening Programme

Phased implementation of the NAAASP began in July 2009. It was introduced after data from a number of studies and existing local screening programmes in England showed a reduction in aneurysm-related mortality when men aged ≥ 65 years were offered ultrasound screening.

The Multicentre Aneurysm Screening Study (MASS) was designed to assess whether or not AAA screening would be beneficial.[19] This study enrolled men aged 65–74 years who were randomised to receive screening or not. Extended follow-up of patients confirmed that screening resulted in a reduction in all-cause mortality. Over 13 years there were 224 AAA-related deaths out of the 33,883 participants in the invited group and 381 AAA-related deaths out of the 33,887 participants in the control group, a 42% relative reduction.[20]

In 2005 this evidence was assessed by the UK National Screening Committee, which concluded that ultrasound screening should be offered to men in their 65th year, with men aged ≥ 65 years being able to self-refer within the NHS.[5]

The initial outcomes from the NAAASP in England identified a lower prevalence of AAA than reported in the MASS (1.4% vs. 4.7%). However, in the MASS, men aged 65–74 years were included, whereas the NAAASP invites men in their 65th year only for screening.

Between 2009 and 31 March 2014 the NAAASP had scanned > 700,000 men and referred > 1000 men with a large AAA for surgery. In the period 2013–14, 491 of the screened men had an elective AAA repair and four of these men died (an elective repair mortality rate of 0.8%). In addition, seven of the 10 screened men who suffered aneurysmal rupture died (a rupture mortality rate of 70%).[21]

Because of the NAAASP a greater number of patients with a small AAA are being detected and, if there were effective treatments to slow AAA growth, this could provide an opportunity to intervene before the AAAs expand significantly and rupture. Also, the NAAASP potentially provides a useful pool of patients for research purposes, not only for logistical reasons but also because this group of patients (who were previously unaware of their AAA) may be receiving less clinical/medical intervention than patients who are already receiving monitoring for their AAA. They are therefore of particular interest for interventional studies.

Current guidelines for the management of small abdominal aortic aneurysms

Given the variability in aneurysm expansion rates,[22] the optimal interval between surveillance scans remains uncertain. Meta-analysis of small AAA growth rates has demonstrated that the screening interval should be dependent on diameter and that long intervals between screening may be safe for the majority of patients.[23] However, guidelines must balance the need to reduce the cost of surveillance programmes and the need to ensure safety, as well as increasing the face-to-face time for direct cardiovascular risk factor education.

The UK guidelines recommend that rescreening intervals should shorten as the aneurysm enlarges and these guidelines are expected to be updated in 2017.[24] Usual clinical practice in the UK, and for those patients in the NAAASP, involves follow-up surveillance imaging at 12-monthly intervals for patients with an AAA of 3.0–4.4 cm in diameter and at 3-monthly intervals for those patients with an AAA diameter between 4.5 cm and 5.4 cm.

Abdominal aortic aneurysm treatment

In both the USA and the UK, elective surgery by either open or endovascular repair is undertaken to prevent AAA rupture and this is generally recommended for patients with an AAA of ≥ 5.5 cm in diameter, for symptomatic aneurysms or for aneurysms that have increased by > 0.5 cm in the past 6 months. The UK Small Aneurysm Trial (UKSAT) demonstrated that the overall mortality of patients with an aneurysm of < 5.5 cm in diameter who received surveillance was similar to that in patients who received early open surgery.[22] Furthermore, surveillance was the more cost-effective option. Subsequent studies that have randomised patients to surveillance or endovascular treatment of AAAs have corroborated this finding.[25,26] There has been an increasing trend in the proportion of repairs performed as endovascular aneurysm repair (EVAR) procedures, increasing from 54% in 2009 to 66% in 2013.[27]

Studies indicate that without surgery the 5-year survival rate for patients with an aneurysm of diameter > 5 cm is about 20%.[28] Surgery to replace the aneurysmal segment or endovascular placement of a covered stent graft excluding the aneurysm is recommended if the risk of aneurysm rupture is high enough to justify the risk of surgery. The rate of rupture of an aneurysm rises exponentially after it reaches 5.5 cm in size, justifying the need for repair in most patients as aneurysm rupture is associated with a high mortality rate. Approximately half of the patients with a ruptured AAA fail to reach hospital and, of those patients who undergo emergency surgery, there is a 35–40% mortality rate at 30 days.[29]

Open surgical repair carries a significant risk of perioperative morbidity and mortality. The 2014 National Vascular Registry report stated that, over the 5 years between 2009 and 2013, in-hospital mortality for open repairs was 3.6%.[27] The less-invasive EVAR technique has significantly lowered perioperative morbidity and mortality rates[27] but not all patients are anatomically suitable for EVAR and there is still debate regarding the long-term benefits of EVAR. Several trials, including the EVAR,[30] DREAM (Dutch Randomized Endovascular Aneurysm Repair)[31] and OVER (Open Versus Endovascular Repair)[32] trials, have found that the advantage of EVAR over open repair is lost during mid-term follow-up, with survival rates beyond 2 years being similar in both groups.

Given the risks involved with AAA repair, strategies to reduce the need for surgery are needed. Currently, there are no clear recommendations on pharmacological treatment approaches to prevent aneurysm progression or reduce the risk of rupture.[33]

Growth rates of small abdominal aortic aneurysms

The growth rate of AAAs is highly variable both between patients and in the same patient over time. Average growth rates increase as the aneurysm enlarges. The average growth rate for a 3.5-cm aneurysm is estimated at 1.90 mm per year, whereas that for a 4.5-cm aneurysm is 3.52 mm/year. Therefore, given an exponentially increasing aneurysm diameter, it would take an average of 6.2 years for a 3.5-cm aneurysm to grow to 5.5 cm, whereas a 4.5-cm aneurysm would grow to 5.5 cm in 2.3 years.[34] These growth rates highlight the need for very accurate measurements of AAA to be obtained in a trial setting.

In the UKSAT, AAA growth was most strongly associated with diameter at baseline[22] and smoking was associated with an incrementally increased growth rate of 0.4 mm per year. Multivariate analysis of other potential risk factors demonstrated that the presence of peripheral arterial disease (adversely) or diabetes (beneficially) influenced AAA growth.

The risk factor profile for aneurysm growth has been reproduced in other studies, with AAA growth being increased in smokers[8,35] and decreased in patients with diabetes.[36]

Average baseline diameters and growth rates reported in the Western Australia screening study,[37] MASS,[19] Propranolol Aneurysm Trial,[7] UKSAT[22] and Second Manifestation of ARTerial disease study[38] are shown in *Table 1*.

TABLE 1 Average baseline diameters and growth rates from the Western Australia Screening study, MASS, Propranolol Aneurysm Trial, UKSAT and SMART study

Study	Mean baseline AAA diameter (cm)	Mean AAA growth rate (mm per year)
Western Australia screening study[37]	3.4	1.6
MASS[19]	3.5	2.6
Propranolol Aneurysm Trial[7]	3.8	2.4
SMART study[38]	3.9	2.5
UKSAT[22]	4.3	2.6

SMART, Second Manifestation of ARTerial disease.

Rupture rates of small abdominal aortic aneurysms

Aneurysm size is one of the strongest predictors of the risk of rupture, with risk increasing considerably for aneurysm diameters of > 5.5 cm. The UKSAT reported the risk of rupture for AAAs up to 5.5 cm in diameter to be < 1 per 100 person-years in men and 3 per 100 person-years in women.[39]

Similarly, the 5-year overall cumulative rupture rate of incidentally diagnosed AAAs in population-based samples is 25–40% for aneurysms of > 5.0 cm diameter and 1–7% for aneurysms of 4.0–5.0 cm in diameter.[40,41]

Rupture rates have been found to be doubled in current smokers compared with ex-smokers or non-smokers ($p = 0.001$) and to increase with mean arterial pressure (per 10 mmHg) ($p = 0.001$).[42]

Blood pressure and abdominal aortic aneurysms

Raised BP was the leading risk factor contributing to the overall global burden of disease in 2010.[43] The recent decrease in case fatality rates associated with acute cardiovascular events in high-income countries has been associated with a rise in the numbers of patients living with cardiovascular disease and the wider use of preventative drugs in the context of primary and secondary prevention.

An association between hypertension and the incidence of AAA is frequently cited.[12,44] The CALIBER (CArdiovascular research using LInked Bespoke studies and Electronic health Records) study used linked electronic health records to assemble a cohort of > 1 million patients aged ≥ 30 years and initially free from cardiovascular disease, one-fifth of whom received BP-lowering treatments.[36]

Of all cardiovascular diseases, AAA had the strongest association with DBP [hazard ratio (HR) per 10 mmHg 1.45, 95% confidence interval (CI) 1.34 to 1.56] and mean arterial pressure (HR 1.61, 95% CI 1.48 to 1.75) and the weakest association with systolic BP (SBP) (HR 1.08, 95% CI 1.00 to 1.17). Furthermore, it was the only cardiovascular outcome for which the association with higher pulse pressure was reversed (HR 0.91, 95% CI 0.86 to 0.98).[36]

However, mean baseline BP levels reported in several large AAA surveillance studies[7,19,22,37] (*Table 2*) are all above what is currently considered as controlled (< 140/90 mmHg[45]) and the AAA growth rates observed in these studies (see *Table 1*) may at least in part be related to these higher BPs.

Despite the relatively strong association between hypertension and the prevalence of AAA, the association between increased BP and the rate of AAA growth or incidence of rupture is not clear and the evidence supporting increased growth as a result of hypertension is lacking.

TABLE 2 Mean baseline BPs reported in the Western Australia Screening study, MASS, Propranolol Aneurysm Trial and UKSAT

Study	Mean baseline BP (mmHg)
Western Australia screening study[37]	157/91
MASS[19]	155/83
Propranolol Aneurysm Trial[7]	143/81
UKSAT[22]	157/86

Non-pharmacological treatments to reduce the growth and rupture rate of abdominal aortic aneurysms

There is clear observational evidence that smoking increases the likelihood of developing an AAA.[11,12,46] For example, in the large ($n = 114,567$) Aneurysm Detection and Management (ADAM) screening study, a history of ever smoking was associated with an odds ratio of 2.97 (95% CI 2.65 to 3.32) for 3.0- to 3.9-cm AAAs and 5.07 (95% CI 4.13 to 6.21) for ≥ 4-cm AAAs.[46] In addition, a recent prospective population-based study of 92,728 men in Oxfordshire found that men aged 65–74 years who were current smokers had a 3% 10-year risk of acute AAA, highlighting the need for screening campaigns to reach this high-risk group.[47]

Furthermore, several studies[8,15,17] and meta-analyses[48] have found higher growth rates in current smokers than in past smokers.

Consequently, the standard non-pharmacological treatment for AAA is smoking cessation. However, it has been suggested that smoking cessation may lose some of its importance once significant aortic dilatation has occurred.[35]

Pharmacological treatments to reduce the growth and rupture rate of abdominal aortic aneurysms

There remains a significant need to find medical therapies that could reduce the growth and rupture rates of small and medium-sized AAAs.

As well as interest in the development of new AAA-specific treatments, there has also been interest in assessing the impact of treatments already in use for other indications. Early evidence often arises from animal studies but a small number of RCTs in humans have been carried out to assess the efficacy of some of the currently available drugs.

Beta-blockers

Evidence that the use of beta-blockers might reduce the growth of AAAs first arose from animal studies.[49,50] However, a placebo-controlled RCT including 548 patients failed to find an association between beta-blocker use and a significant reduction in AAA expansion.[7] Compliance with the medication was a problem, with 117 of 276 (42%) randomised to propranolol and 73 of 272 (27%) allocated to placebo stopping the drugs because of side effects. Furthermore, the increase in AAA diameter was similar in both the propranolol group and the placebo group (2.2 and 2.6 mm per year, respectively; $p = 0.11$) based on an intention-to-treat (ITT) analysis. Patients receiving propranolol also reported a significantly worse quality of life, leading the authors to conclude that the drug did not affect the growth rate of small AAAs and patients with AAAs do not tolerate propranolol well. Similarly, no protective association was observed for beta-blockers in a large observational study of patients with an AAA.[6]

Statins

The evidence supporting the use of statins for the reduction of growth and rupture rates in AAA is inconsistent. The UK Heart Protection Study (UKHPS) compared simvastatin with placebo for the reduction of cardiovascular events over a mean of 5 years in 20,536 patients with vascular disease or at high risk of vascular disease at baseline.[51] This included 6748 patients with peripheral artery disease. The study reported that the requirement for AAA repair was unaffected (1.2% in both groups). The Tromsø study related statin prescription to the development of AAAs in 4345 subjects who were scanned over 7 years.[44] The use of statins was associated with an increased risk of developing an AAA.

Contrary to the UKHPS[51] and Tromsø study,[44] a systematic review in 2008 found that statin use was associated with reduced growth rates of AAAs.[52] This included two cohort studies that both showed reduced growth rates in patients taking statins.[53,54] Evidence suggesting that statins may be of benefit was also presented in a population-based combined case–control and follow-up study, which found that statin use was associated with a reduced risk of ruptured AAA and lower case fatality following ruptured AAA.[55]

Despite inconsistent evidence, current guidelines recommend statin therapy in patients diagnosed with an AAA because of their high cardiovascular risk.[1]

Doxycycline

Doxycycline was investigated as a treatment for AAA as a result of the theory that chlamydia or related infections might be involved in AAA formation and growth.[56] However, clear evidence for the role of infection in the progression of AAAs is limited with small antibiotic trials showing no difference in expansion rate.[57]

More recent studies have investigated the effects of doxycycline as an inhibitor of matrix metalloproteinases. Matrix metalloproteinases are thought to play a role in the destruction of elastin and collagen in the aortic wall, leading to degeneration, and several matrix metalloproteinases have been detected in AAAs, importantly in greater proportions at the site of rupture.[58–60] Doxycycline has been found to inhibit aneurysm development and progression in numerous animal models.[61–63] A small randomised pilot trial ($n = 32$) in patients with small AAAs found that the AAA expansion rate in the doxycycline group was significantly lower than that in the placebo group during both the 6- to 12-month period and the 12- to 18-month period.[64] However, a recent larger randomised trial ($n = 286$) found that 18 months of doxycycline therapy did not reduce aneurysm growth or influence the need for AAA repair or time to repair.[55] Nevertheless, the results of this trial are being challenged in a new American trial, the Non-Invasive Treatment of Abdominal Aortic Aneurysm Clinical Trial (NTA3CT), using transverse aorta CT measurements of AAA growth (NCT01756833). Trials incorporating other protease inhibitors are also expected in the near future.

The role of the renin–angiotensin system

The renin–angiotensin system (RAS) is a peptidergic hormone system that has been recognised to be highly involved in disturbances of the cardiovascular system. RAS blockade by ACE-Is and ARBs has been found to not only decrease arterial pressure but also prevent or reverse endothelial dysfunction and aspects of the atherosclerotic process, which results in a reduction in cardiovascular mortality and morbidity.[65,66]

In experimental studies both angiotensinogen and angiotensin type 1 receptors have been found to be upregulated by approximately twofold in the walls of AAAs compared with the walls of atherosclerotic aortas, although the expression of angiotensin type 2 receptors was similar.[67] In hypercholesterolaemic mice, angiotensin II infusion induces medial dissection of the aorta proximal to aortic branch points, with subsequent formation of suprarenal aortic aneurysms, which can be prevented with the use of ACE-Is.[68]

Furthermore, in a recent study, perindopril (Coversyl arginine, Servier) inhibited aortic degeneration and AAA formation in the experimental AAA model induced by elastase and calcium chloride.[69]

Angiotensin-converting enzyme inhibition

In line with the animal studies that have suggested a potential role of the RAS system in AAA formation and growth, an observational case–control study on a group of > 15,000 patients with AAAs found that patients who received an ACE-I before admission were 20% less likely to present with a ruptured aneurysm.[6] These results remained after adjustments were made for demographic characteristics, comorbidities, contraindications to ACE-Is, measures of health-care use and aneurysm screening. The group noted that the reduction in risk of aortic rupture was distinct from antihypertensive and other medications, suggesting that the mechanism may not be related to a BP-lowering effect. Calcium channel blockers (CCBs) and beta-blockers, for example, were not associated with any reduction in risk.[6] This large-scale study demonstrated an impressive reduction in AAA rupture but there were several potential confounders in this study, not least the compliance with ACE-Is in smokers.

In addition, a recent cohort study of 21,791 patients with AAA identified from Danish registries suggested that treatment with ACE-Is or ARBs was associated with a decreased risk of all-cause death and death from AAA in patients who had not yet undergone surgery for AAA.[70] However, there was no reduction in the need for surgery for AAA.

When considering growth rate modulation by agents acting on the RAS, the evidence is certainly conflicting. The Chichester small AAA surveillance study suggested an association between ARB prescription and reduced AAA progression.[71] However, in contrast, a report from the UK Small Aneurysm Study group reported a small but significant association between ACE-I prescription and increased AAA expansion.[72] This significant difference remained after adjustment for known confounders such as smoking, diabetes, BP and peripheral atherosclerosis.

In summary, currently there is no clear or consistent evidence that medication designed to inhibit the RAS limits AAA progression or leads to a decrease in the risk of rupture.

Designing the trial

To date we are unaware (based on a recent literature review) of any other completed RCTs designed to examine the efficacy of ACE-I or ARBs in limiting or inhibiting AAA progression. This report describes the AARDVARK (Aortic Aneurysmal Regression of Dilation: Value of ACE-Inhibition on RisK) trial, which was commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme to address this need.

Objectives

Primary

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

Secondary

- To evaluate any 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.

Later, pending the results of this pilot trial, our objective was to work with local and national aneurysm screening programmes to conduct a larger, more definitive RCT to investigate the hypothesis that the use of an ACE-I reduces the rate of AAA-related mortality, rupture or elective surgery.

Chapter 2 Methods

Final study design

This randomised, single-blind, placebo-controlled study took place at 14 investigational sites in England. The trial consisted of three parallel randomised arms, with patients receiving 10 mg of perindopril daily (arginine salt), placebo daily (primary comparison) or 5 mg of amlodipine daily (secondary comparison). The perindopril and amlodipine doses used were estimated to have similar effects on BP reduction[73–75] and hence the secondary comparison was included to assess whether or not any benefits of perindopril were independent of BP reduction.

Trial participants

The following factors were taken into consideration when deciding on the inclusion and exclusion criteria for the trial:

1. *Abdominal aortic aneurysm size*. Patients with an AAA of ≥ 5.5 cm diameter would be considered for surgical intervention as per the current clinical guidelines. Therefore, patients with an AAA of ≤ 5.4 cm diameter were included to minimise the rate of patient withdrawal from the study.
2. *Sex*. Although a lower prevalence of AAAs has been found in women, there is no evidence to suggest that the trial medications would have a different mechanism of action between the sexes. Therefore, both men and women were included.
3. *Age*. Assuming potentially differential benefits of ACE-Is for patients with AAAs related to genetic syndromes, a lower age limit (initially 60 years and then amended to 55 years) was set to more effectively screen out this group.
4. *Ethnicity*. Although a higher prevalence of AAAs has been found in Caucasian men than in black and Asian men, there is no evidence to suggest that the trial medications would have a different mechanism of action between races, specifically on AAA growth. Therefore, patients from all ethnicities were included.
5. *Blood pressure*. Regarding the treatment of hypertension, the 2011 National Institute for Health and Care Excellence (NICE) guidelines[45] state:

    - aim for a target clinic BP of < 140/90 mmHg in people aged < 80 years with treated hypertension
    - aim for a target clinic BP of < 150/90 mmHg in people aged ≥ 80 years with treated hypertension.

However, the Quality and Outcomes Framework target for general practitioners (GPs) is a SBP of < 150 mmHg in people aged < 80 years. It seemed reasonable, therefore, to set an inclusion criterion of a SBP of < 150 mmHg in line with this Quality and Outcomes Framework target. Otherwise, eligible patients who had a SBP of ≥ 150 mmHg could be subsequently recruited into the trial but only after suitable BP medication had been supplied and the SBP was controlled to < 150 mmHg (see *Planned drug interventions*).

1. *Medical history*. Patients with any medical conditions that would interfere with their participation in the trial or who would be at an increased risk of adverse effects by taking the study medications were excluded from the trial.
2. *Concomitant medications*. Patients already receiving an ACE-I, a CCB or an ARB could not participate in the trial. The only exception was patients receiving 5 mg of amlodipine because the maximum dosage of amlodipine is 10 mg, thereby allowing the in-trial allocation to a further 5 mg.

The final inclusion and exclusion criteria are listed in the following sections. Only patients who met these criteria were considered for inclusion in the trial.

Inclusion criteria

- Willing and able to give written informed consent.
- Men or women aged at least 55 years.
- With an AAA of 3.0–5.4 cm in diameter by internal or external measurement according to ultrasonography.
- Systolic BP of < 150 mmHg.

Exclusion criteria

- Patients who are already required to take an ACE-I, an ARB or a CCB (with the exception of 5 mg of amlodipine).
- Those with known renal artery stenosis (> 50%) or with a serum creatinine level of > 180 µmol/l.
- Those unable to give informed consent.
- Those too frail to travel for 3-monthly surveillance visits.
- Any clinically significant medical condition that, in the opinion of the investigator, would interfere with the study results and/or reduce life expectancy to < 2 years.
- Participation in another trial of an investigational product or device within the previous 30 days.
- Known allergy or sensitivity to perindopril or amlodipine.
- Unable or unwilling to comply with the requirements of the study, in the opinion of the investigator.

Recruiting centres

Participants were recruited from 14 centres across England (*Figure 1*). Initially, patients were recruited from five centres:

- Imperial College Healthcare NHS Trust (St Mary's Hospital)
- Imperial College Healthcare NHS Trust (Charing Cross Hospital)
- Guy's and St Thomas' NHS Foundation Trust (St Thomas' Hospital)
- Royal Free London NHS Foundation Trust (Royal Free Hospital)
- University Hospitals Coventry and Warwickshire NHS Trust (University Hospital Coventry).

The original arrangement was for there to be only two sonographers in the study, one to perform all of the scans on patients at the London sites with the same mobile ultrasound scanner and one to perform all of the scans on patients from University Hospital Coventry on the same model of ultrasound scanner located in Coventry. This was principally to reduce intersonographer variability.

However, before the first patient was recruited into the study it was decided that patients in London should be screened and recruited at their local research site but that all visits and measurements from baseline onwards would take place at a central hub, the International Centre for Circulatory Health (ICCH), Imperial College London. The advantages of this were that:

1. Patients would have complete flexibility in the days/times of their study visits.
2. In the case of cancellations or missed appointments, patients could be rebooked without restriction, making it less likely for them to fall out of their protocol-defined visit window.
3. Experts in hypertension and antihypertensive medications and their side effects are based on site at ICCH and were available to see at short notice patients who had experienced any AEs.
4. The issue of being able to identify available clinic space to conduct the patient visits at each of the research sites was overcome.
5. In the case that the sonographer was unable to conduct patient visits (because of sickness, annual leave, etc.), the back-up sonographer (who was based at ICCH) was available to conduct visits at short notice with minimal disruption to her other duties.

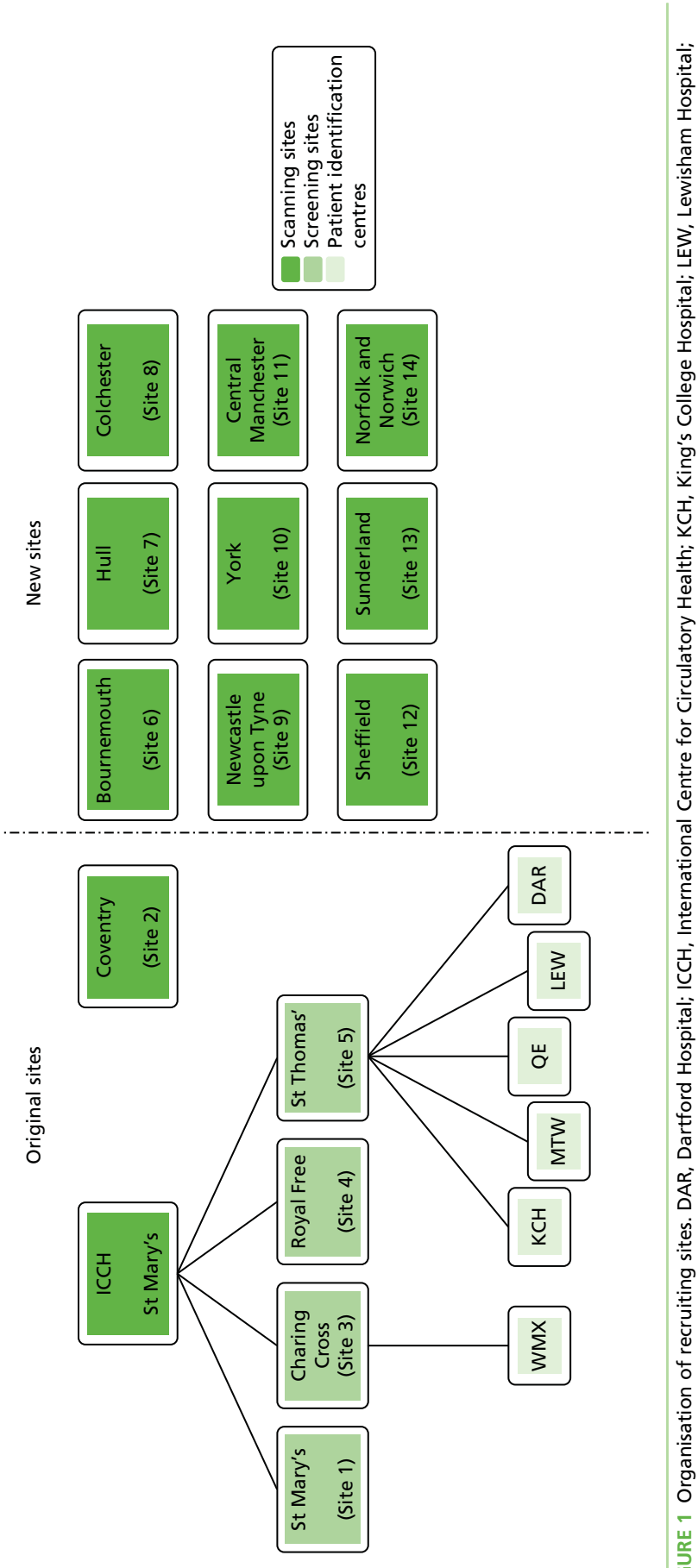


FIGURE 1 Organisation of recruiting sites. DAR, Dartford Hospital; ICCH, International Centre for Circulatory Health; KCH, King's College Hospital; LEW, Lewisham Hospital; MTW, Maidstone and Tunbridge Wells; QE, Queen Elizabeth Hospital, Woolwich; WMX, West Middlesex University Hospital.

Nine further sites were later added to enhance recruitment:

1. Hull and East Yorkshire Hospitals NHS Trust (Hull Royal Infirmary)
2. Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust (Royal Bournemouth Hospital)
3. Colchester Hospital University NHS Foundation Trust (Colchester General Hospital)
4. Newcastle upon Tyne Hospitals NHS Foundation Trust (Freeman Hospital)
5. City Hospitals Sunderland NHS Foundation Trust (Sunderland Royal Hospital)
6. York Teaching Hospitals NHS Foundation Trust (York Hospital)
7. Norfolk and Norwich University Hospitals NHS Foundation Trust (Norfolk and Norwich University Hospital)
8. Central Manchester University Hospitals NHS Foundation Trust (Manchester Royal Infirmary)
9. Sheffield Teaching Hospitals NHS Foundation Trust (Northern General Hospital).

Patient identification centres

Several patient identification centres (PICs) were also added to the study to further enhance recruitment (see *Figure 1*). The PICs identified potential participants for the trial at their sites and referred them to the associated research site for recruitment into the trial. The following PICs were approved for the study:

- West Middlesex University Hospital NHS Trust (West Middlesex University Hospital)
- King's College Hospital NHS Foundation Trust (King's College Hospital)
- Maidstone and Tunbridge Wells NHS Trust (Tunbridge Wells Hospital)
- South London Healthcare NHS Trust (Queen Elizabeth Hospital, Woolwich)
- Lewisham and Greenwich NHS Trust (Lewisham Hospital)
- Dartford and Gravesham NHS Trust (Dartford Hospital).

Recruitment

The clinical registries and the NAAASP databases (when relevant) at the study sites were used to identify patients with an AAA. Permission to recruit NAAASP patients was obtained from the NAAASP research committee. All patients were then prescreened against the inclusion and exclusion criteria. Sites were asked to capture the patient initials for each identified patient and to record the reasons for ineligibility or for non-participation to help inform study progress. These patients were entered onto the Consolidated Standards of Reporting Trials (CONSORT) flow chart. Eligible patients were then subsequently invited to consider entry into the trial.

It was the investigators' responsibility to obtain written informed consent from patients after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study, and before any study procedures commenced. Potential participants were given a copy of the patient information sheet (PIS) and informed consent form (ICF) (see *Appendix 1*). The original copy of the signed and dated ICF was retained by the site.

Patients were given at least 24 hours to read the PIS and consider their participation.

Study correspondence for health professionals

Throughout the study, steps were taken to ensure that the relevant clinical personnel were kept updated on patients' involvement and progress in the trial. The following documents were created, approved by the ethics committee and utilised in the study:

1. *General practitioner letter A*. The purpose of this letter was to inform the patient's GP about his or her involvement in the study, including a brief description of the trial and its requirements, with contact information for the trial administration and clinical staff.

2. *General practitioner letter B*. The purpose of this letter was to inform the patient's GP of the following clinical issues that might require their attention (the relevant statement could be ticked):

    i. the patient's SBP in clinic was found to be > 150 mmHg and the patient has been commenced/or may require commencement on 1.5 mg of slow-release indapamide to potentially be suitable for the study (see *Planned drug interventions*)
    ii. the patient was not found to be taking statin medication and he or she may wish to perform a lipid profile if not already carried out and consider initiating statin therapy
    iii. the creatinine level was found to be > 180 µmol/l.

3. *General practitioner letter C*. The purpose of this letter was to inform the patient's GP that, pending BP assessment, the patient might need an alternative antihypertensive medication to maintain normotension. The letter referred to the 2011 NICE guidelines[45] and invited the GP to contact the chief investigator for advice if required.
4. *End-of-study letter*. This was sent to the patient (with a copy sent to the GP and the relevant referring consultant, if applicable) to say thank you for participating in the study and to inform the patient of the medication that he or she was receiving during the trial.

In addition, for patients who had their follow-up visits at ICCH (St Mary's Hospital), a study results letter was sent to their referring consultant after each visit.

Study documents for patients

All patients were provided with an appointment diary at the start of the study as a method of reducing the number of those missing or forgetting their appointments.

The appointment diary recorded the times and dates of the visits, and space was also available for patients to record any side effects experienced between visits and to record any changes to their concomitant medication or study medication.

Patients were provided with an emergency contact card at the start of the study and were asked to keep this on them at all times. The contact card gave some brief information about the study, including the study name and a list of the potential medications that patients might be receiving as part of the trial. It also provided a 24-hour telephone number for the local site pharmacy who held the unblinding information.

Planned drug interventions

The primary comparison was the effect on AAA growth of the ACE-I compared with placebo; one-third of randomised patients received 10 mg of perindopril arginine daily and one-third received placebo daily. To evaluate the BP-independent effects of the ACE-I, one-third of patients were randomised to a CCB (5 mg of amlodipine daily). It was estimated that, at these doses and in this population, the two drugs would produce similar average BP-lowering effects of approximately 6/4 mmHg. This protocol also allowed both drugs to be compared with placebo to evaluate any BP-lowering impact on AAA growth.

If the SBP of potential trial recruits was > 150 mmHg at screening, sites were asked to arrange for these patients to receive 1.5 mg of slow-release indapamide daily (either prescribed locally or through their GP) or, if this was not appropriate, 5 mg of amlodipine for a 6-week period. Such patients then had their BP measurements repeated after 6 weeks and if their SBP had fallen to < 150 mmHg they were eligible to proceed to randomisation.

The most common side effect of ACE-Is is cough, which affects about 15% of those treated.[76] However, exclusion of those with a pretrial history of ACE-I intolerance was enforced to reduce the incidence of this problem. During the trial, this side effect was monitored, particularly as we anticipated (based on past research) that the majority of patients in the trial would be smokers or ex-smokers who tend to tolerate ACE-Is less well. When in-trial cough was persistent and intolerable, patients stopped medication for 2 weeks and if the cough resolved they were changed to the ARB losartan (100 mg per day). If the cough continued (and hence was deemed to be unrelated to the trial medication), perindopril was restarted.

For all patients recruited into the trial who were not currently receiving a statin, sites were advised to request that the their GP prescribe a drug in this class as per current guidelines.

Visit schedule

The study visit schedule for the AARDVARK trial is shown in *Table 3*.

Each patient had a maximum of 10 planned study visits. The visit schedule and interventions were as follows:

1. *screening* – informed consent, collection of demographic information, past medical history and current medical therapies, review of most recent AAA ultrasound measurement, BP, blood for measurement of creatinine and electrolytes
2. *baseline* – review of informed consent, review of demographic information, review and checking of past medical history, review and checking of current medical therapies, ultrasound of AAA as per study protocol, BP readings in triplicate, review of screening blood test results, collection of urine and blood for the biomarker study (in a subset of patients), confirmation of patient eligibility, randomisation and dispensing of study medication
3. *3 months* – review and check medical history, review and check current medical therapies, collect details of any AEs, ultrasound of AAA as per study protocol, BP readings in triplicate, collection of blood for measurement of creatinine and electrolytes, dispensing of study medication and pill count
4. *6 months* – review and check medical history, review and check current medical therapies, collect details of any AEs, ultrasound of AAA as per study protocol, BP readings in triplicate, dispensing of study medication and pill count
5. *9 months* – review and check medical history, review and check current medical therapies, collect details of any AEs, ultrasound of AAA as per study protocol, BP readings in triplicate, dispensing of study medication and pill count
6. *12 months* – review and check medical history, review and check current medical therapies, collect details of any AEs, ultrasound of AAA as per study protocol, BP readings in triplicate, collection of blood for measurement of creatinine and electrolytes, dispensing of study medication and pill count
7. *15 months* – review and check medical history, review and check current medical therapies, collect details of any AEs, ultrasound of AAA as per study protocol, BP readings in triplicate, dispensing of study medication and pill count
8. *18 months* – review and check medical history, review and check current medical therapies, collect details of any AEs, ultrasound of AAA as per study protocol, BP readings in triplicate, dispensing of study medication and pill count
9. *21 months* – review and check medical history, review and check current medical therapies, collect details of any AEs, ultrasound of AAA as per study protocol, BP readings in triplicate, dispensing of study medication and pill count
10. *24 months* – review and check medical history, review and check current medical therapies, ultrasound of AAA as per study protocol, BP readings in triplicate, collection of urine and blood for biomarker study (in a subset of patients), collection of European Quality of Life-5 Dimensions (EQ-5D) questionnaire, health resource use questionnaire and pill count.

TABLE 3 Visit schedule for the AARDVARK trial

Study procedures	Visit[a]									
	Screening and consent	Randomisation	Treatment							
Months	–3 to 0	0	3[b]	6[c]	9[c]	12[b]	15[d]	18[b]	21[d]	24[b]
Inclusion and exclusion criteria	✗	Check								
Informed consent	✗	Check								
Patient demographics	✗	Review								
Past medical history[e]	✗	Review	✗	✗	✗	✗	✗	✗	✗	✗
Current medical therapies	✗	Review	✗	✗	✗	✗	✗	✗	✗	✗
Ultrasound of AAA	Review	✗	✗	✗	✗	✗	✗	✗	✗	✗
BP[f]	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
AEs			✗	✗	✗	✗	✗	✗	✗	✗
Dispensing of study medication		✗	✗	✗	✗	✗	✗	✗	✗	✗
Pill count			✗	✗	✗	✗	✗	✗	✗	✗
Blood for measurement of creatinine and electrolytes[g]	✗	Review	✗			✗				✗
Blood and urine for biomarker studies[h]		✗				✗				
EQ-5D and health resource use questionnaires						✗				✗

EQ-5D, European Quality of Life-5 Dimensions.
a From baseline onwards visits should have occurred every 3 months ± 7 days when possible.
b These visits (months 3, 12, 18 and 24) had to be undertaken for those who opted for 6-monthly visits.
c For those who opted for 6-monthly visits either the 6- or the 9-month visit had to be undertaken.
d The 15- and 21-month visits could be omitted if the patient was having 6-monthly visits.
e Including smoking/alcohol history and height and weight at baseline.
f Both peripheral and central BP when possible.
g Bloods did not need to be taken at screening if measurement of creatinine and electrolytes had been performed within the last 6 weeks.
h For sites that agreed to participate in the biomarker study.

Blood pressure protocol

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 analyses. Smoking was not permitted in the 30 minutes before BP measurement. Omron 705CP-II machines (OMRON Healthcare, Milton Keynes, UK) were distributed for collection of BP measurements at all except five sites, where BP Plus devices (USCOM, Sydney, NSW, Australia) were used. The purchase of six BP Plus devices was funded by the Foundation for Circulatory Health, Imperial College London. These machines were distributed to the five sites (one machine was kept as a backup) where we expected the highest recruitment levels (St Mary's Hospital, Royal Bournemouth Hospital, Hull Royal Infirmary, Norfolk and Norwich University Hospital and York Hospital). At these sites both peripheral and central BP recordings were collected from the baseline visit onwards for all patients. At ICCH, 20 patients were already participating in the trial prior to the BP Plus machine arriving; these patients had all of their BP measurements taken using an OMRON machine.

Clinical laboratory samples

Angiotensin-converting enzyme inhibitors commonly cause mild increases in serum creatinine as part of the desired result of reducing intraglomerular pressure. This slight rise in serum creatinine is to be expected and is acceptable after starting ACE-Is.[77] Blood tests for measurement of creatinine and electrolytes were therefore carried out at screening and 3, 12 and 24 months (in keeping with best recommended practice for the management of hypertension with ACE-Is) and results were reviewed regularly by the study team and the Data Safety Monitoring Committee (DSMC). If the serum creatinine level rose > 30% above baseline or progressively increased over time, investigators were advised to discontinue the study medication. Lesser increases in serum creatinine were monitored as required more frequent blood tests.

Quality of life

The EQ-5D is a standardised measure of health status developed by the EuroQol group[78] to provide a simple, generic measure of health for clinical and economic appraisal. It is applicable to a wide range of health conditions and treatments, and provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care.

The EQ-5D consists of two pages: a descriptive system and a visual analogue scale. The descriptive system has five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each has three levels of severity (no problems, some problems, extreme problems) in the three-level version and five levels of severity (no problems, slight problems, moderate problems, severe problems and extreme problems) in the five-level version. The three-level version was utilised for the AARDVARK trial (*see Appendix 2*).

The visual analogue scale used to value EQ-5D health states is presented as a 20-cm vertical line calibrated from zero ('worst imaginable health state') to 100 ('best imaginable health state'). It asks respondents to 'mark an ✗ on the scale to indicate how your health is today'.

This questionnaire was administered after 12 and 24 months of follow-up to allow quality of life to be compared among the three randomised groups during treatment as part of the safety analyses.

Health resource use questionnaire

The health resource use questionnaire (see *Appendix 3*) was created specifically for this study to evaluate the associated costs and burden of AAA patients to the NHS if there was a significant effect of ACE-Is on aneurysm growth.

The questionnaire collects information relating to patients' health service use (e.g. visits to their doctor, nurse or GP) for reasons related to their aneurysm, use of social services, the amount of help they receive from their family and carers and service use for reasons not related to their aneurysm.

This questionnaire was administered after 12 and 24 months of follow-up.

Data collection

Data were collected by the study team onto paper case report forms (CRFs) (see *Appendix 4*) and were then entered onto corresponding electronic forms on the InForm™ ITM (Integrated Trial Management) system (Oracle Corporation UK Ltd, Reading, UK). This is a web-based data entry system that builds an Oracle database for each individual clinical trial. Bespoke web-based electronic CRFs with built-in validation rules were designed to identify data entry errors in real time and provide a full audit trail of data entry and changes. All persons entering data were trained prior to start-up and given personal login details with access to forms restricted according to site and role. The electronic CRFs were designed in accordance with the requirements of the trial protocol and complied with regulatory requirements. An automated audit trail was recorded when (and by which user) records were created, updated or deleted. Error reports were generated when data clarification was required and data queries were resolved by research nurses at trial sites.

Trial reporting

The trial team was required to submit annual reports on trial progress, data completion rates and safety and protocol compliance to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC). Reports were also prepared for all trial-oversight committees.

In addition, monthly key figures and 6-monthly reports were prepared for the funding body (the NIHR HTA programme). Monitoring meetings to discuss trial progress were also held with the NIHR at its request.

Trial monitoring

The data collected for the study were monitored on a regular basis to ensure that the integrity of the data and the rights and well-being of participants were protected. Monitoring was completed at a central level and a site level to check for any data errors, deviations or protocol non-compliance.

Validation checks were built into the InForm system, which enabled validation reports to be generated. Any missing values, values out of range or spurious values within the data set were flagged. Queries were sent to sites and followed up for resolution prior to data lock.

All sites were visited prior to opening to recruitment, within 2 weeks of randomising their first patient and then as required to achieve the following:

- Source data verification of 100% of ICFs signed since previous visit to ensure correct completion.
- Drug accountability for 100% of patients.
- Verification that all serious adverse events (SAEs) had been reported correctly.
- Source data verification of at least 50% of subjects randomised (a list of random patient numbers was provided by the statistician in advance) should have been performed by the end of the study for the following:
    - Eligibility – the data on the screening worksheets should have been checked against the inclusion/exclusion checklist and the subjects' medical notes; for scanning sites, this eligibility should also have been entered correctly on InForm.
    - Existence – verification that subjects' name and date of birth on the study worksheets and ICFs match the details in the medical notes.
    - Aneurysm measurements – by comparison of data on InForm against the study worksheets to ensure that the measurements had been entered correctly.
    - EQ-5D – by comparison of data on InForm against the hard copy of the questionnaire completed by the patient.
    - Health resource use questionnaire – by comparison of data on InForm against the hard copy of the questionnaire completed by the patient.
    - AEs and SAEs – by comparison of data on InForm against worksheets and medical notes.
    - Blood pressure – by comparison of data on InForm against the data recorded on the study worksheets. For BP measurements recorded using an OMRON machine with a printer, a printout of the results should have been attached to the worksheets. If a BP Plus machine was used, the measurements entered on InForm should have been checked against the study worksheets and, if available, against the electronic BP Plus database.

Randomisation

Randomisation was performed using a 1 : 1 : 1 ratio stratified by centre and by baseline size of aneurysm stratified into two size ranges: 3.0–4.5 cm and 4.51–5.40 cm. The randomisation code was generated by an independent statistician using randomly permutated blocks of varying sizes using SAS computer software (SAS Institute, Cary, NC, USA).

Any subjects successfully screened for the study and found to be eligible to proceed in the study were then randomised via the InForm system by a trained member of the research team after appropriate consent. Patients were allocated a unique study number for use in all future data collection.

Investigational medicinal products

Perindopril, amlodipine and placebo were produced in accordance with good manufacturing practice[79] and packaged and labelled by the Royal Free Hospital Pharmacy Manufacturing Unit. Overencapsulation of the tablets for this pilot study proved too costly; therefore, the amlodipine, perindopril and placebo tablets were not identical. The three investigational medicinal products (IMPs) were randomly allocated to either bottle A, bottle B or bottle C by a statistician and this information was provided to the Royal Free Manufacturing Unit to allow the IMPs to be deblistered and packed into the corresponding bottles.

Perindopril arginine (10 mg) was provided by Servier at no cost. All products were checked by a qualified person at the Royal Free Manufacturing Unit prior to release.

The Royal Free Manufacturing Unit held a manufacturer's authorisation for IMPs (called the Manufacturing and Importation Authorisation at the time of this study). Blinded treatment kits were labelled as per European Commission *Good Manufacturing Practice Guidelines*, Annex 13[79] to enable the treatment to be identified and the batch source of the materials traced.

The IMPs were supplied to the participating sites on a demand basis with minimal wastage of materials. Bottle accountability logs were maintained by all parties to allow full reconciliation of IMPs, including assignment to patients.

Although the study was classed as single blind because the tablets were not identical, the following measures were taken to avoid site staff becoming aware of treatment allocation:

- At no point during the study were the site staff informed of the contents of bottles A, B and C.
- Bottles A, B and C were the same colour and opaque so that the tablets could not be seen by participating staff.
- Sites were advised that returned tablets should be counted only by the pharmacy staff. This was to avoid any members of the research team identifying any of the tablets by their appearance.

Consequently, for all practical purposes the trial might reasonably be considered double blind.

Slow-release indapamide (1.5 mg) or amlodipine (5 mg) for use in the treatment of BP in those with a SBP > 150 mmHg following the initial screening visit was supplied by the site pharmacy or patients' GPs in blister packs (not blinded). Losartan (100 mg) (an ARB) for use in patients who developed a cough during the trial was supplied by the site pharmacy or patients' GP in blister packs (not blinded).

Study drug administration and compliance

Either a 3- or a 6-month supply of study drug was dispensed at each visit (depending on the timing of the next visit). For the initial 2 weeks following randomisation, patients were asked to take half doses of the IMP dispensed (i.e. 5 mg of perindopril, 2.5 mg of amlodipine and half of the placebo tablet). This is in line with standard clinical practice for the initiation of perindopril and hence was applied to all three randomised groups. All patients were provided with pill cutters at their randomisation visit for this purpose. After 2 weeks they were instructed to take the full dose. Patients were instructed to take their tablets at the same time each morning.

Patient compliance with the trial IMPs and potential side effects of drug treatment were monitored closely. When an in-trial cough was persistent and intolerable, patients stopped medication for 2 weeks and if the cough resolved they were changed to losartan (100 mg per day). If the cough continued (and hence was deemed to be unrelated to the trial medication), the study treatment was restarted. All patients who were switched to an ARB continued in the trial and were followed up on an ITT basis.

To encourage continued involvement in the trial, retention techniques (follow-up telephone calls, study keyrings and Christmas cards) were used.

Compliance with study medication was evaluated using pill counts. Compliance (expressed as a percentage) was calculated as the ratio of tablets taken (based on pill counts of tablets returned) divided by the number of tablets that should have been consumed based on the dates that they were dispensed and returned.

Unblinding procedures

In the event of a medical emergency it may have been considered important for a clinician to be aware of which treatment a patient had been using. It may have therefore been necessary for the trial code to be broken and the treatment allocation to be revealed.

All sites were advised to provide a number on the patients' emergency contact card to call for the pharmacist or pharmacist-on-call (out of hours).

It was planned that all unblinding requests be discussed with the chief investigator of the trial, principal investigator (PI) of the site or delegate during working hours.

The pharmacy department held an out-of-hours contact number for the PI (or delegate) so that authorisation to unblind could be given. If the PI or delegate could not be contacted out of hours, the pharmacists were permitted to break the code.

The pharmacists were advised to record the name, post, address and contact number of the person requesting the unblinding, as well as the patient's identification number, name and reason for unblinding.

Adverse event management

The following AEs were collected as part of the study:

- SAEs
- a single diagnosis or symptom that led to discontinuation of the trial drug
- AEs thought to be secondary to trial medication.

For each AE the following was recorded:

- start and end date and severity
- the likely causal relationship between the IMP and the AE in the opinion of the PI or delegate was indicated as possible, probable or definite.

In addition, sites were requested to report any other AEs that impacted on patients' participation in the trial or that they felt should be reviewed by the medical monitors. AEs were followed up according to local practice until they had stabilised or resolved.

Serious adverse events were defined as any untoward medical occurrence or effect that:

- resulted in death
- was life-threatening, that is, an event in which the subject was at risk of death at the time of the event; it did not refer to an event that hypothetically might have caused death if it were more severe
- required hospitalisation or prolongation of an existing hospitalisation
- resulted in persistent or significant disability or incapacity
- resulted in a congenital abnormality or birth defect.

Medical judgement was exercised in deciding whether or not an AE/adverse reaction was serious in other situations. Important AEs/adverse reactions that were not immediately life-threatening or that did not result in death or hospitalisation but which may have jeopardised the health of a subject or may have required intervention to prevent one of the other outcomes listed in the definition above were also considered serious.

Any planned/elective hospitalisations that were scheduled prior to signing the informed consent but which took place during participation in the study, as well as elective AAA repair, did not require reporting as SAEs.

Reporting of protocol violations and deviations

Sites were requested to report all deviations from the study protocol. The site research staff were responsible for ensuring that procedures were undertaken and treatment given in accordance with the protocol. Any suspected protocol violation or deviation was reported on a protocol deviation form and also recorded on the InForm system. The AARDVARK management team was responsible for reviewing all protocol deviations and informing the sponsor as appropriate. Participants continued to participate in the trial except if they had been randomised in error or if they requested to be totally withdrawn from the study. Fully consented patients enrolled on the trial were followed up and analysed as per ITT analysis.

Subject confidentiality

All study staff were responsible for ensuring that participant confidentiality was maintained at all times. On the study worksheets or any other documents submitted to the sponsor, subjects were identified by a subject ID number and initials only.

The chief investigator and PIs were permitted direct access to subjects' records and source documents only for the purposes of monitoring, auditing or inspection by the sponsor, authorised representatives of the sponsor, regulatory authorities and REC.

Retention of trial documents

This trial was coordinated by the Imperial Clinical Trials Unit (ICTU), which has well-established protocols for the protection of data and facilities for the retention of documents in place. Data will be stored for a minimum of 10 years (or according to changes in regulatory requirements) following completion of this trial. Data generated by this work will be processed in accordance with the Data Protection Act 1998.[80] The ICTU adheres to the Imperial College Code of Practice, drawn up in association with the College's data protection policy, relating to the collection, holding and disclosure of data relating to individuals. The principal applicant and co-applicants act as custodians of the data and are responsible for its security. The chief investigator or delegate will ensure the continued storage of the documents, even if they leave the clinic/practice or retire before the end of the required storage period. Delegation will be documented in writing. The PI at each site is responsible for the archiving of all of the essential trial documents, including the Investigator Site File, in accordance with regulatory requirements.

The chief investigator and PIs were expected to retain a comprehensive and centralised filing system of all study-related documentation that was suitable for inspection by the sponsor and representatives of regulatory authorities.

Primary efficacy variables

The primary outcome measure was the growth of AAA external diameter (measured in the longitudinal plane) as per the results of the intra-/inter-variability studies (see *Chapter 3*).

In the absence of any convincing evidence regarding the best method of measuring AAAs, it was decided to inspect the within-trial assessments of measurement repeatability and base the primary outcome on the modality (internal or external) with the greatest within-trial repeatability for the AP diameter in the longitudinal plane.

Secondary efficacy variables

Secondary outcome measures included:

- time taken for the aneurysm to reach the threshold for intervention (diameter of 5.5 cm)
- aneurysm rupture
- aneurysm repair/referral for repair
- repeatability of internal and external aneurysm diameters
- quality of life (EQ-5D) and a health resource use questionnaire (12 and 24 months)
- intolerance of ACE-Is
- drug compliance
- reduction in BP.

Safety variables

Safety was assessed during the trial by:

- assessment of AEs and SAEs
- monitoring changes in serum creatinine levels.

Statistical methods

Sample size

Based on the inclusion of 225 patients with a baseline AAA diameter of ≤ 5.4 cm and an estimated growth rate (based on UKSAT) of 2.6 mm per year,[22] the trial was powered to 90% at the 5% level to detect a 38% reduction in growth rate associated with the ACE-I compared with placebo. 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-Is rather than other antihypertensive drugs, 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 10% attrition (see *Attrition*).

The placebo-corrected AAA growth rate in the amlodipine group could be used for evaluation of the extent to which any ACE-I effect on AAA growth was attributable to BP reduction. The events of aneurysm repair, aneurysm rupture and death were to be documented and patients censored at these time points or in the absence of these events at the end of the study.

Attrition

Over a 2-year follow-up period, a total attrition rate of 10% was included in the power calculations for the trial. Participants were included in the attrition rate if data from fewer than two study visits were available for analysis and hence they could not contribute data to the measurement of AAA growth rate.

Outcome measures

The primary outcome measure was growth rate of AAA diameter measured using outer-to-outer (OTO) measurements in the longitudinal plane, estimated using multilevel modelling. Secondary outcome measures included AAA rupture, AAA repair/or referral for repair, time taken for the AAA diameter to reach the threshold for intervention (5.5 cm), 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.

Baseline demographics

Baseline demographic variables (including age, sex, ethnicity, smoking, alcohol, height and weight) and other relevant clinical baseline characteristics (including other coexisting medical conditions, use of statins, pulse pressure, BP, AAA diameter and serum creatinine level) are summarised for each treatment group.

Summaries of continuous variables are presented as means and standard deviations (SDs) if normally distributed and as medians and interquartile ranges for skewed data, whereas categorical variables are presented as frequencies and percentages as planned a priori in the statistical analysis plan.

Primary efficacy analysis

The AAA diameter growth from baseline to month 24 was analysed using linear mixed models (multilevel modelling) in which repeated measurements were nested within subjects. The growth rate was estimated from the individual specific trajectories of AAA diameter over time and the multilevel model has the advantage of using all of the available measurements and of taking into account both between- and within-individual variability over time. The model, described in detail below, gives an estimate of the average growth rate and the difference in growth rate between treatment groups. To check for non-linearity in AAA diameter growth with time, quadratic and cubic models were also fitted. We fitted the following random-intercept model (under the standard assumptions):

$$y_{ij} = \beta_1 + \beta_2 time_{ij} + \varsigma_{1j} + \varepsilon_{ij}, \quad (1)$$

where y_{ij} is the diameter for each subject j at occasion i, $time_{ij}$ is the corresponding time point, the parameters β_1 and β_2 are the fixed effect, with β_1 representing the mean diameter at baseline and β_2 the mean difference in diameter for a unit increase in time, ς_{1j} is the random intercept, that is, the deviation of the individual-specific intercept from the population intercept and ϵ_{ij} is the residual error. Although 3- or 6-monthly measurements were used to fit the model, the results are presented with 1 year as the unit of time (as annual growth rates are most commonly reported in the literature).

We then specified a random-coefficient model adding a random slope ς_{2j} of time to allow patients to differ in their rate of diameter growth:

$$y_{ij} = \beta_1 + \beta_2 time_{ij} + \varsigma_{1j} + \varsigma_{2j} time_{ij} + \varepsilon_{ij}, \quad (2)$$

where ς_{2j} represents the deviation of the individual-specific slope from the population slope.

The model assumption is that the random intercept and slope components had a joint normal distribution, with a zero mean, a constant SD across individual-specific intercepts, a constant SD across individual-specific slopes and a correlation between the random intercepts and random slopes. The residual error was assumed to be normally distributed with a zero mean and constant SD.

To investigate the difference in growth rate between treatment groups we added two dummy variables for the groups and their interaction with time to the fixed part. The primary comparison was perindopril compared with placebo (B vs. A):

$$y_{ij} = \beta_1 + \beta_2 time_{ij} + \beta_3 groupB_j + \beta_4 groupC_j + \beta_5 time_{ij} \times groupB_j + \beta_6 time_{ij} \times groupC_j + \varsigma_{1j} + \varsigma_{2j} time_{ij} + \varepsilon_{ij}, \quad (3)$$

where β_1 and β_2 are the mean intercept and slope for group A, β_3 is the parameter representing the difference in estimated mean diameter at baseline in group B compared with group A and β_5 is the parameter representing the difference in the estimated change in diameter over time for group B compared with group A (same interpretation for β_4 and β_6 for group C compared with group A). A further assumption of this model was that the variation between individual intercepts and slopes and the variation of the residual errors did not differ between groups.

We also checked for a potential site effect adding the site in the model as a random effect. In the sensitivity analysis we examined the site effect as a fixed term.

Secondary efficacy analysis

All secondary end points were summarised in the form of frequency distributions and descriptive statistics at each visit. Differences within groups were tested using paired *t*-tests and differences at different time points between groups were analysed using linear regression adjusted for baseline. Log-transformation was used for non-normally distributed variables.

The survival secondary end point (time taken to reach 5.5 cm or referred to surgery) was analysed using Kaplan–Meier plots for descriptive analysis and the log-rank test was used to assess differences between treatments.

The repeatability of measurement of internal and external aneurysm diameters was analysed using Bland–Altman methodology. Using repeated measurements taken on the same patient on the same day by different sonographers the repeatability coefficient for each sonographer was reported for intrasonographer variability and the 95% limits of agreement for each sonographer compared with the most experienced vascular scientist were reported for intersonographer variability.

General methodology

Histograms and box plots were used to assess the distributional assumptions and check for possible outliers.

All treatment evaluations were performed under the ITT principle unless otherwise specified. All statistical tests were two-tailed at the 5% significance level.

All of the available AAA diameter measurements were included in the analysis (also from patients who underwent AAA repair, who were withdrawn or who were lost to follow-up). An advantage of using multilevel modelling for the analysis of repeated measurements is that all available information can be used and it gives robust estimation with incomplete data under the assumption of 'missing at random'. Therefore, no extra missing data imputation was performed.

Nevertheless, before starting the data analysis, the level, pattern and likely causes of the missing data in the baseline variables and outcomes were investigated. Some intermittent missing data were anticipated as patients and sites were given the option of undertaking 6-monthly visits (and we can assume that this intermittent missingness is missing at random).

Interim analysis

A preliminary analysis was undertaken in February 2015 and approval for this analysis was given by the DSMC, Trial Steering Committee (TSC), NIHR HTA programme and Trial Management Group (TMG). The main purpose of this analysis was to undertake a practice run of the final analysis to identify any early potential problems and to give thought to a large-scale trial if warranted.

The results of this preliminary analysis were presented to the study writing committee. The writing committee was also unblinded at this stage to help direct and support the writing of the final report. Subsequent to being unblinded, members of the writing committee had no further involvement in data collection for the trial.

Research governance and management

This IMP trial was conducted in accordance with Medical Research Council (MRC) Guidelines for Good Clinical Practice[81] and the Medicines for Human Use (Clinical Trials) Regulations 2004.[82] Imperial College London acted as the trial sponsor. A clinical trial authorisation was applied for and received from the MHRA. A site agreement between Imperial College London and the participating sites outlined the responsibilities of all parties and was signed prior to commencement of recruitment at the participating sites.

Three committees were established to govern the conduct of the trial: the TSC, the independent DSMC and the TMG. These committees functioned in accordance with ICTU standard operating procedures.

Trial Steering Committee

The TSC consisted of three independent members [two vascular surgeons (one as chairperson) and a patient representative] and two members of the trial team (chief investigator and trial manager).

The responsibilities of the TSC were to approve the main study protocol and any amendments, monitor and supervise the trial with regard to its interim and overall objectives, review relevant information from other sources, consider the recommendations of the DSMC and resolve problems brought by the trial co-ordinating centres. The TSC, therefore, provided overall supervision for the trial on behalf of the HTA programme and Imperial College London (sponsor) to ensure that the trial was conducted to the rigorous standards set out in the MRC Guidelines for Good Clinical Practice.[81] Meetings were held by teleconference at regular intervals determined by need and not less than once a year.

Data Safety Monitoring Committee

The DSMC consisted of an independent statistician (chairperson), a vascular surgeon, an expert in hypertension and the trial statistician. In addition, two members of the trial team (the chief investigator and trial manager) attended the open sessions of the DSMC meetings.

The DSMC was responsible for reviewing the progress of the trial and accruing data and providing advice on the conduct of the trial to the TMG and TSC. The DSMC was required to inform the chairperson of the TMG if, in its view:

- there were concerns about the safety of one or more of the treatment arms
- the results showed a benefit of one treatment arm over another that was so large, and precise, that it was likely to convince a broad range of clinicians to change practice
- it was evident that if the trial continued it would fail to show a clear benefit for any treatment arm
- accrual of patients was so low that it was unlikely that a sufficient number of patients would be recruited to provide meaningful results.

It also had a specific role in reviewing the trial's progress with the aim of:

- monitoring evidence for treatment harm (e.g. toxicity data, SAEs, deaths)
- suggesting additional data analyses, for example of main outcome measures, but only when this was relevant to the trial continuing or stopping early
- deciding whether or not to recommend that the trial continued to recruit participants or if recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups
- monitoring planned sample size assumptions and recommend amendments if appropriate
- monitoring recruitment figures and losses to follow-up
- advising on major protocol modifications suggested by investigators or sponsors such as changing the main end points
- assessing data quality, including completeness
- monitoring compliance with the protocol by participants and investigators
- monitoring the continuing appropriateness of patient information
- assessing the impact and relevance of external evidence.

Trial Management Group

The TMG consisted of the chief investigator, co-applicants, PIs, trial manager, monitors, project administrators, statisticians, research nurses and patient representative. This group was responsible for the day-to-day management of the trial. The group met on a monthly basis during the recruitment period of the trial and on an ad hoc basis during the follow-up and close-out period.

Patient and public involvement

Several patients with small AAAs were consulted to seek their opinions about the design and running of the trial. All of these patients reported that they would feel reassured by the increased surveillance of their AAA. In addition, a close relative of one patient approached emphasised the painful and stressful nature of the surgery that his relative had undergone and how he wished that there had been an alternative to that surgery. Therefore, anything that could be done to slow the growth of the AAA, to prevent or delay the need for distressing major surgery, was seen as positive.

A patient representative was present on the TMG and was involved in the design of the trial as well as review of protocol amendments and changes to the patient literature.

Protocol changes

All changes to the trial protocol and study conduct were reviewed by the sponsor and submitted to the REC and MHRA for approval as appropriate.

A summary of the amendments made prior to participant recruitment, during recruitment and after recruitment are provided in *Tables 4–6*, respectively.

TABLE 4 Amendments made prior to participant recruitment

Amendment number	Documents amendment relates to	Date of approval
1	• The new SPC from Sandoz Ltd • The amendments application form • A copy of the amended EudraCT application form	11 May 2011
2	• Protocol version 3 • Summary of changes from protocol version 2 to version 3 • PIS version 5 • Contact card version 3 • New appointment diary version 1	5 August 2011

EudraCT, European Union Drug Regulating Authorities Clinical Trials; SPC, Summary of Product Characteristics.

TABLE 5 Amendments made during participant recruitment

Amendment number	Documents amendment relates to	Date of approval
3	• Protocol version 4 (clean and tracked) • Summary of changes from protocol version 3 to version 4 • PIS and ICF version 6 • Patient invitation letter version 1 • Trial poster version 1	30 January 2012
4	• Protocol version 5 (clean and tracked) • Summary of changes from protocol version 4 to version 5 • PIS and ICF version 7 (clean and tracked for biomarker and non-biomarker sites) • GP letters A and B version 2	4 May 2012
5	• Protocol version 6 (clean and tracked) • Summary of changes from protocol version 5 to version 6 • PIS and ICF version 8 (clean and tracked for biomarker and non-biomarker sites) • GP letter A version 3 • Patient invitation letter version 2	17 July 2012
6	• Protocol version 7 (clean and tracked) • Summary of changes from protocol version 5 to version 7 • PIS and ICF version 9 (clean and tracked for biomarker and non-biomarker sites) • Patient invitation letter B version 1	4 September 2013

TABLE 6 Amendments made post participant recruitment

Amendment number	Documents amendment relates to	Date of approval
7	• GP letter C • End-of-study letter	14 November 2014

Chapter 3 Ultrasound measurements and quality assurance

Obtaining abdominal aortic aneurysm measurements

Accurate initial and repeat measurements of AAAs are essential to correctly ascertain growth rates in a trial setting and also to direct clinical management. Ultrasonography is a widely used, non-invasive and effective method for screening and obtaining measurements of AAA diameter. Static images are produced by freezing the image obtained using ultrasound and then accurate measurements can be taken using callipers.

Ultrasonography has been found to be accurate when used to assess AAA diameters by trained observers when compared with CT, and 95% of the differences between the two measurements can be expected to be < 3.5 mm.[83] Similar accuracy was obtained for trained screeners in the UKSAT[22] and other aneurysm screening[19] and observation[84] studies.

In a clinical setting, ultrasound studies of AAAs are most often undertaken by vascular scientists and sonographers who have been trained extensively to undertake such studies. However, staff with no or limited previous experience of ultrasonography can be trained rapidly to identify the presence of AAAs reliably.[85–87] This model of training is used extensively in the NAAASP.

The visualisation of the abdominal aorta may be dependent on the sonographer's experience and the extent of the patient's bowel gas and body mass index. However, in a study by Hoffman *et al.*,[88] despite the level of difficulty reported, the accuracy of aortic measurements by the novices was independent of obesity and central adiposity.

Other common difficulties when scanning include 'eccentric' aneurysms and tortuous aortas, as well as the incorrect identification of other structures that appear tubular in cross-section (e.g. the inferior vena cava, the superior mesenteric artery and the gall bladder). The accurate selection of the boundaries of the aorta is also clearly important.[89] It is important that these factors are addressed and that quality improvement strategies are appropriately implemented in trials using ultrasound measurements.

When using ultrasound it is generally accepted that AP abdominal aortic diameters are recorded as standard because of their superior repeatability compared with transverse diameters.[90] However, the most reliable method of measuring AAA diameter remains debatable. The two main methods are measuring the internal diameters [i.e. inner anterior wall to the inner posterior wall (inner to inner or ITI) or intima to intima] or measuring the external diameters [i.e. from the outer anterior to the outer posterior wall (OTO) or adventitia to adventitia] (*Figure 2*). Some studies also use leading edge to leading edge measurements.

Screening technicians employed by NAAASP are trained to correctly identify and take ITI measurements of AAAs by undertaking a 3-month accredited training programme. For trained screening technicians, the ITI method has been found to have better reliability and reproducibility than OTO measurement.[91] Conversely, when comparing the reliability and reproducibility of measurements taken by vascular scientists, it has been suggested that the OTO method is superior, with the ITI method underestimating the aortic size[92] and having greater variability because of difficulty identifying the internal wall because of thrombus[93] (see *Figure 2*), that is, aneurysm growth rates measured using internal diameters have greater noise or scatter than growth rates measured using external diameters.[42]

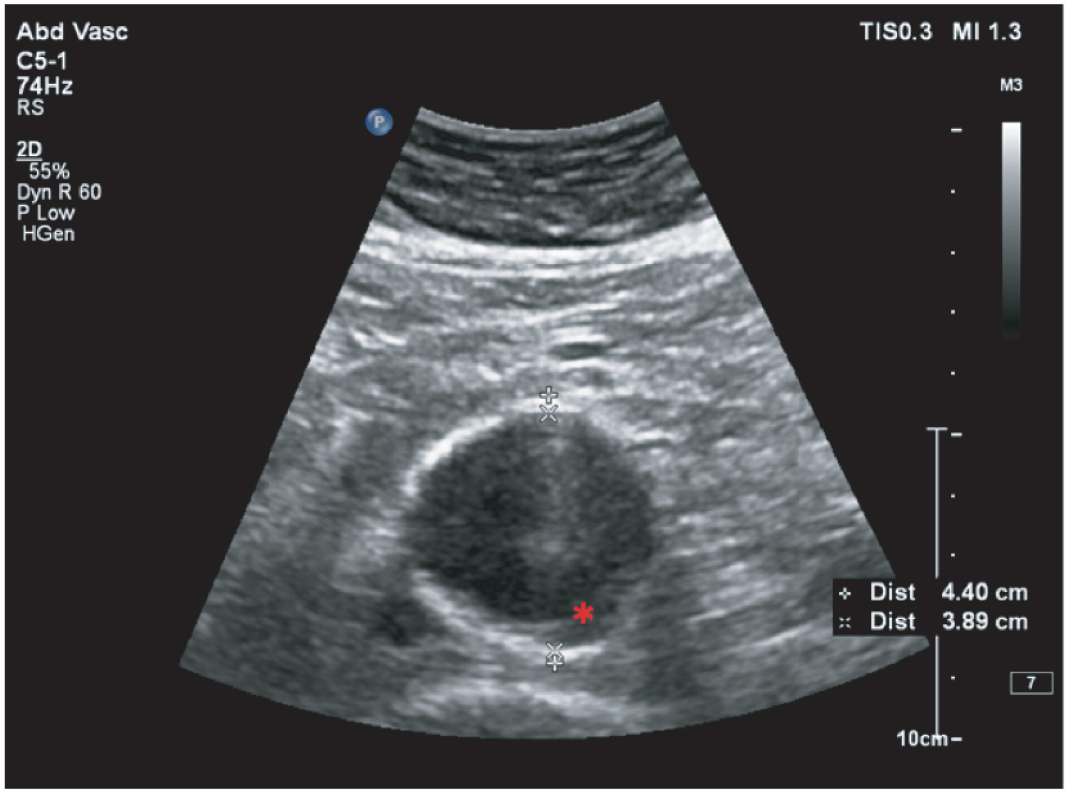


FIGURE 2 An image of an AAA in the transverse plane showing internal and external AP measurements. The crosses (×) indicate the position of the inner anterior and inner posterior wall and the pluses (+) indicate the position of the outer anterior and outer posterior wall. The asterisk indicates the inner border of an area of thrombus on the posterior wall and it is important that the posterior inner wall calliper is not placed on the inner border of the thrombus.

The purpose of the trial quality assurance (QA) process was to:

1. ensure that there was adequate completeness of data collection by all sites
2. ensure the use of a standard protocol in the ultrasound scans carried out across 11 scanning sites by different sonographers on different ultrasound scanning systems
3. ensure the reliability of the results in terms of inter- and intra-observer variability
4. evaluate the reliability of AP AAA measurements taken using internal and external methods in both transverse and longitudinal planes to determine which provided the most repeatable measurements.

Abdominal aortic aneurysm measurement terminology

To ensure accurate comparison with both past and present research it is important to define the terminology used in this report.

Planes

In this study, AP measurements of the AAAs were taken on a transverse plane (referred to as transverse measurements within this report) and on a longitudinal plane (referred to as longitudinal measurements within this report). *Figure 3* shows the transverse and longitudinal body planes.

Direction of the ultrasound probe

Figure 4 shows the direction of the probe required to obtain an AP diameter in a longitudinal plane. An example of an image that would be obtained in this view in shown in *Figure 5*.

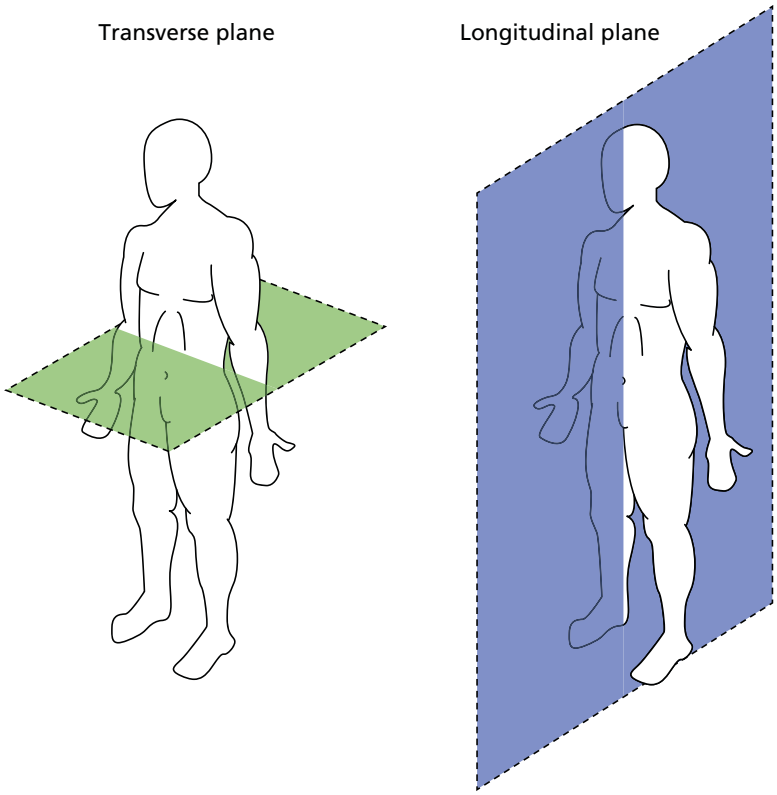


FIGURE 3 Transverse and longitudinal body planes.

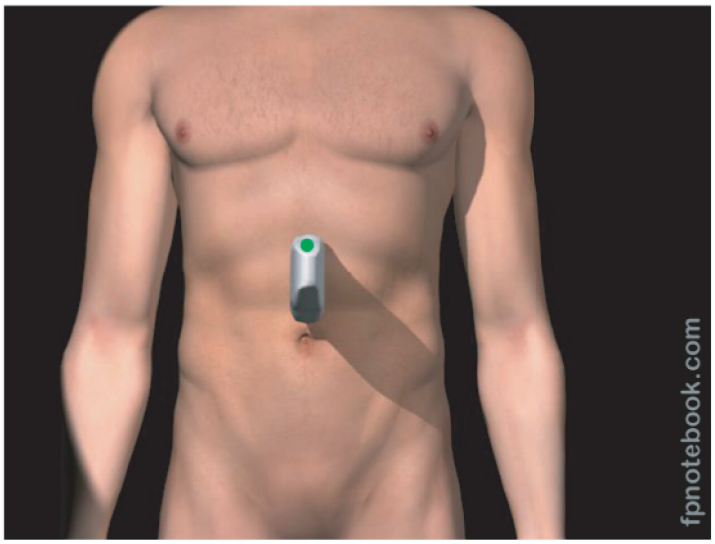


FIGURE 4 Direction of probe required for an image in the longitudinal plane. Reproduced with permission from Fpnotebook.com.

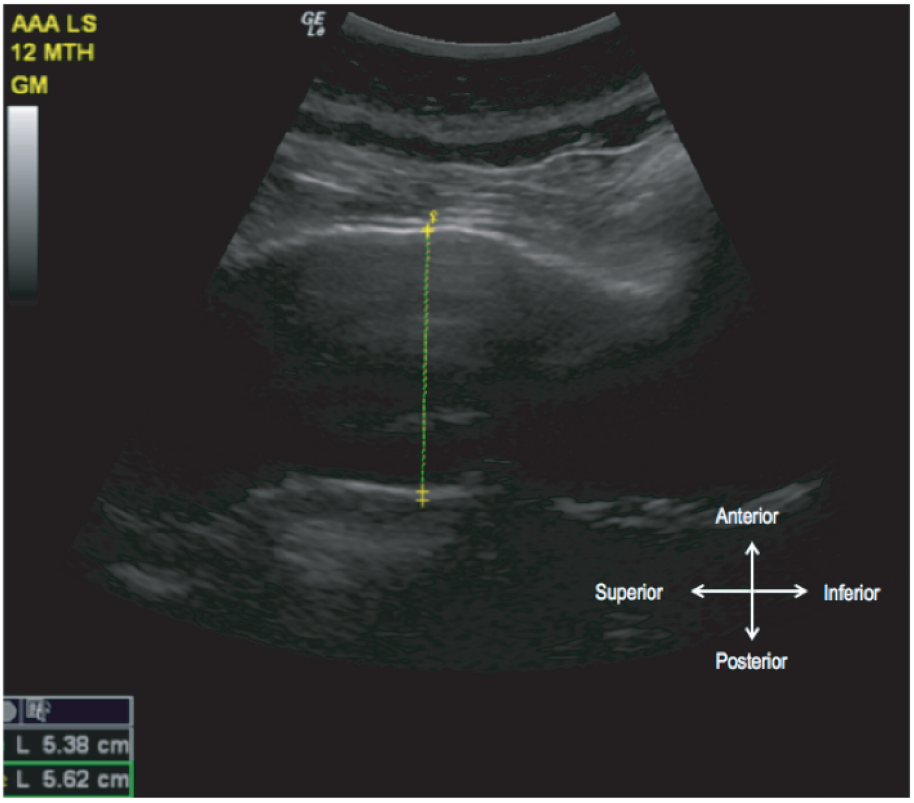


FIGURE 5 Example of an AP diameter taken in the longitudinal plane.

Figure 6 shows the direction of the probe required to obtain an AP diameter in a transverse plane. An example of an image that would be obtained in this view is shown in *Figure 7*.

An example of a lateral wall to lateral wall diameter taken in a transverse plane is shown in *Figure 8*. Lateral wall to lateral wall diameters were not collected in this trial. This is because tortuosity of the aorta is common in aneurysmal disease as the aorta grows in length as well as width and these diameters can be considerably inaccurate.

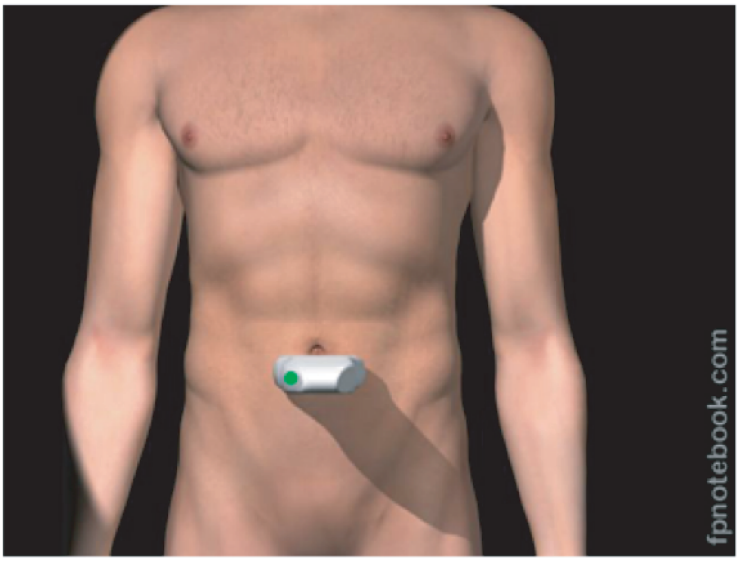


FIGURE 6 Direction of probe required for an image in the transverse plane. Reproduced with permission from Fpnotebook.com.

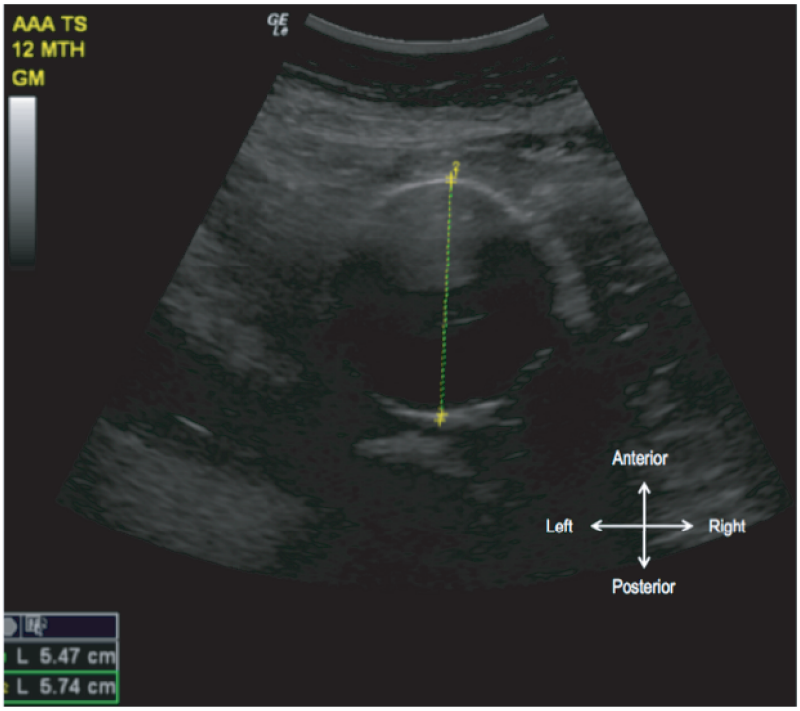


FIGURE 7 Example of an AP diameter taken in the transverse plane.

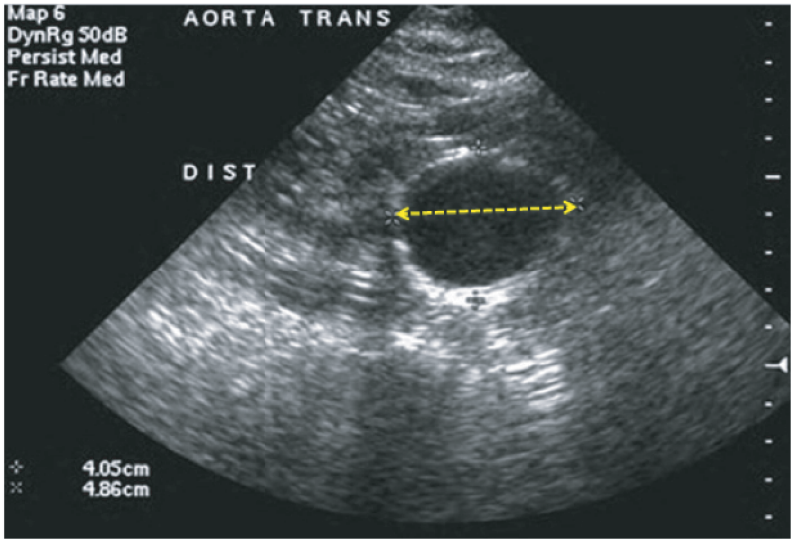


FIGURE 8 Example of an AAA image in the transverse plane with the measurements taken from lateral wall to lateral wall.

Ultrasound scanning protocol

At the time of this study there still remained debate over the best method of obtaining AAA measurements, as highlighted earlier. Therefore, four measurements in total – both maximum AP internal and external measurements in the transverse and longitudinal planes – were recorded on all patients, to enable a reliable comparison and to inform future practice.

The study was initially designed to have just two dedicated scanning staff between five sites (four in London and one in Coventry) to enhance the accuracy and repeatability of measurements. After 6 months it became clear that fewer patients than anticipated were eligible for the trial at these sites and therefore we were required to expand the study to recruit at 14 sites to meet the recruitment target, with scanning taking place at 11 sites (patients from all four London recruiting sites were scanned at ICCH, St Mary's Hospital; see *Figure 1*).

This required more rigorous scanning and quality control protocols to be implemented to ensure maximum accuracy in the measurement of AAAs at all sites. A scanning protocol was provided to all participating sites to ensure the highest possible standard and accuracy in the ultrasound scans carried out across the 11 scanning sites. The final version of the scanning protocol is provided in *Box 1*.

BOX 1 Ultrasound scanning protocol

- At each site it is requested that a single fully trained sonographer, vascular scientist or ultrasound screening technician performs all scans when possible.
- When alternative arrangements for the sonographers are made at some sites (e.g. vacation, illness), sonographers should follow identical protocols and should ensure that there is internal consistency in recorded measurements from the site.
- The same ultrasound system and probes should be used for each subject on each occasion.
- The patient should be brought into the room and allowed to rest on the couch in the semi-recumbent position for a period of 5 minutes for acclimatisation (while details are entered onto the duplex system).
- Once scanning is to be performed, the patient should be laid flat on the examination couch with abdomen exposed from xiphisternum to pubic symphysis.
- The room should be appropriately lit to facilitate accurate scanning in a standard fashion (i.e. similar on all occasions).
- Review previous image to determine the point from which to begin measurement.
- Perform an initial scan, checking for compressibility, pulsation and anterior branches, to enable the aorta to be correctly identified.
- The aorta should then be scanned in both longitudinal and transverse planes from the renal arteries to the bifurcation of the iliac arteries.
- The point of maximum dilatation in both transverse and longitudinal planes should be identified.
- Image optimisation should be achieved using gain/depth etc. control to produce an image with the clearest wall appearance.
- All images must be taken with the highest quality and accuracy.
- Following maximum point identification, the longitudinal image should be frozen on screen.
- Four images in total must be saved.

BOX 1 Ultrasound scanning protocol (*continued*)

Longitudinal measurement

- Measurements are now taken using the calipers from the anterior side of the aorta to the posterior side. The measurements taken should be at 90° to the wall.
- An ITI measurement should be made by placing the calipers on the inside of the aortic wall, taking care not to misidentify plaque or thrombus as in the inner wall.
- This image should be saved after labelling the scan image with LS (for longitudinal view), ITI and the time of the scan within the study (baseline, 3 months, 6 months, etc.) and adding the sonographer's initials.
- An OTO measurement should be made by placing the calipers on the outer walls, taking care not to misidentify the surface of the spine or other structures as the posterior wall.
- This image should be saved after labelling the scan image with LS, OTO and the time of the scan within the study (baseline, 3 months, 6 months, etc.) and adding the sonographer's initials.

Transverse measurements

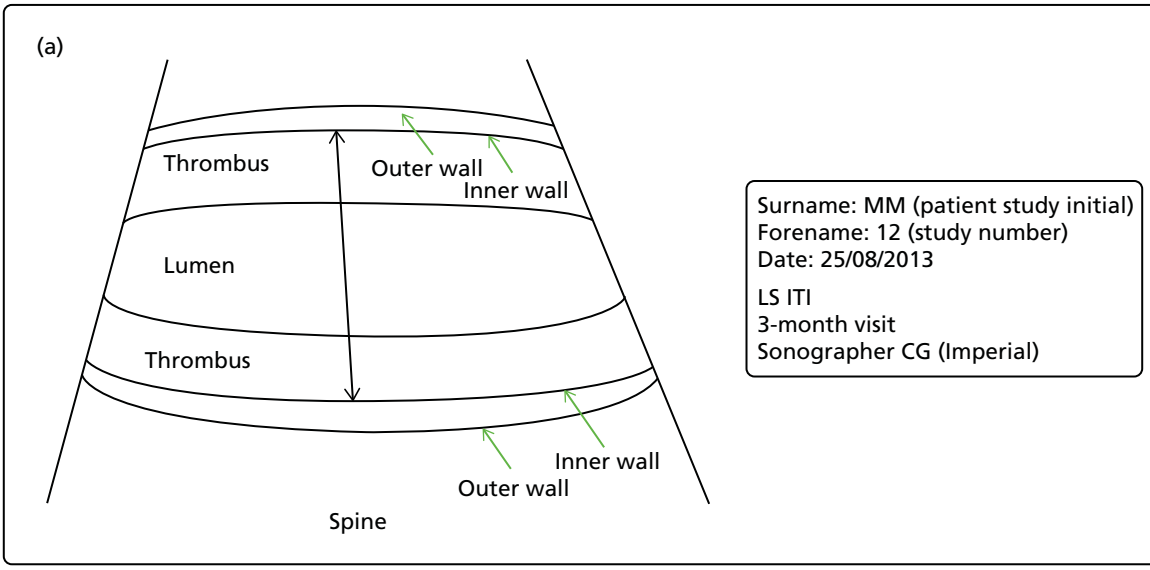
- The ultrasound probe should be pivoted 90° at the same point (of maximum size) on the aorta. This image in the transverse plane should be frozen.
- An ITI measurement should be made by placing the calipers on the inside of the aortic wall, taking care not to misidentify plaque or thrombus as in the inner wall.
- This image should be saved after labelling the scan image with TS (for transverse view), ITI and the time of the scan within the study (baseline, 3 months, 6 months, etc.) and adding the sonographer's initials.
- Check the results that have been obtained. If the ITI and OTO measurements in TS and LS are not similar then the patient should be rescanned and checked – if there is a reason for disagreement such as tortuosity of the vessel, make a comment on the record.
- Problematic measurements: if you are experiencing difficulty defining and measuring the aorta and its aneurysm, please consult a more senior sonographer for assistance and make a note on the 'Relevant comments' section of the scanning log.

Storage of images

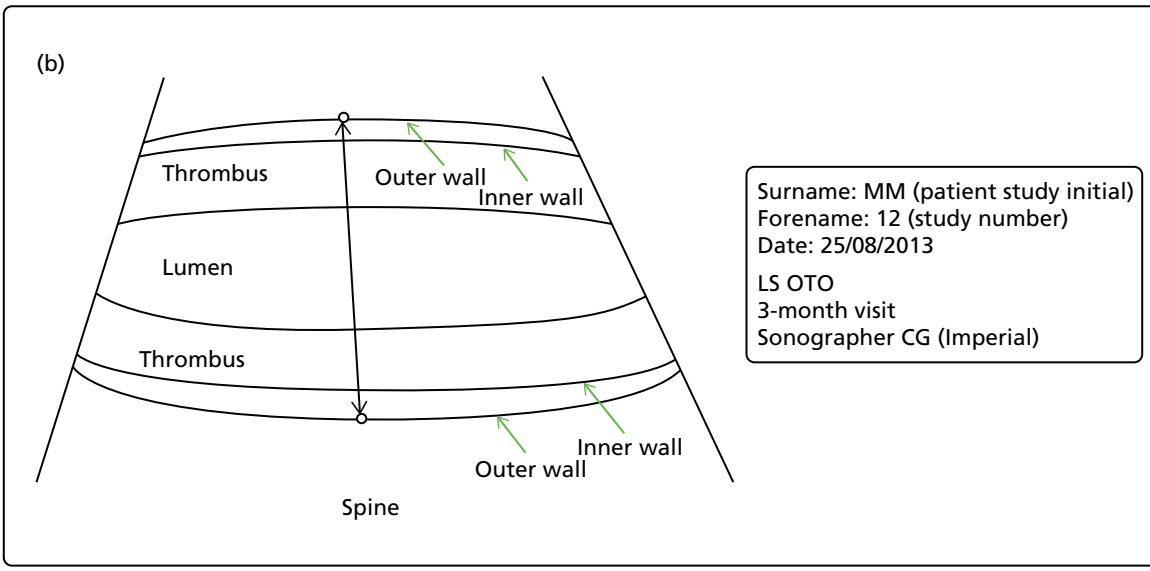
Images, with measurements and labelled as described in the scanning protocol, will be stored on the hard drive of the scanner and subsequently downloaded onto the Picture Archiving and Communication System or other storage devices at the co-ordinating centre. All sites will be required to download all images onto a CD to be sent to the co-ordinating centre for QA purposes.

BOX 1 Ultrasound scanning protocol (*continued*)

Longitudinal anteroposterior inner-to-inner measurements

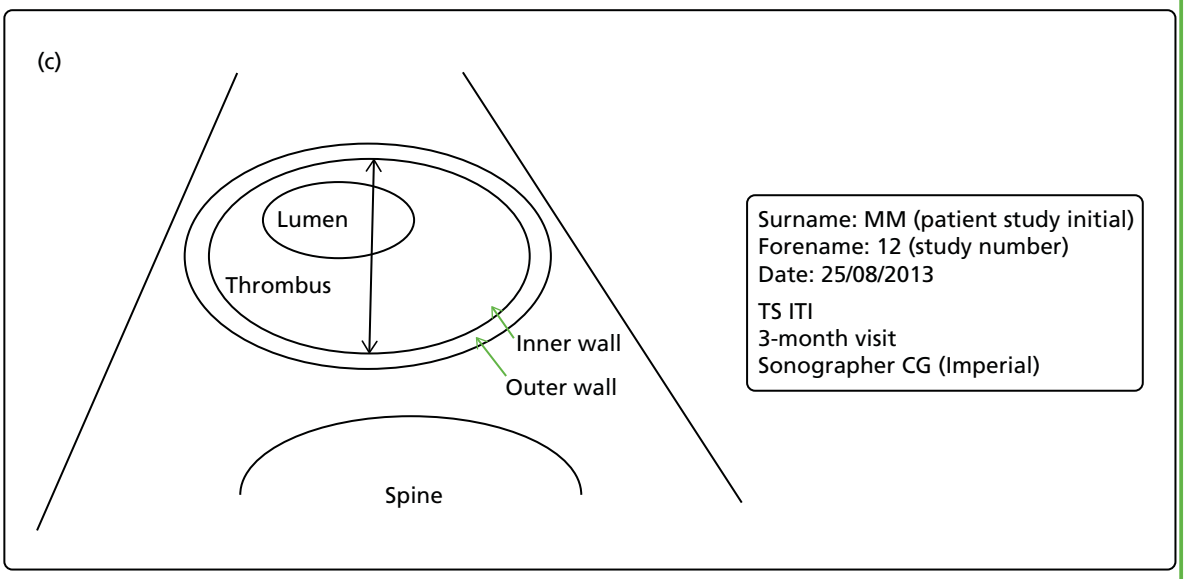


Longitudinal anteroposterior outer-to-outer measurements

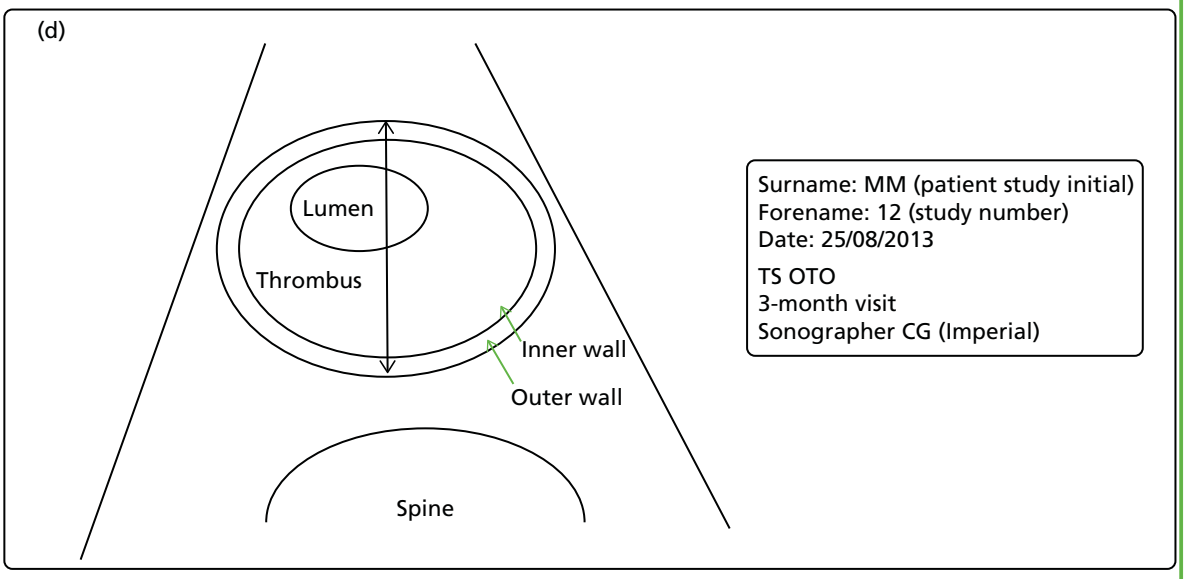


BOX 1 Ultrasound scanning protocol (*continued*)

Transverse anteroposterior inner-to-inner measurements



Transverse anteroposterior outer-to-outer measurements



Performance in data collection

Recording of the four AAA measurements was required for each patient at each visit. A key performance indicator for sites was that of completeness of data recording for all four required measurements. The completeness of data collection at each visit was between 94% and 100%. *Table 7* describes the percentages of patients who attended who had all four required measurements recorded at the end of the study visit.

TABLE 7 Numbers and percentages of patients with required AAA measurements collected at each visit

Measurement	Placebo	Perindopril	Amlodipine	Total
***Randomisation* (n)**	***79***	***73***	***72***	***224***
External diameter longitudinal	79 (100)	71 (97)	71 (99)	221 (99)
Internal diameter longitudinal	78 (99)	71 (97)	68 (94)	217 (97)
External diameter transverse	79 (100)	73 (100)	72 (100)	224 (100)
Internal diameter transverse	78 (99)	71 (97)	69 (96)	218 (97)
***3-month visit* (n)**	***76***	***68***	***67***	***211***
External diameter longitudinal	74 (97)	65 (96)	65 (97)	204 (97)
Internal diameter longitudinal	74 (97)	65 (96)	65 (97)	204 (97)
External diameter transverse	74 (97)	65 (96)	65 (97)	204 (97)
Internal diameter transverse	74 (97)	65 (96)	65 (97)	204 (97)
***6-month visit* (n)**	***69***	***62***	***62***	***193***
External diameter longitudinal	66 (96)	61 (98)	60 (97)	187 (97)
Internal diameter longitudinal	66 (96)	61 (98)	60 (97)	187 (97)
External diameter transverse	67 (97)	61 (98)	60 (97)	188 (97)
Internal diameter transverse	68 (99)	61 (98)	60 (97)	189 (98)
***9-month visit* (n)**	***64***	***57***	***57***	***178***
External diameter longitudinal	63 (98)	56 (98)	54 (95)	173 (97)
Internal diameter longitudinal	63 (98)	56 (98)	54 (95)	173 (97)
External diameter transverse	62 (97)	56 (98)	54 (95)	172 (97)
Internal diameter transverse	62 (97)	56 (98)	54 (95)	172 (97)
***12-month visit* (n)**	***71***	***61***	***54***	***186***
External diameter longitudinal	68 (96)	60 (98)	51 (94)	179 (96)
Internal diameter longitudinal	69 (97)	60 (98)	51 (94)	180 (97)
External diameter transverse	68 (96)	60 (98)	52 (96)	180 (97)
Internal diameter transverse	69 (97)	60 (98)	52 (96)	181 (97)
***15-month visit* (n)**	***60***	***49***	***47***	***156***
External diameter longitudinal	57 (95)	47 (96)	44 (94)	148 (95)
Internal diameter longitudinal	57 (95)	47 (96)	44 (94)	148 (95)
External diameter transverse	57 (95)	47 (96)	44 (94)	148 (95)
Internal diameter transverse	57 (95)	47 (96)	44 (94)	148 (95)

TABLE 7 Numbers and percentages of patients with required AAA measurements collected at each visit (*continued*)

Measurement	Placebo	Perindopril	Amlodipine	Total
***18-month visit* (n)**	***61***	***52***	***49***	***162***
External diameter longitudinal	60 (98)	49 (94)	47 (96)	156 (96)
Internal diameter longitudinal	60 (98)	49 (94)	47 (96)	156 (96)
External diameter transverse	60 (98)	49 (94)	47 (96)	156 (96)
Internal diameter transverse	60 (98)	49 (94)	47 (96)	156 (96)
***21-month visit* (n)**	***54***	***44***	***47***	***145***
External diameter longitudinal	52 (96)	43 (98)	47 (100)	142 (98)
Internal diameter longitudinal	52 (96)	44 (100)	47 (100)	143 (99)
External diameter transverse	52 (96)	43 (98)	47 (100)	142 (98)
Internal diameter transverse	52 (96)	44 (100)	47 (100)	143 (99)
***24-month visit* (n)**	***59***	***53***	***49***	***161***
External diameter longitudinal	56 (95)	52 (98)	47 (96)	155 (96)
Internal diameter longitudinal	56 (95)	52 (98)	48 (98)	156 (97)
External diameter transverse	56 (95)	52 (98)	47 (96)	155 (96)
Internal diameter transverse	56 (95)	52 (98)	48 (98)	156 (97)

Quality assurance events

Inter- and intraobserver QA scanning events were organised to ensure consistency between sonographers, screening technicians and others responsible for aortic measurements and between measurements by the same observers. Specific aims of the QA events were:

1. to ensure the reliability of the results in terms of inter- and intra-observer variability.
2. to evaluate which was the most accurate and repeatable of AP AAA measurements taken using ITI and OTO methods in both transverse and longitudinal planes.

Three QA days were arranged, one each in York, Hull and London. A total of 19 observers scanned patients over the course of the trial (*Table 8*). Of these, 12 (63%) attended the QA days. At least one observer from each of the 11 scanning sites attended one of the QA events. The numbers of observers attending and scanning centre locations are documented in *Table 8*. Six volunteers were scanned on 8 July 2013, five volunteers were scanned on 13 September 2013 and five volunteers were scanned on 8 November 2013.

At each event the following took place:

- review of the scanning requirements as documented in the protocol
- discussion of example problem cases as a teaching prompt
- highlighting of known improvement strategies to reduce variability as needed
- scanning of volunteer patients for inter- and intraobserver variability studies.

Patients with an AAA who were part of the trial were invited to attend the QA days. Each was informed that they were to have their AAA measured on at least two occasions by each sonographer who was able to attend that QA session.

TABLE 8 Attendance at the QA events

Site	QA event date			Number of sonographers from the site	Number of sonographers attending
	8 July 2013	13 September 2013	8 November 2013		
Royal Bournemouth Hospital	Yes			1	1
Norfolk and Norwich University Hospital	Yes			4	1
Colchester General Hospital	Yes			1	1
Northern General Hospital, Sheffield		Yes		2	2
Freeman Hospital, Newcastle		Yes		2	1
University Hospital Coventry		Yes		1	1
Sunderland Royal Hospital			Yes	1	1
York Hospital		Yes		2	1
London sites		Yes		3	1
Manchester Royal Infirmary		Yes	Yes	1	1
Hull Royal Infirmary			Yes	1	1
AARDVARK trial vascular scientist	Yes	Yes	Yes	NA	NA
Total	3	6	3	19	12

NA, not applicable.

The scanning protocol was reviewed by all of the clinicians. Teaching on problem cases and strategies for best practice were presented and the structure for the day outlined in full.

All of the sonographers who had scanned trial patients were observed scanning at least one subject following the scanning protocol until the trial sonographer was convinced that appropriate protocols were being followed and adequate images were being obtained consistently. Each of the sonographers from the sites then scanned each of the AAA patients using the scanning protocol. All sonographers were blinded to the clinical details, size and anatomical configurations of the aneurysms of patients as far as possible. Volunteers were not named but were allocated an identifier for anonymity in an attempt to minimise bias. All four required measurements were recorded and handed to the trial manager. All patients were measured on at least two occasions by each sonographer. The trial clinical vascular scientist also performed a set of measurements for each patient.

The mean intraobserver variability is documented in *Table 9.* The mean intraobserver variability repeatability coefficient is documented for each of the four measurements obtained by observers in the study along with the SD and range. The repeatability coefficient is the value below which the absolute difference between repeated test results is expected to lie with a probability of 95%.

Clearly, measurements in the longitudinal plane were more repeatable than measurements in the transverse plane. The differences in the mean (range) ITI and OTO intrasonographer repeatability coefficients for longitudinal measurements were similar at 0.32 (0.24–0.39) cm for ITI measurements and 0.33 (0.21–0.45) cm for OTO measurements. This was compared with 0.48 (0.23–1.07) cm and 0.50 (0.20–1.24) cm for transverse ITI and OTO measurements, respectively.

As most sites used more than one observer to follow up the enrolled trial patients, interobserver variability was of great importance.

TABLE 9 Intraobserver variability at the QA days

Measure of intraobserver variability	Longitudinal ITI (cm)	Longitudinal OTO (cm)	Transverse ITI (cm)	Transverse OTO (cm)
Mean	0.32	0.33	0.48	0.50
SD	0.05	0.09	0.27	0.34
Minimum	0.24	0.21	0.23	0.20
Maximum	0.39	0.45	1.07	1.24

The differences between the AAA measurements taken by the sonographers and those taken by the senior clinical vascular scientist in the same patients were used to calculate the intersonographer variability by using Bland–Altman 95% limits of agreement (*Table 10*). The limits of agreement define the range within which 95% of the differences between two measurements made by two observers are likely to fall. *Figure 9* shows the variability in the measurements of external longitudinal diameter compared with the measurements of the senior clinical vascular scientist (expert). Thirteen pairs disagreed by > ±4 mm for ITI measurements, whereas seven pairs disagreed by > ±4 mm for OTO measurements. These data suggest that the interobserver repeatability is better for longitudinal OTO measurements than for longitudinal ITI measurements.

TABLE 10 Results of the QA event days

	Intraobserver variability repeatability coefficient (cm)				Interobserver variability[b] Bland–Altman 95% limits of agreement (cm)			
Observer[a]	Long in	Long out	Tran in	Tran out	Long in	Long out	Tran in	Tran out
A1 July	0.39	0.26	0.42	0.34	–0.87 to 0.32	–0.42 to 0.31	–0.54 to 0.19	–0.42 to 0.47
A2 July	0.35	0.44	0.44	0.31	–0.59 to 0.42	–0.59 to 0.48	–0.29 to 0.36	–0.28 to 0.34
A3 July	0.34	0.42	0.33	0.36	–0.32 to 0.25	–0.30 to 0.60	–0.32 to 0.33	–0.25 to 0.54
A1 September	0.36	0.26	1.07	1.24	–0.67 to 0.19	–0.5 to 0.35	–0.57 to 0.04	–0.61 to 0.41
A3 September	0.26	0.24	0.29	0.25	–0.004 to 0.40	–0.34 to 0.26	–0.15 to 0.50	–0.33 to 0.13
A4 September	0.37	0.45	0.41	0.49	–0.06 to 0.71	–0.26 to 0.64	–0.05 to 0.61	–0.34 to 0.68
A5 September	0.34	0.43	0.45	0.48	–0.15 to 0.56	–0.42 to 0.59	–0.13 to 0.38	–0.34 to 0.40
A6 September	0.30	0.34	0.94	1.04	–0.21 to 0.31	–0.65 to 0.62	–0.62 to 1.26	–0.91 to 1.59
A7 September	0.24	0.21	0.68	0.75	–0.44 to 0.22	–0.4 to 0.65	–0.53 to 0.16	–0.4 to 0.63
A1 November	0.27	0.24	0.23	0.25	–0.87 to 0.69	–0.48 to 0.69	–0.87 to 0.66	–0.65 to 0.65
A2 November	0.26	0.28	0.24	0.20	–1.37 to 0.71	–0.87 to 0.74	–1.33 to 0.76	–0.80 to 0.72
A3 November	0.39	0.42	0.28	0.24	–1.10 to 0.69	–0.77 to 0.48	–1.25 to 0.94	–1.01 to 0.76

Long in, longitudinal plane ITI measurement; Long out, longitudinal plane OTO measurement; Tran in, transverse plane ITI measurement; Tran out, transverse plane OTO measurement.
a A1, A2 = attendee 1, attendee 2, etc.
b Each compared with the senior clinical vascular scientist.
Note
The intraobserver variability describes the variation between measurements taken by the same observer in the same patient over the day in the longitudinal plane and transverse plane. The interobserver variability describes the variability of measurements taken by different observers in the same patients using the Bland–Altman method.

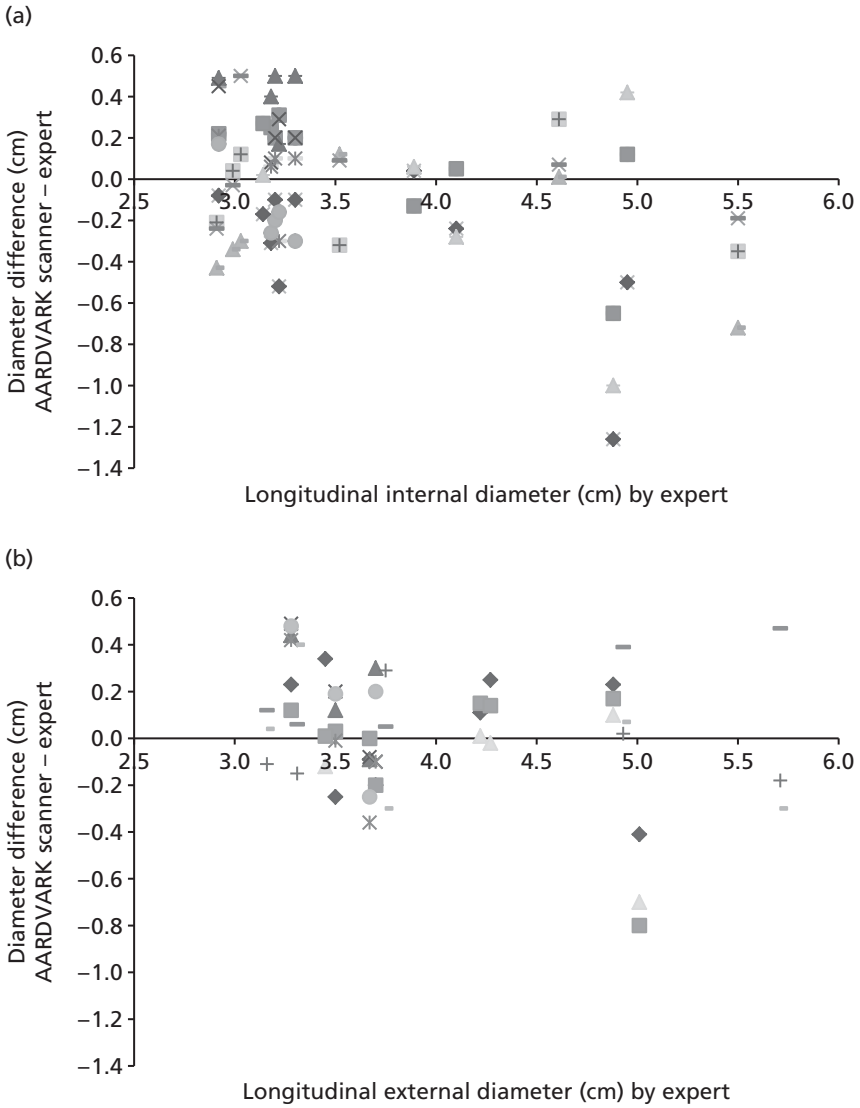


FIGURE 9 Interobserver repeatability graphs (longitudinal diameters). (a) Longitudinal internal diameter; and (b) longitudinal external diameter. Each symbol on the graphs represents a different AARDVARK scanner (three from the July event, three from the November event and six from the September event). Five or more patients are shown for each event, so 10 vertical scatters have only three points and five vertical scatters have six points. Each vertical scatter is a separate patient.

Quality control of ultrasound scans

The quality of the ultrasound images obtained in trial was assessed centrally to ensure that a reliable standard of ultrasound scans was obtained across the 11 scanning sites by different sonographers on different ultrasound scanning systems. The following protocol was used:

- The baseline images for all of the patients in the trial were reviewed as soon as possible after the first monitoring visit.
- All patients at a site or a minimum of 10 patients at a site (for sites with > 10 patients) had each of their 3-monthly images reviewed. Review was undertaken by the senior clinical vascular scientist. Up to 10 random patients were selected by the trial statistician for quality control analysis. If one of the selected patients reached an end point or withdrew from the study or did not attend the visit, the number of images checked might be less than baseline in certain cases. In addition, we asked for additional images to be checked if poor image quality was found at sites. Hence, > 10 images were checked at certain visits. The numbers of recorded images reviewed from each site by the senior clinical vascular scientist are provided in *Table 11*.
- All sites were informed of the scans that needed to be forwarded to the trial centre.
- Each site was asked to save images from longitudinal and transverse planes at the point of maximum dilation to include ITI and OTO calliper placement records.
- The senior clinical vascular scientist reviewed all images sent to the trial centre. All of the images had patient-identifiable information removed and the senior clinical vascular scientist was blinded to treatment allocations.
- Each image was assessed on clarity (looking at depth, gain, focus and good wall definition) and calliper placement (ITI and OTO). The following criteria were used to judge an image as acceptable:
    - the image was of the highest image quality possible
    - the callipers were placed correctly for both ITI and OTO measurements in relation to the wall
    - measurements were taken at right angles to the aneurysm sac wall
    - the image was labelled correctly
    - the image was judged to be taken in a true transverse and true longitudinal plane.

Each image that was reviewed was classified as acceptable or unacceptable.

This protocol was based on the standard operating procedures for the NAAASP [see www.gov.uk/government/collections/aaa-screening-supporting-documents (accessed 3 June 2016)], with the addition of the following assessment criteria: measurements to be taken at right angles to the aneurysmal sac and judged to be in the transverse and longitudinal planes.

If an image was deemed unacceptable, the site was contacted and asked to review the image to ensure that the correct image had been sent, the callipers had been placed correctly and the AARDVARK scanning protocol had been followed. If required, the senior clinical vascular scientist responsible for quality control and the relevant sonographer liaised directly until a resolution was reached.

Sites/observers with unacceptable images were contacted. When a single image taken by an observer was unacceptable, the observer was contacted to review the image. If more than two images were unacceptable then the site was visited and all observers underwent further dedicated training sessions. In these training sessions the site was visited by the lead sonographer for the study and (1) the scanning protocol was reviewed and relevant teaching given and (2) each of the images that was deemed unacceptable was reviewed. This was required at only one site.

TABLE 11 Numbers of recorded images reviewed from each site by the senior clinical vascular scientist

	Visit								
Site	Baseline	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24
Colchester General Hospital	17	8	11	11	10	11	11	10	10
Freeman Hospital, Newcastle	5	3	2	2	2	2	2	0	2
Hull Royal Infirmary	40	22	33	18	8	9	9	10	10
Manchester Royal Infirmary	3	3	3	3	1	0	0	0	3
Norfolk and Norwich University Hospital	14	8	8	8	8	8	8	8	8
Northern General Hospital, Sheffield	2	2	2	0	2	0	2	0	2
Royal Bournemouth Hospital	50	24	17	11	10	10	10	11	11
Royal Free Hospital, London	9	9	7	8	8	8	8	7	9
St Thomas' Hospital, London	25	12	18	11	8	7	7	7	11
St Mary's Hospital/Charing Cross Hospital, London	17	10	16	10	9	11	11	11	11
Sunderland Royal Hospital	4	4	4	4	3	3	1	0	3
University Hospital Coventry	28	14	21	12	9	9	9	9	10
York Hospital	6	4	4	4	3	0	3	3	3

Quality control of the final ultrasound data

In addition to quality control of the ultrasound images and the QA events, the ultrasound measurement database as a whole was monitored for any anomalies or spurious results. Sites were requested to measure the maximum AP diameter of the AAA at each visit. Therefore, the ITI transverse and longitudinal measurements and the OTO transverse and longitudinal measurements at each visit were expected to be within ±3 mm of each other.

If the longitudinal and transverse measurements varied by > ±3 mm, sites were contacted and asked to recheck their scans and measurements to ensure that the maximum AP diameter had been accurately measured. Cases were accepted or rejected accordingly and remeasured when an obvious error had been made.

In total, 107 ITI measurements and 35 OTO measurements had differences > ±3 mm. This, together with the results of the interobserver variability study and the use of multiple observers for the trial, suggested that the longitudinal OTO measurement was the most reliable measurement on which to base aneurysm growth rate. Therefore, longitudinal OTO measurements were used for the evaluation of the trial end points.

The 35 OTO measurements were reconsidered as this measurement was the primary measurement to be used in the main trial analyses. Four measurements were amended after obvious measurement errors were made. Adjusted measurements were used for the analyses in the trial.

Justification for the choice of diameter used for primary end point

The mean (range) intrasonographer repeatability coefficient for longitudinal measurements was 0.33 (0.21–0.45) cm for OTO measurements and 0.32 (0.24–0.39) cm for ITI measurements compared with 0.48 (0.23–1.07) cm and 0.50 (0.20–1.24) cm for transverse ITI and OTO measurements, respectively. Longitudinal plane measurements were therefore used for the primary analyses.

However, possibly reflecting the small number of patients included ($n = 11$), there was no meaningful difference between the variability of OTO and ITI measurements reported in intraobserver variability studies that could determine the superiority of OTO or ITI measurements for use as the primary end point in the study. Considering ITI interobserver variability measurements, 13 pairs of measurements (by an observer and the senior clinical vascular scientist) differed by > ±4 mm, whereas for OTO measurements seven pairs of measurements differed by > ±4 mm. These data suggest that interobserver repeatability was better for longitudinal OTO measurements than for longitudinal ITI measurements

When comparing transverse and longitudinal maximum diameters in the same patient at each time point there was less variation between OTO measurements than between ITI measurements (35 vs. 107 measurements were different by > 0.3 mm, respectively). In addition, there was less variation in the SDs of AAA measurements for most time points in the study of OTO measurements (see *Table 19*).

Therefore, OTO diameters measured from longitudinal images were used for evaluation of the primary outcome measure.

Chapter 4 Results

Site recruitment

Recruitment was originally to take place at five sites: Imperial College Healthcare NHS Trust (St Mary's and Charing Cross Hospitals), Royal Free London NHS Foundation Trust, Guy's and St Thomas' NHS Foundation Trust and University Hospitals Coventry and Warwickshire NHS Trust. We identified a pool of approximately 860 patients potentially eligible for the trial from existing databases from these four hospital trusts (200, 90, 380 and 189, respectively). We also predicted that expansion of the NAAASP was likely to increase this patient pool before trial recruitment started, with approximately 4% of men screened expected to have an AAA. Against this, we estimated that 30% of patients would be ineligible for the trial because they were already receiving ACE-I therapy or because they had an unsuitable BP, that is, SBP could not be controlled to < 150 mmHg before randomisation. Assuming a 15% refusal rate in the remaining 262 patients, the target of 225 patients seemed achievable given a steady influx of newly screened and eligible patients over the recruitment period.

The first trial site was opened to recruitment in September 2011, with recruitment due to end after 12 months. However, to meet the recruitment target a further nine sites were added during the trial. The four sites in London became recruitment and screening sites, with patients having all other study visits at the ICCH, Imperial College London. The remaining 10 scanning sites were located across the country and performed all study visits locally.

Participant recruitment

A recruitment extension of 7 months was required before the recruitment target was successfully met. The reasons for this were as follows:

- The number of patients taking ACE-Is was higher than anticipated and this was the main barrier to recruitment. At the time of the HTA programme commissioned call in 2009, approximately 32.3% of the population aged > 60 years received ACE-Is; by 2012 this had increased to 52.9% (Health Survey for England).[94]
- The proportion of patients with an AAA picked up through the NAAASP was less than half the proportion expected: 4% of patients screened were expected to have an AAA, whereas in reality this proportion was 1.2%.
- Progress was slow in securing NHS research governance approval at some of the participating sites. The quickest research and development approval was granted in 33 working days (approximately 1.5 months), whereas the longest approval took 147 working days (6 months). After waiting 168 working days (7 months) with approval still not granted in one further site, attempts to gain approval were abandoned.

To try and overcome some of the barriers to recruitment, the following strategies and actions were implemented approximately 6 months into the study:

- Review of methods of approaching patients – sites were requested to review their methods of contacting patients and try different strategies (i.e. speaking to patients at their next visit instead of cold-calling) in an attempt to increase uptake into the trial.
- Breakdowns of site recruitment were requested monthly and were reviewed at the monthly management meetings to try and identify and address any specific issues.
- Addition of PICs – some centres had PIC sites set up to widen the pool of potential participants.

- The age range was expanded to include those aged ≥ 55 years (originally set at ≥ 60 years).
- Patient invitation letter – this was created because some site investigators felt that the PIS was too lengthy and daunting as a first introduction to the trial.
- Trial poster – this was created and put on the noticeboards in relevant clinical areas (e.g. in the vascular ultrasound laboratories) at some sites to create awareness of the trial.
- AARDVARK trial web page – this was set up via the ICTU website and was available as a resource for both patients and site staff. The site contained general information about the trial and was updated regularly with current recruitment numbers.
- Update/simplify the PIS – some sites felt that the original PIS was written in such a way that the side effects and risks of the study were unduly worrying to potential participants. Therefore, the PIS was reworded and a list of side effects tabulated as an appendix.
- Additional research sites – by far the most successful strategy for increasing recruitment was increasing the number of research sites, specifically targeting those with large populations and time/resources to conduct the study.
- Chief investigator presence at site initiation visits – the chief investigator visited all sites as part of the site initiation visits to stress the importance of the trial and answer any clinical queries.

In total, 227 patients were initially randomised to the trial. However, the randomisation of three patients was subsequently discovered to be a protocol violation because these patients did not meet all of the entry criteria for the trial. *Table 12* shows the final recruitment numbers by site. The Royal Bournemouth Hospital and Hull Royal Infirmary were the top recruiting sites, with 50 and 40 patients randomised, respectively. The first patient was randomised to the study on 16 December 2011 and the last patient was randomised to the study on 19 April 2013 (*Figure 10*).

Table 13 shows that the number of patients randomised to each treatment arm was well balanced, with 79 patients randomised to placebo, 73 randomised to perindopril and 72 randomised to amlodipine.

TABLE 12 Number of patients randomised at each participating site

Site	Randomised, *n* (%)
Charing Cross Hospital, London	4 (1.8)
Colchester General Hospital	17 (7.6)
Freeman Hospital, Newcastle	5 (2.2)
Hull Royal Infirmary	40 (17.9)
Manchester Royal Infirmary	3 (1.3)
Norfolk and Norwich University Hospital	14 (6.3)
Northern General Hospital, Sheffield	2 (0.9)
Royal Bournemouth Hospital	50 (22.3)
Royal Free Hospital, London	9 (4.0)
St Thomas' Hospital, London	25 (11.2)
St Mary's Hospital, London	17 (7.6)
Sunderland Royal Hospital	4 (1.8)
University Hospital Coventry	28 (12.5)
York Hospital	6 (2.7)
Total	224

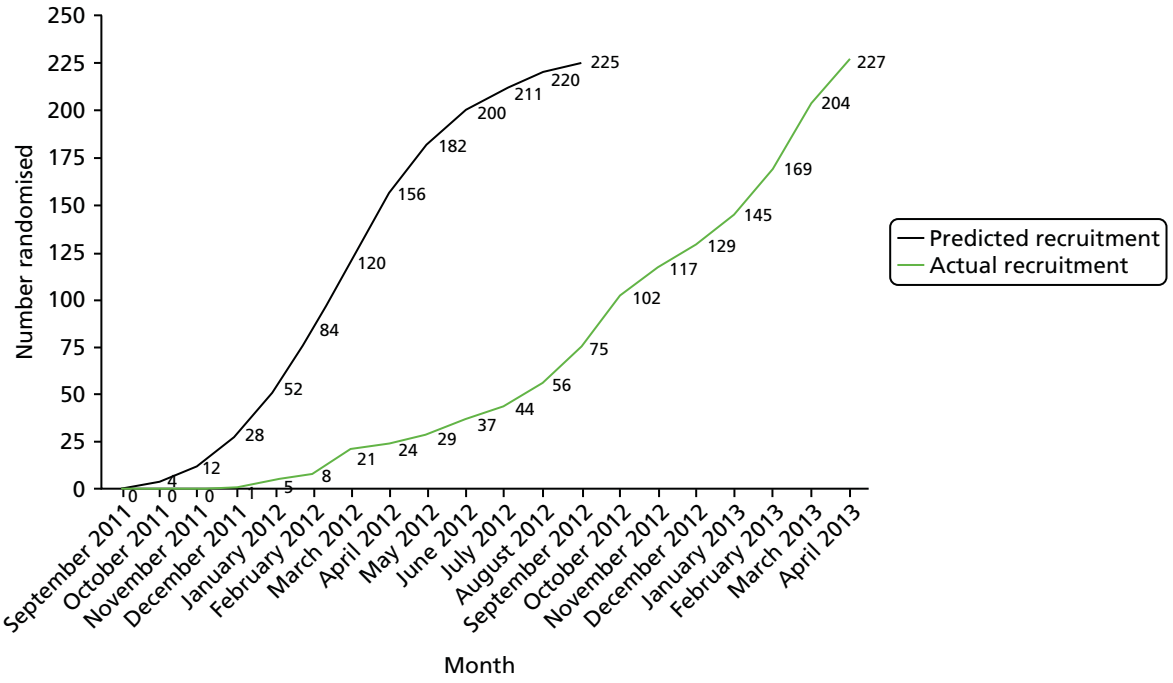


FIGURE 10 Participant recruitment by month.

TABLE 13 Numbers of participants randomised to each treatment arm

Site	Placebo	Perindopril	Amlodipine	Total
Charing Cross Hospital, London	1	1	2	4
Colchester General Hospital	6	6	5	17
Freeman Hospital, Newcastle	2	2	1	5
Hull Royal Infirmary	14	13	13	40
Manchester Royal Infirmary	2	1	0	3
Norfolk and Norwich University Hospital	5	5	4	14
Northern General Hospital, Sheffield	1	1	0	2
Royal Bournemouth Hospital	17	16	17	50
Royal Free Hospital, London	3	3	3	9
St Thomas' Hospital, London	8	8	9	25
St Mary's Hospital, London	7	5	5	17
Sunderland Royal Hospital	1	1	2	4
University Hospital Coventry	10	9	9	28
York Hospital	2	2	2	6
Total	79	73	72	224

Non-recruited patients

During the trial recruitment period we requested that the sites capture details of reasons why patients with an AAA were not recruited into the trial. These data were collected by prospective pre-screening by recruiting staff, mainly by case note and clinical database review. Unfortunately, limited research nurse availability and clinical service pressures prevented reliable collection of these data at some centres. However, data were collected from a total of 1912 non-recruited patients. The patients were excluded on the basis of ineligibility (*Figure 11*) or because they declined to participate (*Figure 12*). The main reason for ineligibility was already taking ACE-Is; this excluded 643 patients from participating in the trial. Unfortunately, a specific reason for declining to participate was not recorded for 107 patients; however, 56 patients declined because they did not want to participate in a clinical trial.

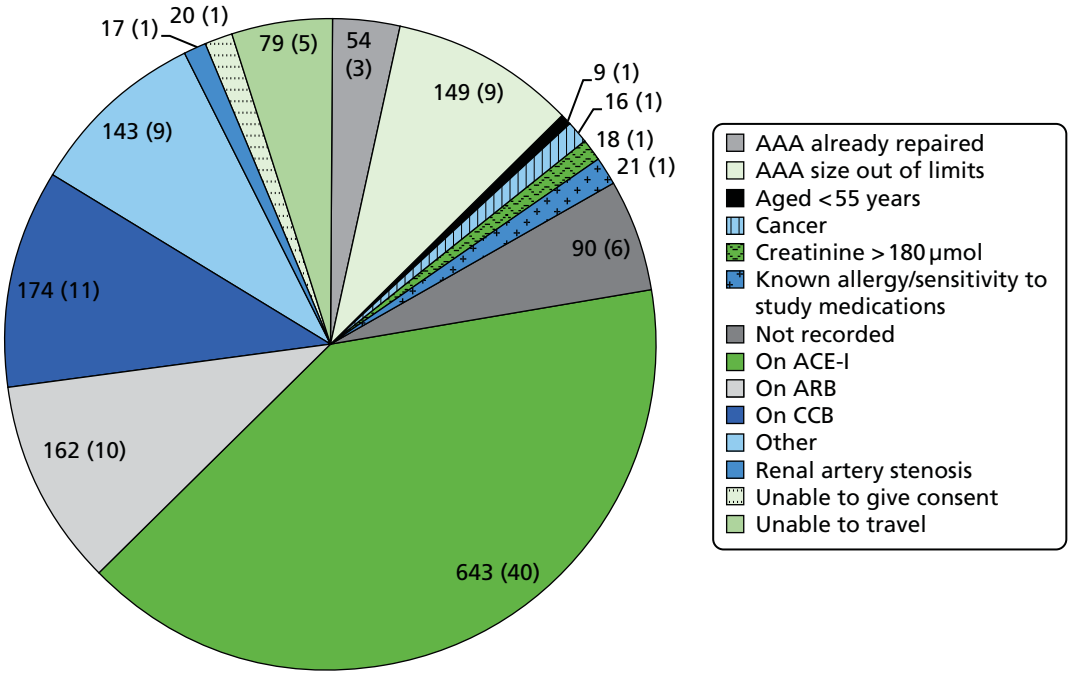


FIGURE 11 Reasons for trial ineligibility, *n* (%) (*N* = 1595).

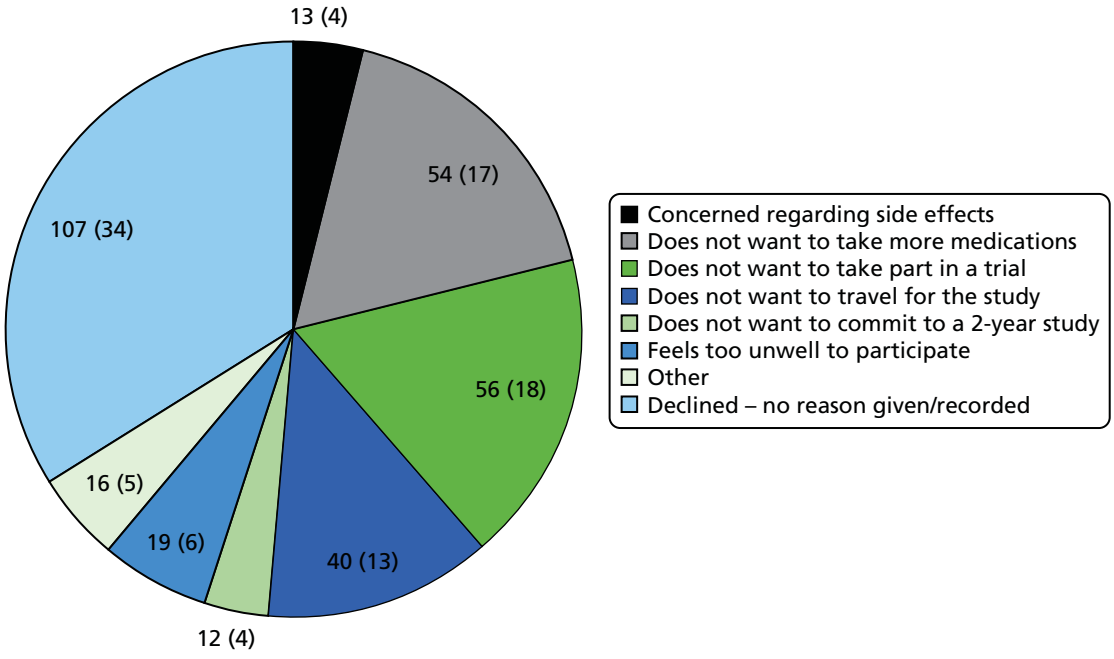


FIGURE 12 Reasons for declining the trial, *n* (%) (*N* = 317).

Status of patients in the study

Table 14 shows the numbers of patients who completed each study visit across the three groups. In total, 161 patients (71%) successfully completed all study visits.

As previously described, a 10% attrition rate was included in the power calculations for the trial. Participants were included in the attrition rate if data from fewer than two study visits were available for analysis. A total of 13 patients counted towards the attrition rate: three patients who were randomised in error and 10 patients who withdrew from the study before completing at least two study visits. The patients randomised in error were not included in the final analyses; however, the remaining 10 patients were included on an ITT basis. The final attrition rate for the study was therefore 6%. The CONSORT diagram (*Figure 13*) shows the status of patients at the end of the trial. Six patients withdrew from the trial because of AEs attributed to the study medications ($n = 2$ perindopril, $n = 4$ amlodipine). Four patients ($n = 3$ perindopril, $n = 1$ amlodipine) switched to losartan because of cough. No patients suffered AAA rupture and 26 underwent elective surgery ($n = 9$ placebo, $n = 10$ perindopril, $n = 7$ amlodipine) during the trial period.

TABLE 14 Numbers of patients who completed the study visits

Visit	Placebo	Perindopril	Amlodipine	Total
Baseline	79	73	72	224
Month 3	76	68	67	211
Month 6	69	62	62	193
Month 9	64	57	57	178
Month 12	71	61	54	186
Month 15	60	49	47	156
Month 18	61	52	49	162
Month 21	54	44	47	145
Month 24	59	53	49	161
Unscheduled	10	2	2	14

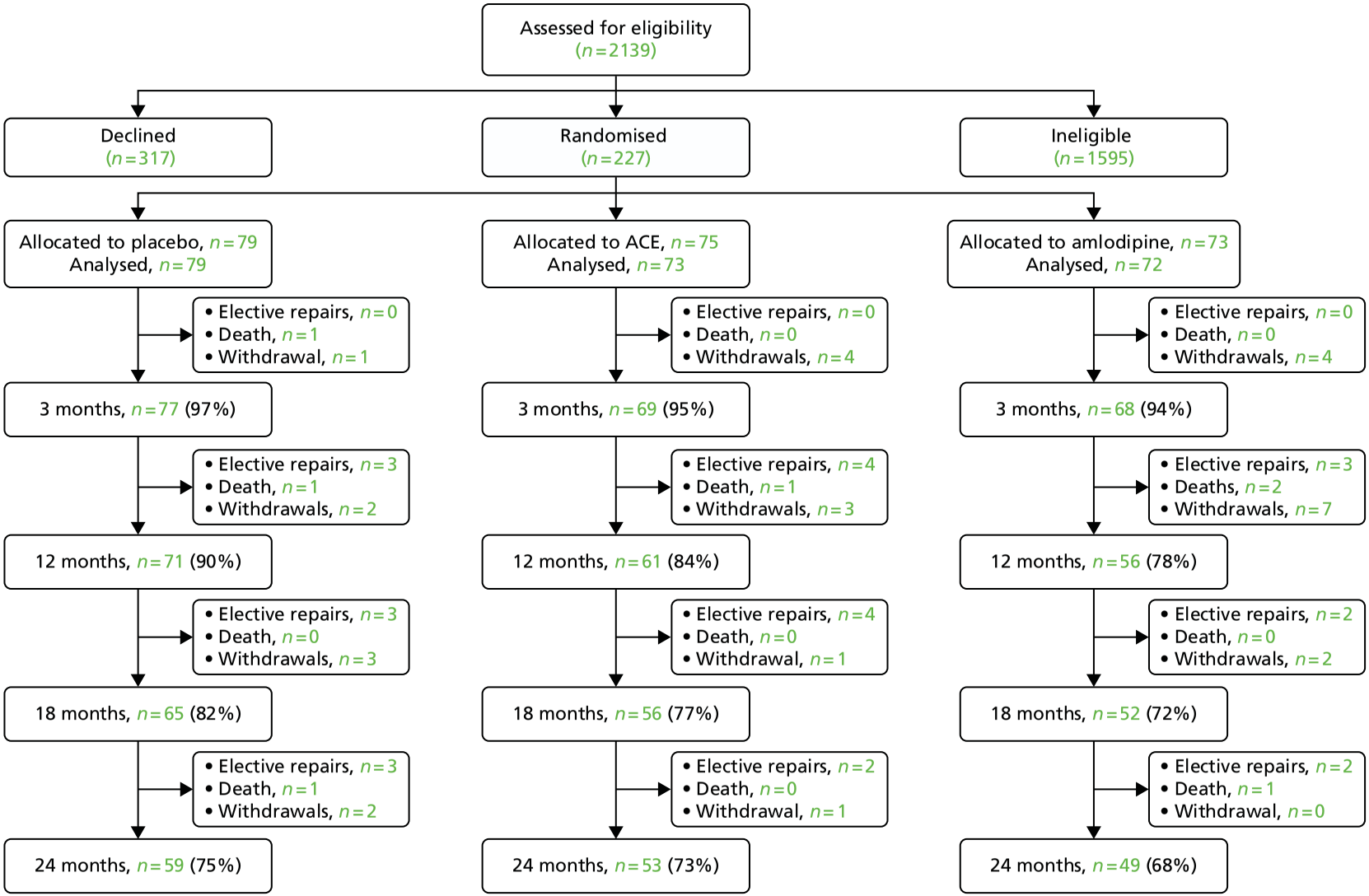


FIGURE 13 The AARDVARK trial CONSORT diagram. Reproduced from Bicknell *et al*. 2016.[95] © Bicknell *et al*. 2016. Published by Oxford University Press on behalf of the European Society of Cardiology. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited.

Baseline comparability of randomised groups

The baseline characteristics for all patients in the study are shown in *Table 15*. Although groups were randomised and generally well matched, there were some small imbalances between the groups that may influence aneurysm growth, for example presence of diabetes [$n = 8$ (10.1%) placebo, $n = 2$ (2.7%) perindopril, $n = 6$ (8.3%) amlodipine] and use of statins [$n = 48$ (61%) placebo, $n = 53$ (73%) perindopril, $n = 45$ (63%) amlodipine]. All patients but one were Caucasian.

TABLE 15 Baseline characteristics of randomised patients[a]

Characteristic	Placebo	Perindopril	Amlodipine
n[b]	79	73	72
Age (years)	70.7 (7.5)	71.6 (6.9)	71.5 (6.7)
Male, *n* (%)	74 (94)	71 (97)	66 (92)
Caucasian, *n* (%)	79 (100)	73 (100)	71 (99)
SBP (mmHg)	131.7 (12.2)	130.9 (11.5)	131.9 (13)
DBP (mmHg)	77.9 (7.6)	76.7 (8)	78 (7)
Use of statins, *n* (%)	48 (61)	53 (73)	45 (63)
AAA external diameter longitudinal (cm)	4.06 (0.67)	4.05 (0.65)	4.03 (0.69)
AAA internal diameter longitudinal (cm)	3.67 (0.67)	3.66 (0.68)	3.61 (0.71)
AAA external diameter transverse (cm)	4.05 (0.68)	4.09 (0.65)	4.04 (0.67)
AAA internal diameter transverse (cm)	3.65 (0.69)	3.68 (0.68)	3.61 (0.7)
Current smokers, *n* (%)	17 (22)	21 (29)	18 (25)
Pack-years current smokers	32.9 (28)	33.1 (24)	29.3 (17.3)
Past smokers, *n* (%)	56 (72)	41 (57)	44 (63)
Pack-years past smokers	42.2 (45.5)	42 (33.8)	40.5 (36.8)
Height (cm)	174.4 (8.5)	175.9 (8.3)	173.7 (8.7)
Weight (kg)	84.3 (16.1)	84.3 (16.6)	81.2 (13.8)
Diabetes, *n* (%)	8 (10.1)	2 (2.7)	6 (8.3)
Antiplatelet therapy, *n* (%)	28 (35.4)	37 (50.6)	33 (45.8)

a Mean (SD) unless otherwise stated.
b Small variation in numbers for some variables.
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Abdominal aortic aneurysm growth

The changes in AAA diameter over the duration of the trial are shown in *Table 16* (summary longitudinal AAA measurements) and *Table 17* (differences in longitudinal AAA measurements). See *Appendix 5* for a summary of the transverse AAA measurement data.

There was a small increase in the mean internal and external AAA diameter across all three treatment groups. The mean difference between month 24 and baseline for the longitudinal external diameter was 0.27 cm for the three groups combined. Similar results were observed for the mean external transverse measurements. Comparisons of 2-year changes across the three randomised groups are invalid because of the variable reduction in numbers in each group over time. The SDs of the diameters recorded in the longitudinal plane for the ITI measures (see *Table 16*) were generally systematically higher than those for the OTO measures at each time point, as were the SDs of the differences between baseline and each time point (see *Table 17*).

TABLE 16 Abdominal aortic aneurysm diameter in the longitudinal plane: summary data by randomised group and combined at each trial visit

	Longitudinal internal diameter (cm)					Longitudinal external diameter (cm)				
Visit	*n*	Mean	SD	Minimum	Maximum	*n*	Mean	SD	Minimum	Maximum
Placebo										
Baseline	78	3.67	0.67	2.33	5.26	79	4.06	0.67	3.00	5.44
Month 3	74	3.72	0.72	2.46	5.48	74	4.10	0.72	3.01	6.08
Month 6	66	3.74	0.65	2.61	5.55	66	4.13	0.62	3.02	5.83
Month 9	63	3.74	0.70	2.30	5.37	63	4.11	0.68	3.05	5.67
Month 12	69	3.77	0.64	2.48	5.22	68	4.13	0.64	3.00	5.51
Month 15	57	3.78	0.68	2.52	5.41	57	4.15	0.70	3.01	6.01
Month 18	60	3.83	0.65	2.68	5.27	60	4.20	0.68	3.06	5.85
Month 21	52	3.84	0.63	2.71	5.30	52	4.18	0.67	3.04	5.86
Month 24	56	3.79	0.63	2.39	5.37	56	4.12	0.63	3.08	5.58

TABLE 16 Abdominal aortic aneurysm diameter in the longitudinal plane: summary data by randomised group and combined at each trial visit (*continued*)

	Longitudinal internal diameter (cm)					Longitudinal external diameter (cm)				
Visit	*n*	Mean	SD	Minimum	Maximum	*n*	Mean	SD	Minimum	Maximum
Perindopril										
Baseline	71	3.66	0.68	2.38	5.05	71	4.05	0.65	3.04	5.40
Month 3	65	3.65	0.68	2.27	5.02	65	4.05	0.65	3.04	5.42
Month 6	61	3.72	0.71	2.17	5.18	61	4.11	0.72	3.01	5.93
Month 9	56	3.72	0.72	2.32	5.38	56	4.10	0.69	3.04	5.78
Month 12	60	3.76	0.73	2.51	5.50	60	4.12	0.72	3.03	5.79
Month 15	47	3.75	0.72	2.54	5.49	47	4.09	0.71	3.03	5.74
Month 18	49	3.75	0.62	2.45	5.50	49	4.09	0.64	3.08	5.83
Month 21	44	3.74	0.65	2.57	5.74	43	4.08	0.69	3.08	5.99
Month 24	52	3.71	0.60	2.54	5.28	52	4.03	0.57	3.05	5.42
Amlodipine										
Baseline	68	3.61	0.71	2.20	4.99	71	4.03	0.69	3.00	5.50
Month 3	65	3.70	0.70	2.02	5.10	65	4.10	0.67	3.05	5.60
Month 6	60	3.78	0.74	2.27	5.24	60	4.14	0.69	3.04	5.47
Month 9	54	3.87	0.70	2.64	5.52	54	4.22	0.68	3.02	5.75
Month 12	51	3.82	0.70	2.26	5.25	51	4.18	0.69	2.97	5.80
Month 15	44	3.82	0.71	2.15	5.21	44	4.19	0.67	3.00	5.59
Month 18	47	3.87	0.72	2.46	5.51	47	4.17	0.70	3.01	5.78
Month 21	47	3.90	0.74	2.62	5.54	47	4.21	0.72	3.00	5.88
Month 24	48	3.83	0.73	2.44	5.50	47	4.18	0.67	3.02	5.67
Total										
Baseline	217	3.65	0.68	2.20	5.26	221	4.05	0.66	3.00	5.50
Month 3	204	3.69	0.70	2.02	5.48	204	4.09	0.68	3.01	6.08
Month 6	187	3.75	0.69	2.17	5.55	187	4.13	0.67	3.01	5.93
Month 9	173	3.77	0.70	2.30	5.52	173	4.14	0.68	3.02	5.78
Month 12	180	3.78	0.69	2.26	5.50	179	4.14	0.68	2.97	5.80
Month 15	148	3.78	0.70	2.15	5.49	148	4.14	0.69	3.00	6.01
Month 18	156	3.82	0.66	2.45	5.51	156	4.16	0.67	3.01	5.85
Month 21	143	3.83	0.67	2.57	5.74	142	4.16	0.69	3.00	5.99
Month 24	156	3.78	0.65	2.39	5.50	155	4.11	0.62	3.02	5.67

TABLE 17 Differences in longitudinal AAA diameter compared with baseline by randomised group and combined

	AAA longitudinal internal diameter (cm)					AAA longitudinal external diameter (cm)				
Study period	*n*	Mean	SD	Minimum	Maximum	*n*	Mean	SD	Minimum	Maximum
Placebo										
Month 3 – baseline	73	0.08	0.23	–0.3	0.87	74	0.06	0.24	–0.73	1.04
Month 6 – baseline	65	0.11	0.27	–0.54	0.84	66	0.08	0.24	–0.61	0.70
Month 12 – baseline	68	0.18	0.31	–0.68	0.91	68	0.14	0.28	–0.57	0.92
Month 18 – baseline	59	0.28	0.29	–0.20	0.94	60	0.26	0.29	–0.19	1.27
Month 24 – baseline	55	0.31	0.35	–0.27	1.20	56	0.27	0.30	–0.22	1.11
Perindopril										
Month 3 – baseline	64	0.02	0.26	–0.72	0.86	64	0.05	0.21	–0.65	0.69
Month 6 – baseline	60	0.11	0.24	–0.33	1.06	60	0.12	0.22	–0.42	0.97
Month 12 – baseline	59	0.22	0.30	–0.27	1.35	59	0.19	0.27	–0.40	1.18
Month 18 – baseline	48	0.26	0.26	–0.18	1.04	48	0.23	0.26	–0.35	1.26
Month 24 – baseline	51	0.27	0.21	–0.16	1.00	51	0.23	0.22	–0.35	0.82
Amlodipine										
Month 3 – baseline	61	0.08	0.29	–0.7	1.21	64	0.05	0.24	–0.69	0.90
Month 6 – baseline	56	0.18	0.42	–0.84	1.74	59	0.12	0.30	–0.77	1.11
Month 12 – baseline	47	0.29	0.49	–0.69	2.61	50	0.22	0.31	–0.52	1.18
Month 18 – baseline	43	0.35	0.33	–0.3	1.47	46	0.27	0.32	–0.32	1.16
Month 24 – baseline	44	0.37	0.41	–0.73	1.43	46	0.33	0.36	–0.68	1.17
Total										
Month 3 – baseline	198	0.06	0.26	–0.72	1.21	202	0.05	0.23	–0.73	1.04
Month 6 – baseline	181	0.13	0.32	–0.84	1.74	185	0.10	0.26	–0.77	1.11
Month 12 – baseline	174	0.22	0.36	–0.69	2.61	177	0.18	0.29	–0.57	1.18
Month 18 – baseline	150	0.29	0.29	–0.3	1.47	154	0.25	0.29	–0.35	1.27
Month 24 – baseline	150	0.31	0.33	–0.73	1.43	153	0.27	0.29	–0.68	1.17

The AAA growth trajectories in each patient by group are shown in *Figure 14* (placebo), *Figure 15* (perindopril) and *Figure 16* (amlodipine). Most of the patients had slow growth rates but there were a small number of patients with faster growth rates in each randomised group.

Figure 17 shows the observed mean AAA diameter for each treatment group at each visit time point. The numbers of patients were different across each visit, with lower numbers of patients in the later visits. There were no significant differences between the groups over time and any apparent differences between the groups must be considered in the context of the changing numbers of participants. This is especially relevant when patients with an AAA of ≥ 5.5 cm who are taken for surgery and do not complete any further measurements are considered.

FIGURE 14 Abdominal aortic aneurysm growth trajectories by patients in the placebo group.

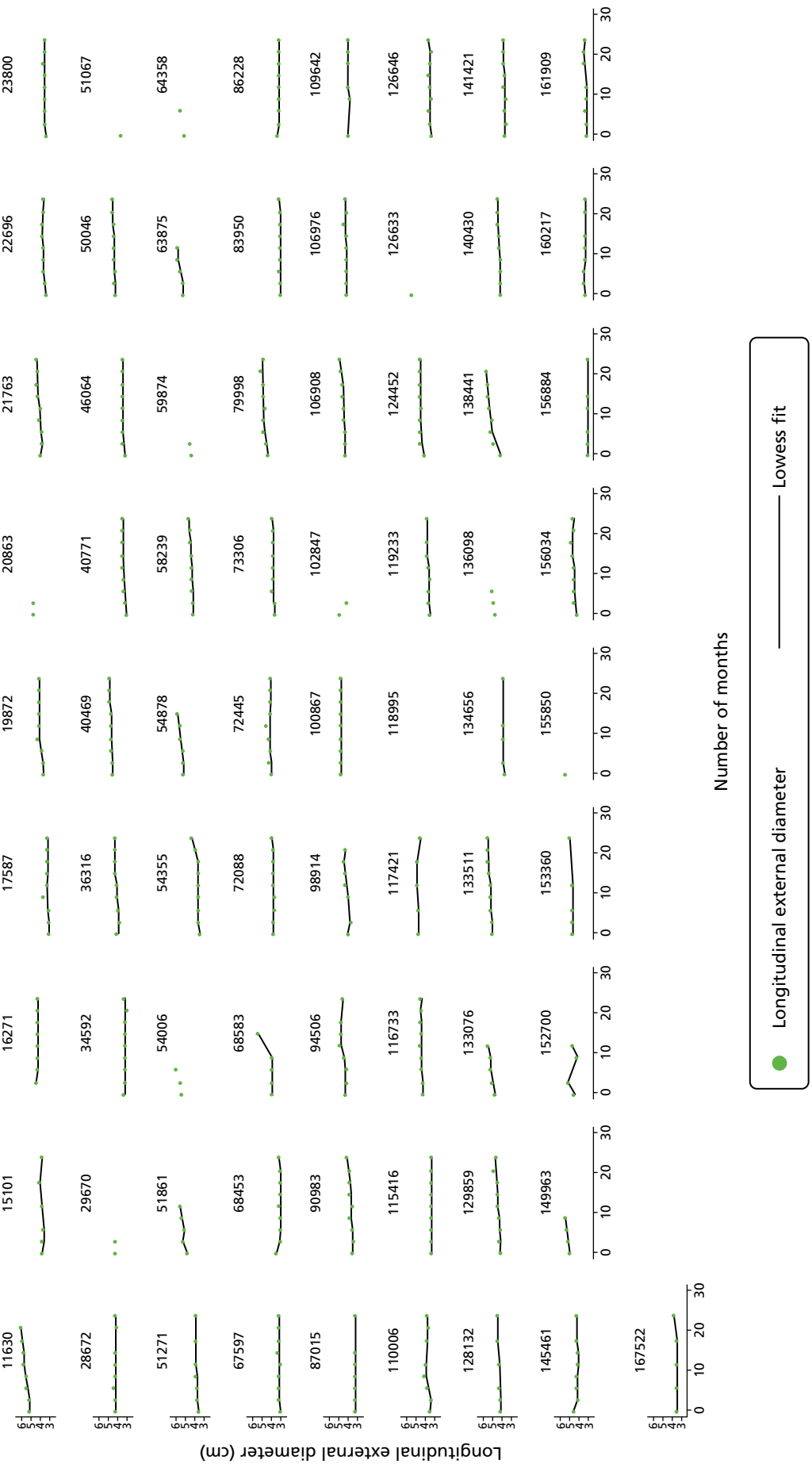
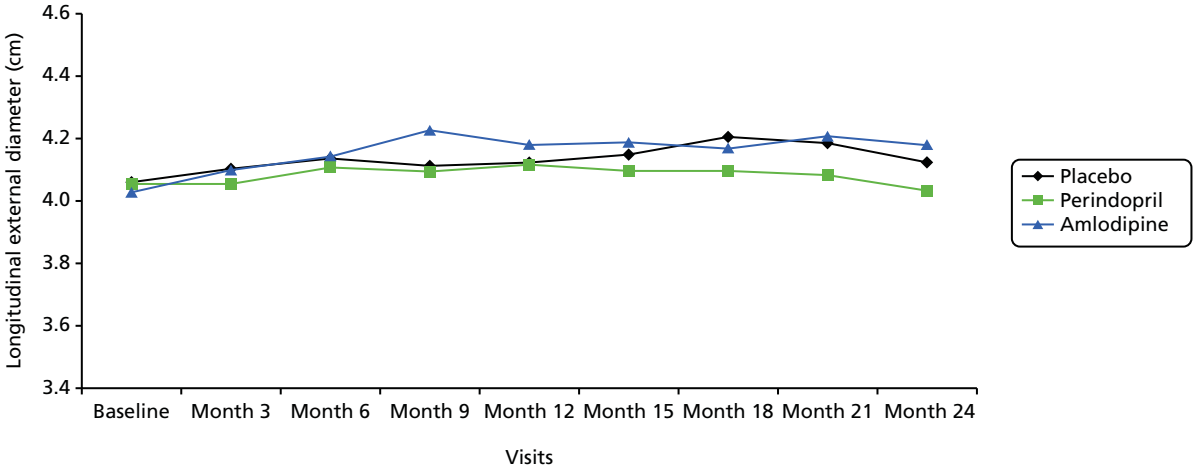


FIGURE 15 Abdominal aortic aneurysm growth trajectories by patients in the perindopril group.

FIGURE 16 Abdominal aortic aneurysm growth trajectories by patients in the amlodipine group.



Number of patients at each visit

	Baseline	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24
Placebo	79	74	66	63	68	57	60	52	56
Perindopril	71	65	61	56	60	47	49	43	52
Amlodipine	71	65	60	54	51	44	47	47	47

FIGURE 17 Mean longitudinal external diameter over time by randomised group.

Histograms of change in longitudinal external AAA diameter from baseline to 3, 12 and 24 months are shown in *Figures 18–20*, respectively (for the histograms at 6 and 18 months see *Appendix 6*). These histograms show the distribution of the difference in the data between the two specified time points. Overall, no obvious differences were apparent across groups at any of the three time points, whereas in all three histograms growth was apparent overall at 12 and 24 months reflected by the shift of bars to the right of the graphs.

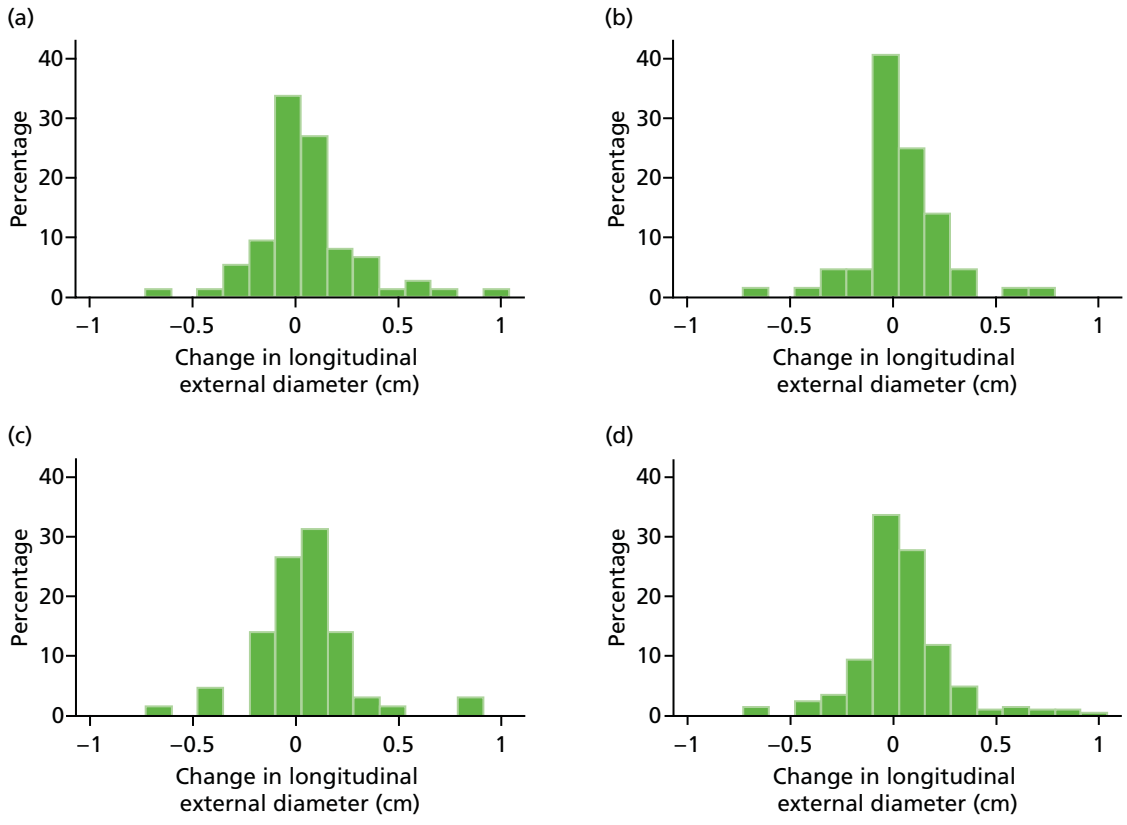


FIGURE 18 Histograms of change in AAA longitudinal external diameter from baseline to month 3. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

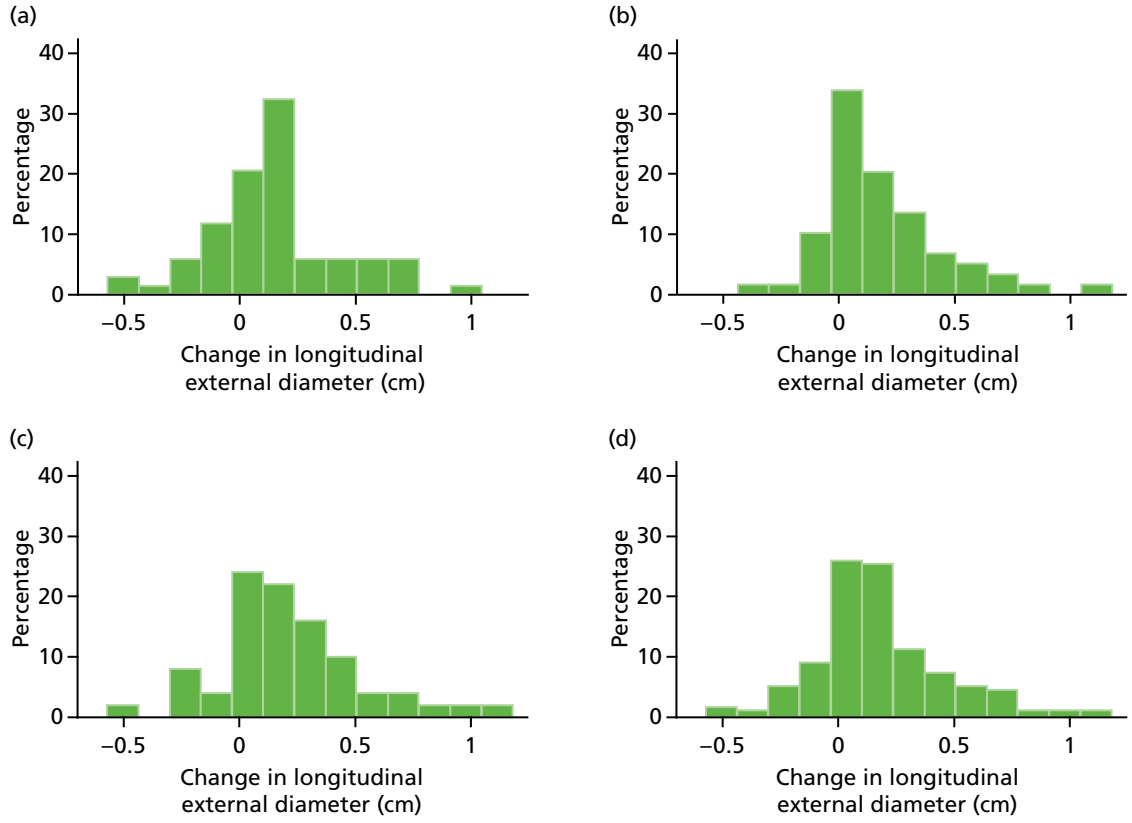


FIGURE 19 Histograms of change in AAA longitudinal external diameter from baseline to month 12. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

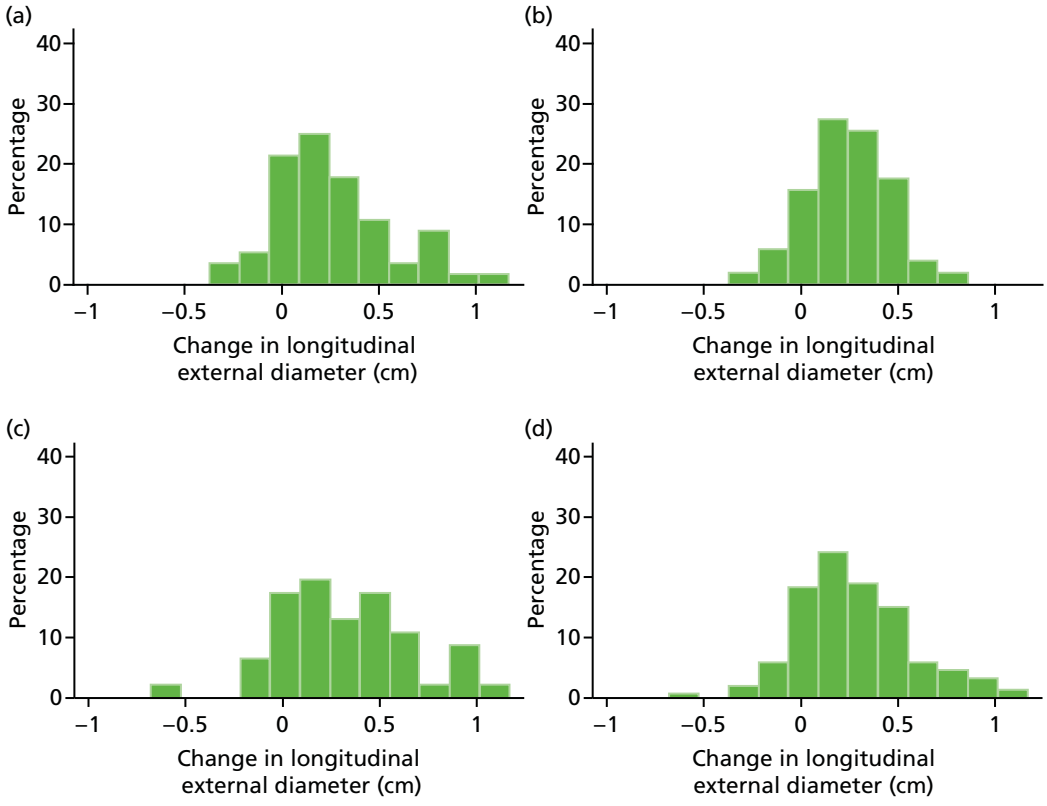


FIGURE 20 Histograms of change in AAA longitudinal external diameter from baseline to month 24. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

Counting those AAAs that exhibit fast growth rates (as defined by growth of > 0.5 cm per year) in these histograms ($n = 14$ placebo, $n = 8$ perindopril, $n = 14$ amlodipine) suggested possible differential effects among the three treatment groups. Formal analyses of the number of patients who exhibit fast growth rates in each of the three groups (taking into account aneurysm size and adjusting for confounders) was not undertaken as part of the main analyses of this trial but will be considered as part of future research plans.

Box plots of change in longitudinal external AAA diameter from baseline to 3, 12 and 24 months are shown in *Figures 21–23*, respectively (the box plots for change from baseline to 6 and 18 months can be found in *Appendix 7*). These figures confirm the findings shown in *Figures 18–20* in that there are no apparent differences in change in diameter at 3, 12 or 24 months across the three groups and growth of a similar magnitude is apparent in all three groups at 12 and 24 months.

Histograms and box plots of change in diameter for longitudinal internal diameters and transverse external and internal diameters are provided in *Appendices 8–13*.

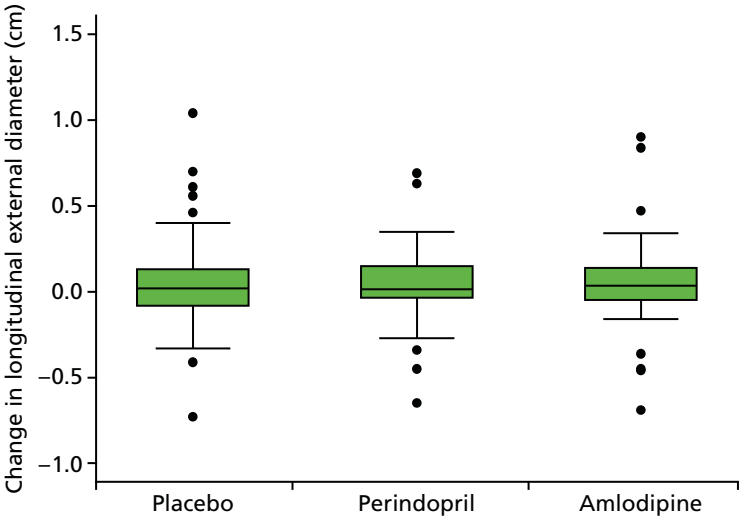


FIGURE 21 Box plot of change in AAA longitudinal external diameter from baseline to month 3. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

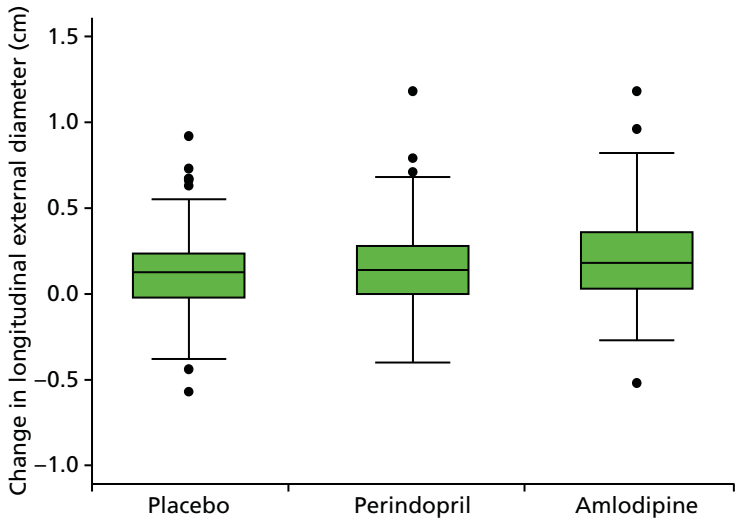


FIGURE 22 Box plot of change in AAA longitudinal external diameter from baseline to month 12. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

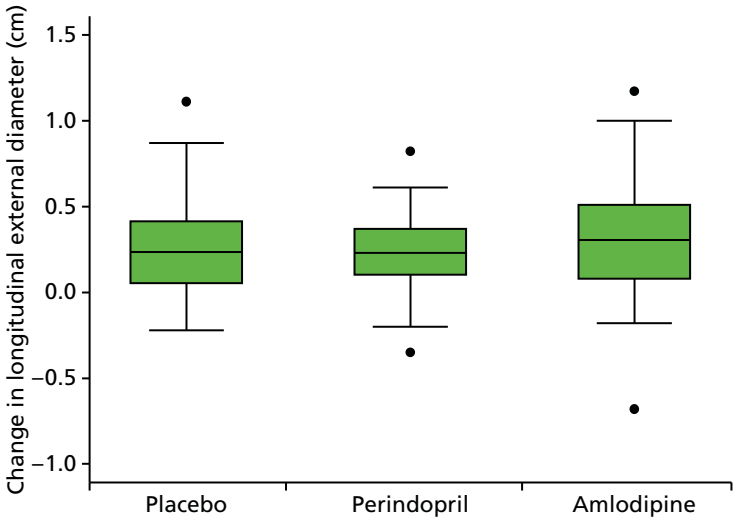


FIGURE 23 Box plot of change in AAA longitudinal external diameter from baseline to month 24. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

Primary outcome

Multilevel modelling was used to determine the maximum likelihood estimates for AAA diameter growth. *Table 18* provides these results for the longitudinal external AAA diameter. The estimates for annual diameter growth were as follows:

- 1.68 mm [standard error (SE) 0.02 mm] in the placebo group
- 1.77 mm (SE 0.02 mm) in the perindopril group
- 1.81 mm (SE 0.02 mm) in the amlodipine group.

TABLE 18 Maximum likelihood estimates for AAA longitudinal external diameter growth

	Linear model with interaction	
Treatment and visit	**Estimate**	**95% CI**
Fixed part		
Baseline diameter (cm) for the control group (β_1)	4.074	3.931 to 4.218
Change in diameter growth (cm) for a yearly increase in time (β_2)	0.168	0.129 to 0.208
Difference in baseline diameter (cm)		
β_3(perindopril vs. placebo)	–0.008	–0.217 to 0.200
β_4(amlodipine vs. placebo)	–0.021	–0.229 to 0.188
Difference in diameter growth (cm) for a yearly increase in time		
β_5(perindopril vs. placebo)	0.008	–0.050 to 0.065
β_6(amlodipine vs. placebo)	0.012	–0.046 to 0.070
Random part (cm)		
SD of individual intercepts (ς_{1j})	0.646	0.587 to 0.710
SD of individual slopes (ς_{2j})	0.149	0.128 to 0.173
Correlation between random effects	0.455	0.296 to 0.589
SD of residual errors	0.136	0.130 to 0.141

Source: adapted from Bicknell *et al*. 2016.[95] © Bicknell *et al*. 2016. Published by Oxford University Press on behalf of the European Society of Cardiology. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited.

The differences in the slopes 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 slope between perindopril and placebo plus amlodipine combined was also not significant ($p = 0.92$).

Sensitivity analyses

Exclusion of patients with diabetes gave very similar results (*Table 19*). The estimated difference in annual growth rate between perindopril and placebo was –0.01 mm with a 95% CI of –0.6 to 0.6 mm. Adjustment for baseline age, sex, current smoking status and statin use also gave similar results (*Table 20*).

TABLE 19 Maximum likelihood estimates for AAA longitudinal external diameter growth excluding patients with diabetes: sensitivity analysis

	Linear model with interaction	
Treatment and visit	**Estimate**	**95% CI**
Fixed part		
Baseline diameter (cm) for the control group (β_1)	4.046	3.895 to 4.198
Change in diameter growth (cm) for a yearly increase in time (β_2)	0.176	0.135 to 0.217
Difference in baseline diameter (cm)		
β_3(perindopril vs. placebo)	0.018	–0.198 to 0.232
β_4(amlodipine vs. placebo)	–0.030	–0.249 to 0.188
Difference in diameter growth (cm) for a yearly increase in time		
β_5(perindopril vs. placebo)	–0.001	–0.059 to 0.057
β_6(amlodipine vs. placebo)	0.009	–0.051 to 0.069
Random part (cm)		
SD of individual intercepts (ς_{1j})	0.646	0.585 to 0.712
SD of individual slopes (ς_{2j})	0.146	0.125 to 0.171
Correlation between random effects	0.495	0.333 to 0.629
SD of residual errors	0.136	0.130 to 0.142

TABLE 20 Maximum likelihood estimates for AAA longitudinal external diameter growth adjusted for age, sex, statin use and current smoking status

	Adjusted for baseline age and sex ($n = 223$)		Adjusted for baseline statin use ($n = 223$)		Adjusted for baseline current smoking status ($n = 223$)	
Treatment and visit	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Fixed part (cm)						
Intercept (β_1)	3.681	2.754 to 4.607	4.029	3.851 to 4.207	4.084	3.934 to 4.233
Change in diameter for a yearly increase in time (β_2)	0.168	0.129 to 0.207	0.169	0.129 to 0.208	0.169	0.129 to 0.208
Difference in baseline diameter						
β_3(perindopril vs. placebo)	–0.014	–0.222 to 0.195	–0.018	–0.227 to 0.191	–0.005	–0.214 to 0.204
β_4(amlodipine vs. placebo)	–0.025	–0.233 to 0.183	–0.022	–0.230 to 0.186	–0.019	–0.228 to 0.189
Difference in diameter growth for a yearly increase in time						
β_5(perindopril vs. placebo)	0.008	–0.049 to 0.066	0.008	–0.049 to 0.066	0.008	–0.049 to 0.066
β_6(amlodipine vs. placebo)	0.012	–0.046 to 0.070	0.012	–0.046 to 0.070	0.012	–0.046 to 0.070
Random part (cm)						
SD of individual intercepts (ς_{1j})	0.644	0.586 to 0.709	0.645	0.587 to 0.710	0.646	0.588 to 0.711
SD of individual slopes (ς_{2j})	0.149	0.128 to 0.173	0.149	0.128 to 0.173	0.149	0.128 to 0.173
Correlation between random effects	0.455	0.296 to 0.589	0.459	0.301 to 0.592	0.460	0.300 to 0.595
SD of residual errors	0.136	0.130 to 0.141	0.136	0.130 to 0.141	0.136	0.130 to 0.141

Blood pressure reduction

Summary BP statistics for the duration of the trial are shown in *Table 21* and BP differences from baseline are shown in *Table 22*. There was an increase in mean SBP in the placebo group from baseline to month 24 (+2.5 mmHg) and a decrease in in mean SBP in both the perindopril (–5.0 mmHg) and amlodipine (–2.8 mmHg) groups from baseline to month 24. There was little change in mean DBP between baseline and month 24 in the placebo group (–0.7 mmHg) but reductions were seen in the perindopril and amlodipine groups (–5.2 mmHg and –3.3 mmHg, respectively). Mean SBP and DBP over the duration of the trial are shown in *Figures 24* and *25*, respectively.

Figures 26–28 show the histograms of change in SBP from baseline to 3, 12 and 24 months, respectively, by randomised group and combined. These histograms show the distribution of the difference in the data between the two specified time points. Negative values indicate a decrease in BP and positive values indicate an increase in BP. The histograms for the placebo group generally follow a normal distribution around zero, whereas reductions in SBP in the perindopril and amlodipine groups are shown by the increased density of bars on the left-hand side of each histogram, particularly at 12 and 24 months. For histograms of the change in SBP from baseline to 6 and 18 months see *Appendix 14*.

TABLE 21 Mean SBP and DBP levels by randomised group at each trial visit

		SBP (mmHg)				DBP (mmHg)			
Visit	*n*	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum
Placebo									
Baseline	79	131.7	12.2	101	152	77.9	7.6	63	95
Month 3	76	132.5	18.0	89	167	77.4	10.0	54	97
Month 6	69	129.8	14.1	104	164	76.5	8.2	55	96
Month 9	64	131.8	13.8	102	161	77.5	8.1	62	96
Month 12	70	132.8	14.7	102	166	77.9	9.4	61	99
Month 15	59	129.6	14.5	96	167	76.7	9.5	58	98
Month 18	59	129.7	15.3	89	169	75.7	9.0	54	100
Month 21	53	131.3	18.3	98	198	76.0	9.9	52	97
Month 24	59	134.7	18.7	95	197	77.3	10.3	58	102
Perindopril									
Baseline	73	130.9	11.5	105	148	76.7	8.0	60	98
Month 3	68	120.4	16.3	85	162	71.0	9.5	47	92
Month 6	62	126.3	17.4	93	182	72.8	9.3	46	93
Month 9	56	122.1	14.8	94	166	72.1	8.7	54	92
Month 12	60	121.4	14.1	85	160	71.0	8.9	44	96
Month 15	49	125.8	18.2	87	172	71.9	8.4	52	88
Month 18	52	120.2	15.2	89	173	69.4	8.2	51	89
Month 21	44	124.0	17.2	93	170	71.8	9.2	51	95
Month 24	53	125.6	17.3	95	169	71.8	10.9	50	102
Amlodipine									
Baseline	72	131.9	13.0	104	155	78.0	7.0	63	93
Month 3	67	127.8	13.5	102	176	74.5	8.0	56	98
Month 6	61	127.4	14.2	98	178	74.7	7.8	59	93
Month 9	56	124.7	16.2	98	166	73.7	8.4	54	92
Month 12	54	124.7	13.9	99	159	73.3	8.2	54	89
Month 15	46	127.0	17.1	97	173	74.0	8.3	59	96
Month 18	49	126.3	13.3	101	156	73.8	7.4	59	94
Month 21	47	125.8	14.4	98	165	72.8	6.5	60	89
Month 24	49	127.9	15.2	107	165	74.2	7.3	60	91

TABLE 21 Mean SBP and DBP levels by randomised group at each trial visit (*continued*)

		SBP (mmHg)				DBP (mmHg)			
Visit	*n*	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum
Total									
Baseline	224	131.5	12.2	101	155	77.5	7.5	60	98
Month 3	211	127.1	16.8	85	176	74.4	9.6	47	98
Month 6	192	127.9	15.2	93	182	74.8	8.5	46	96
Month 9	176	126.5	15.4	94	166	74.6	8.6	54	96
Month 12	184	126.7	15.0	85	166	74.3	9.3	44	99
Month 15	154	127.6	16.5	87	173	74.4	9.0	52	98
Month 18	160	125.6	15.1	89	173	73.1	8.6	51	100
Month 21	144	127.3	16.9	93	198	73.7	8.8	51	97
Month 24	161	129.6	17.6	95	197	74.5	10.0	50	102

TABLE 22 Differences in SBP and DBP from baseline by randomised group and combined

		SBP (mmHg)				DBP (mmHg)			
Visit	*n*	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum
Placebo									
Month 3 – baseline	76	0.8	15.5	–26.5	45.0	–0.6	7.1	–17.5	12.5
Month 6 – baseline	69	–1.9	13.6	–31.5	30.0	–1.7	7.0	–18.5	14.0
Month 12 – baseline	70	0.5	14.3	–33.5	44.5	–0.2	7.3	–22.0	12.5
Month 18 – baseline	59	–1.8	14.2	–34.5	26.0	–2.1	8.4	–21.5	16.5
Month 24 – baseline	59	2.5	16.5	–31.0	69.0	–0.7	7.9	–20.0	19.5
Perindopril									
Month 3 – baseline	68	–11.1	14.2	–420	20.0	–5.9	8.9	–26.5	22.5
Month 6 – baseline	62	–5.7	17.4	–34.0	43.5	–4.5	8.0	–20.5	17.0
Month 12 – baseline	60	–9.5	13.1	–35.0	21.5	–5.8	8.1	–300	22.0
Month 18 – baseline	52	–9.6	14.6	–42.5	38.0	–7.9	7.8	–24.5	15.5
Month 24 – baseline	53	–5.0	16.3	–38.5	38.5	–5.2	10.0	–25.0	23.5
Amlodipine									
Month 3 – baseline	67	–3.7	13.0	–360	23.0	–3.6	8.3	–26.5	13.5
Month 6 – baseline	61	–4.4	14.3	–51.5	290	–3.5	8.1	–25.5	12.0
Month 12 – baseline	54	–6.7	12.0	–37.0	31.0	–4.7	7.5	–24.5	16.0
Month 18 – baseline	49	–5.4	10.6	–28.5	22.5	–4.5	6.7	–17.5	11.0
Month 24 – baseline	49	–2.8	11.7	–24.5	25.5	–3.3	6.3	–18.5	8.5
Total									
Month 3 – baseline	211	–4.5	15.1	–42	45.0	–3.3	8.4	–26.5	22.5
Month 6 – baseline	192	–3.9	15.1	–51.5	43.5	–3.2	7.8	–25.5	170
Month 12 – baseline	184	–4.9	13.9	–37	44.5	–3.4	8.0	–30.0	22.0
Month 18 – baseline	160	–5.4	13.7	–42.5	38.0	–4.7	8.1	–24.5	16.5
Month 24 – baseline	161	–1.6	15.4	–38.5	69.0	–3.0	8.4	–25.0	23.5

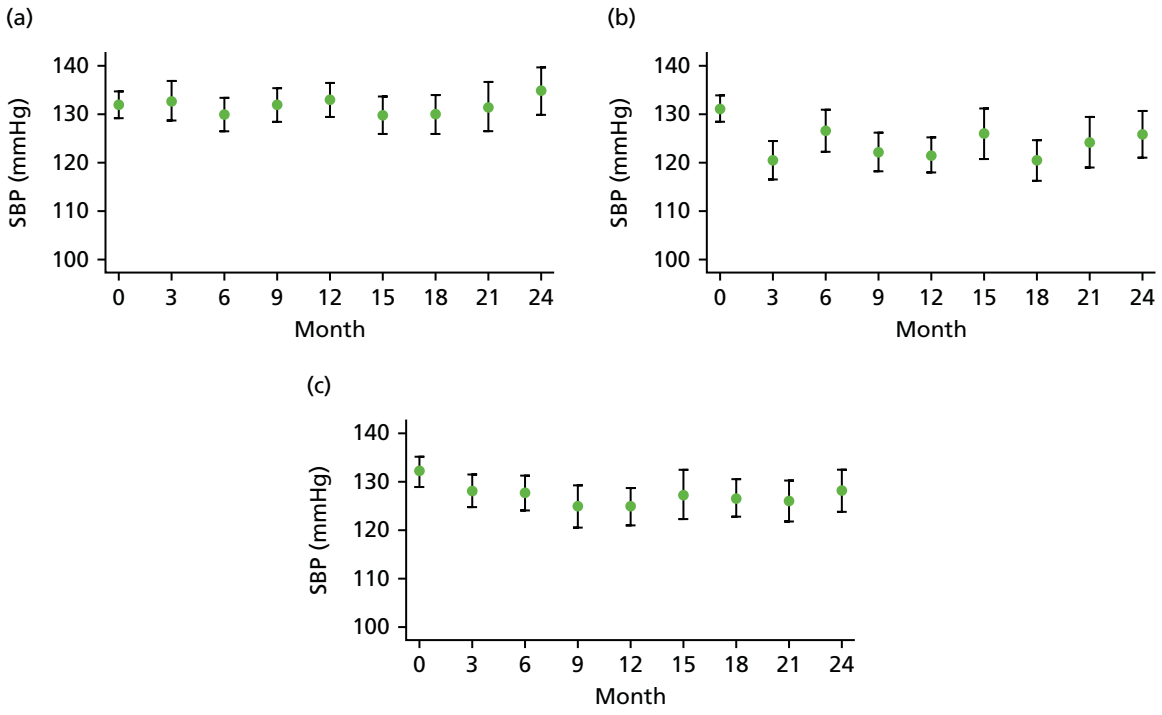


FIGURE 24 Mean SBP over the duration of the trial by randomised group. (a) Placebo; (b) perindopril; and (c) amlodipine. Vertical bars represent the 95% CIs for the means. Reproduced from Bicknell *et al*. 2016.[95]

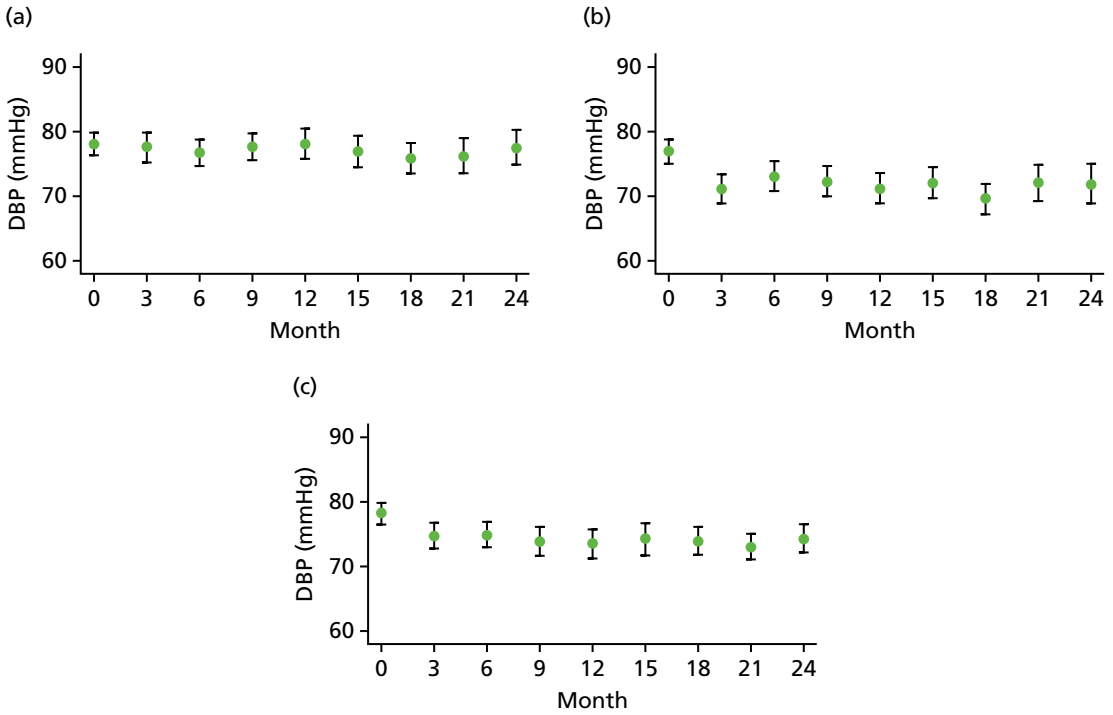


FIGURE 25 Mean DBP over the duration of the trial by randomised group. (a) Placebo; (b) perindopril; and (c) amlodipine. Vertical bars represent the 95% CIs for the means. Reproduced from Bicknell *et al*. 2016.[95]

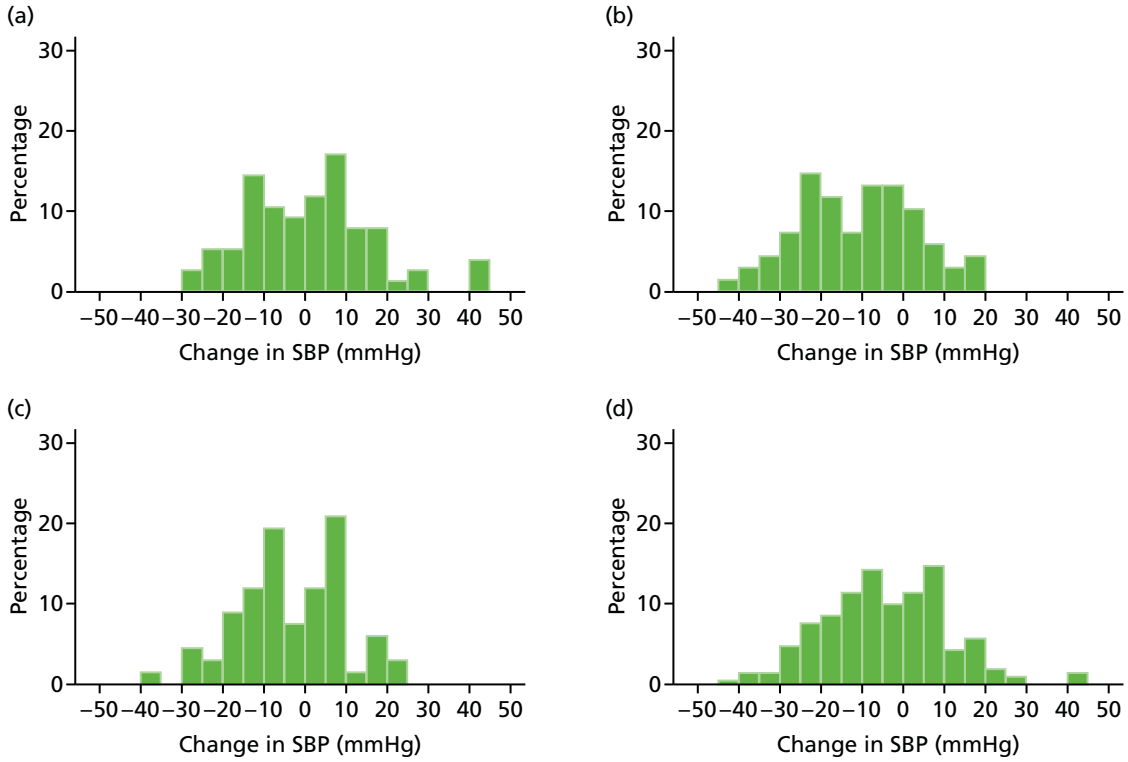


FIGURE 26 Histograms of change in SBP from baseline to month 3. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

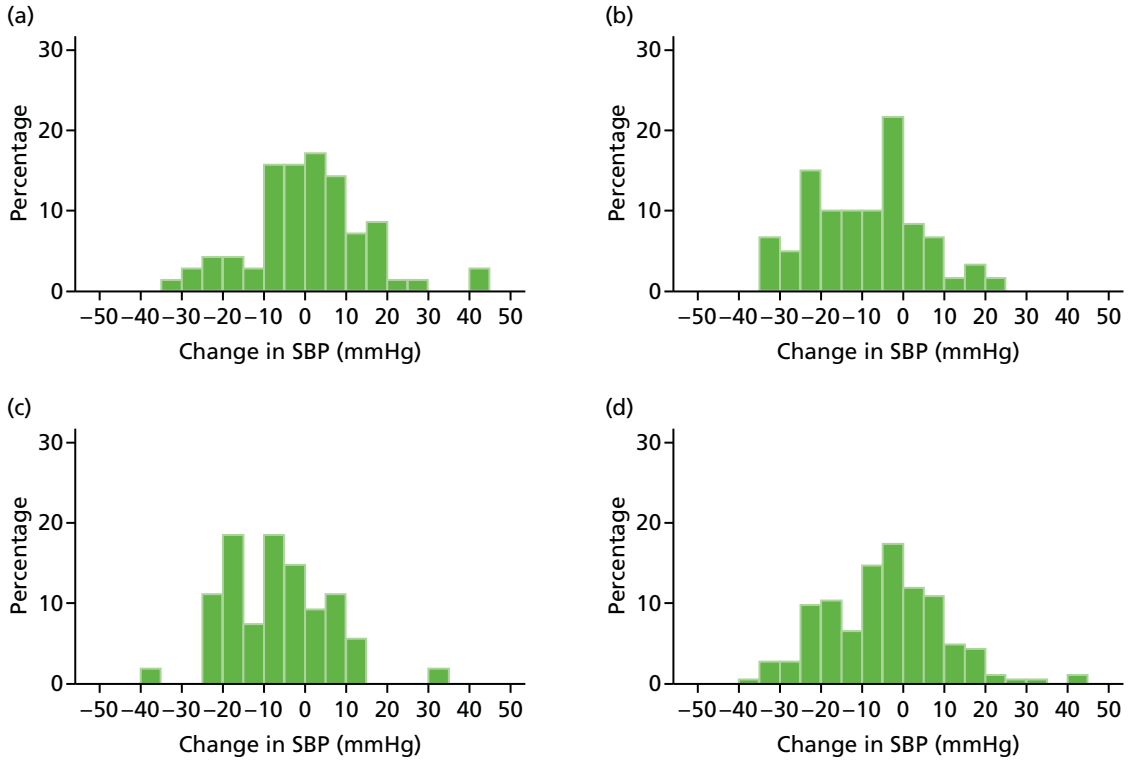


FIGURE 27 Histograms of change in SBP from baseline to month 12. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

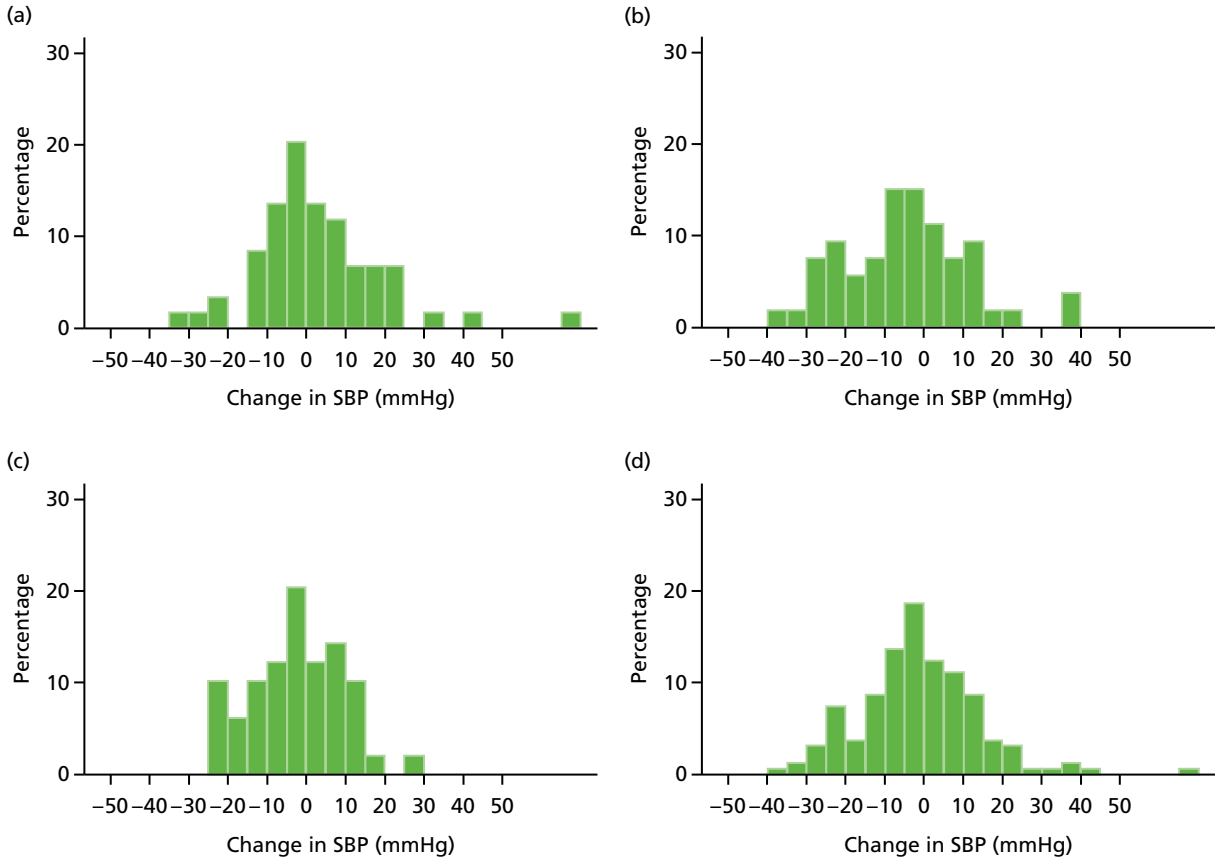


FIGURE 28 Histograms of change in SBP from baseline to month 24. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

Box plots of change in SBP from baseline to 3, 12 and 24 months are shown in *Figures 29–31*, respectively. These show that there was little change in SBP in the placebo group but a reduction in SBP in the perindopril and amlodipine groups. For box plots of change in SBP from baseline to 6 and 18 months see *Appendix 15*.

Figures 32–34 show the histograms of change in DBP from baseline to 3, 12 and 24 months, respectively. In line with the changes seen in SBP, the histograms for the placebo group generally follow a normal distribution, whereas the reductions in DBP in the perindopril and amlodipine group are shown by the increased density of bars to the left-hand side of each histogram. For histograms of change in DBP from baseline to 6 and 18 months see *Appendix 16*.

Box plots of change in DBP from baseline to 3, 12 and 24 months are shown in *Figures 35–37*, respectively. These show that there was little change in DBP in the placebo group but a reduction in DBP in both the perindopril group and the amlodipine group. For the box plots of change in DBP from baseline to 6 and 18 months see *Appendix 17*.

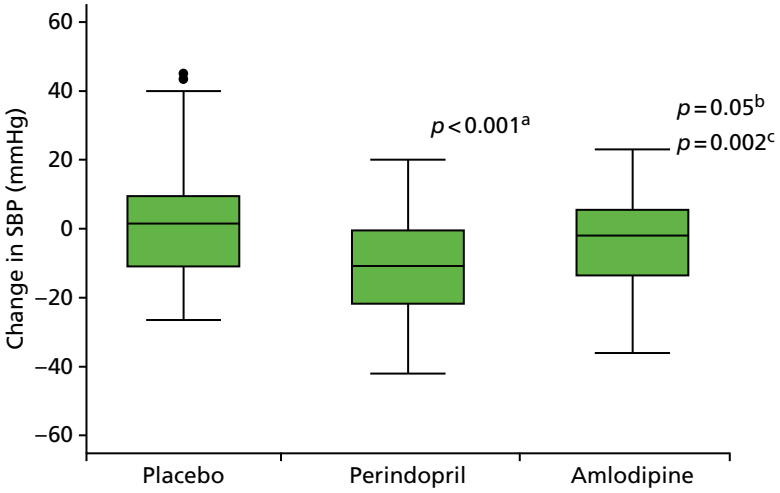


FIGURE 29 Box plot of change in SBP from baseline to month 3. *p*-value from regression of SBP at 3 months on treatment adjusted for SBP at baseline. a, perindopril vs. placebo; b, amlodipine vs. placebo; c, amlodipine vs. perindopril. Circle is outside value. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

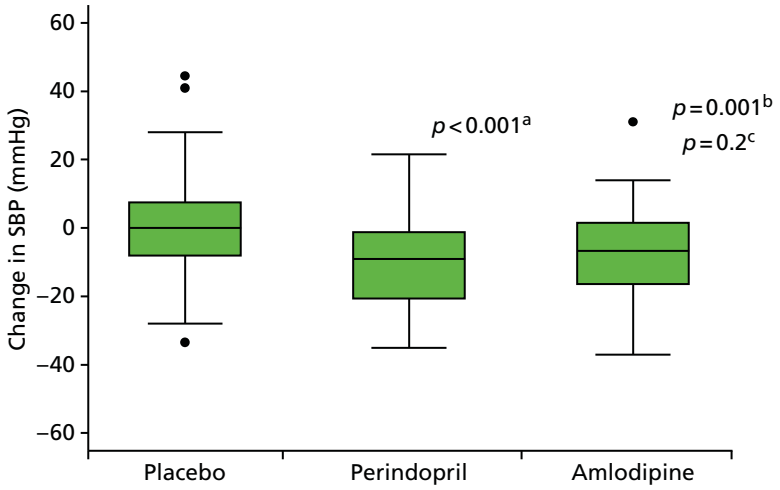


FIGURE 30 Box plot of change in SBP from baseline to month 12. *p*-value from regression of SBP at 3 months on treatment adjusted for SBP at baseline. a, perindopril vs. placebo; b, amlodipine vs. placebo; c, amlodipine vs. perindopril. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

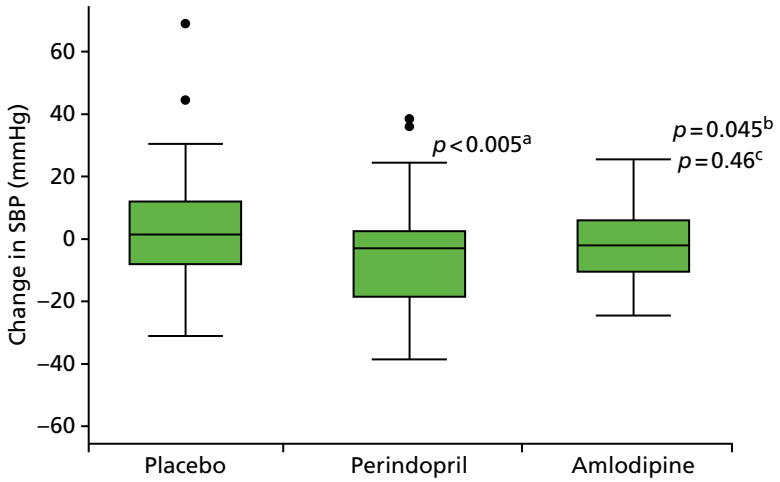


FIGURE 31 Box plot of change in SBP from baseline to month 24. *p*-value from regression of SBP at 3 months on treatment adjusted for SBP at baseline. a, perindopril vs. placebo; b, amlodipine vs. placebo; c, amlodipine vs. perindopril. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

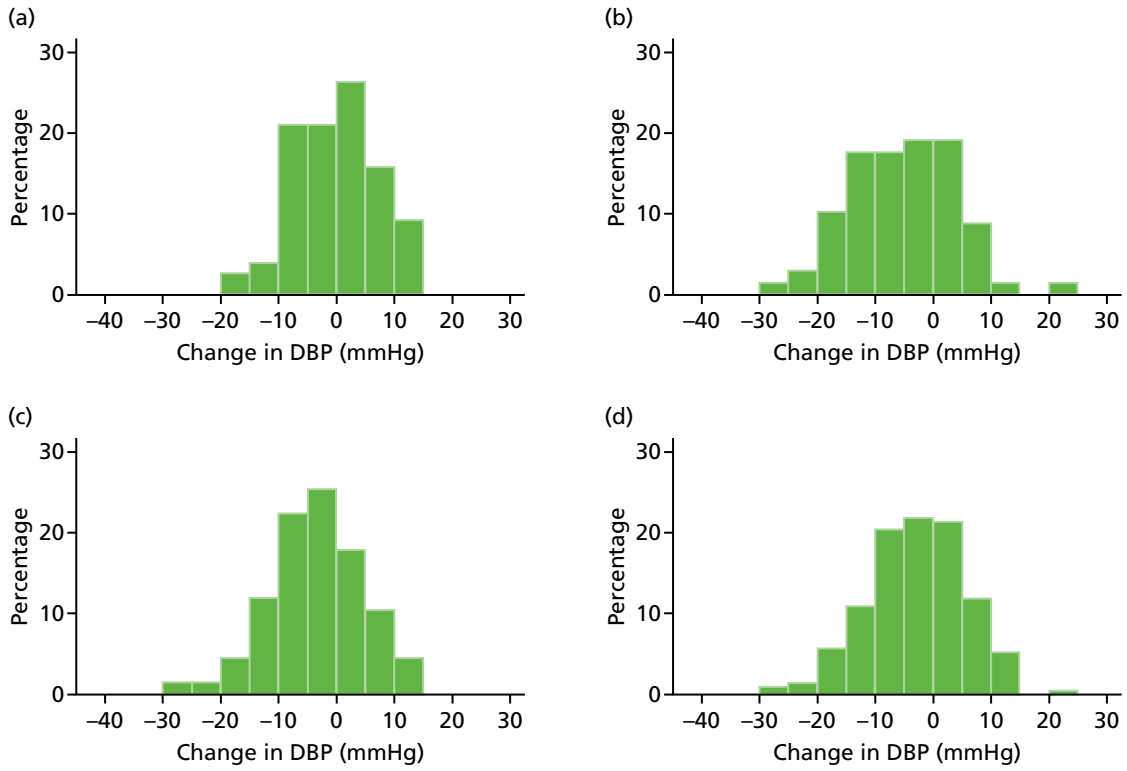


FIGURE 32 Histograms of change in DBP from baseline to month 3. (a) Placebo; (b) perindopril; (c) amlodipine; and and (d) total.

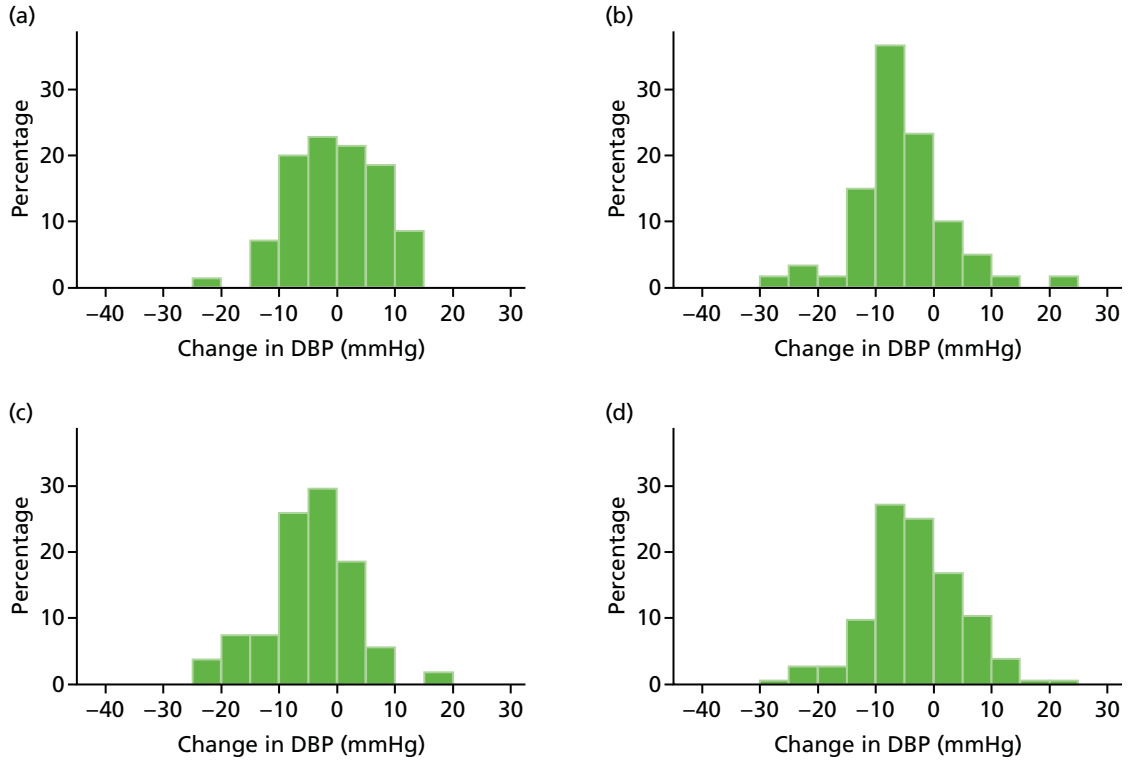


FIGURE 33 Histograms of change in DBP from baseline to month 12. (a) Placebo; (b) perindopril; (c) amlodipine; (d) total.

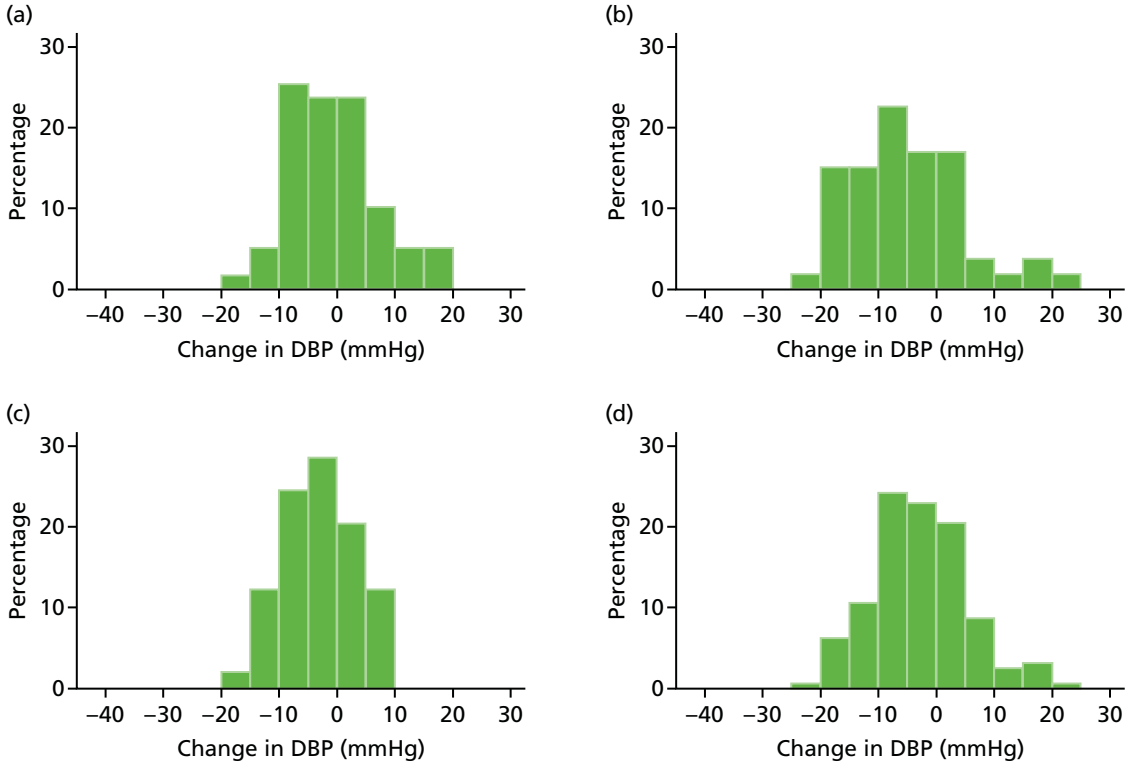


FIGURE 34 Histograms of change in DBP from baseline to month 24. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

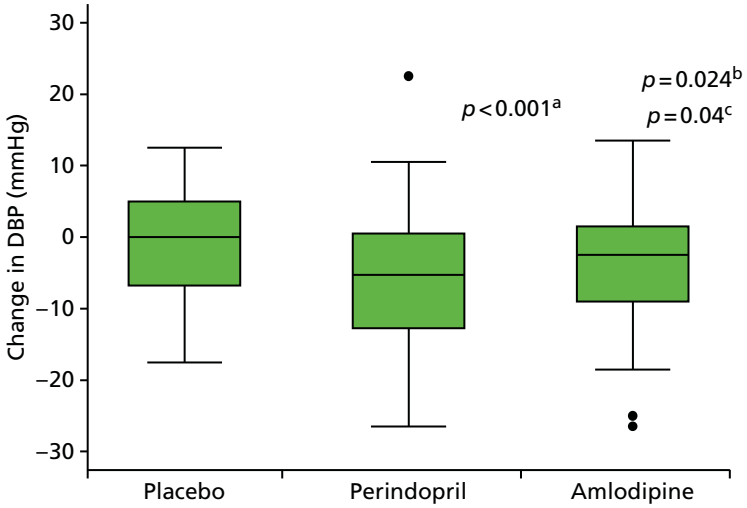


FIGURE 35 Box plot of change in DBP from baseline to month 3. *p*-value from regression of DBP at 3 months on treatment adjusted for DBP at baseline. a, perindopril vs. placebo; b, amlodipine vs. placebo; c, amlodipine vs. perindopril. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

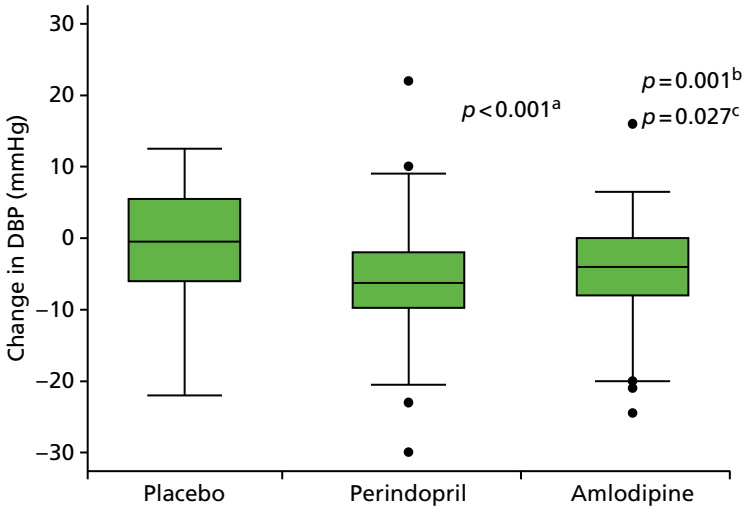


FIGURE 36 Box plot of change in DBP from baseline to month 12. *p*-value from regression of DBP at 3 months on treatment adjusted for DBP at baseline. a, perindopril vs. placebo; b, amlodipine vs. placebo; c, amlodipine vs. perindopril. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

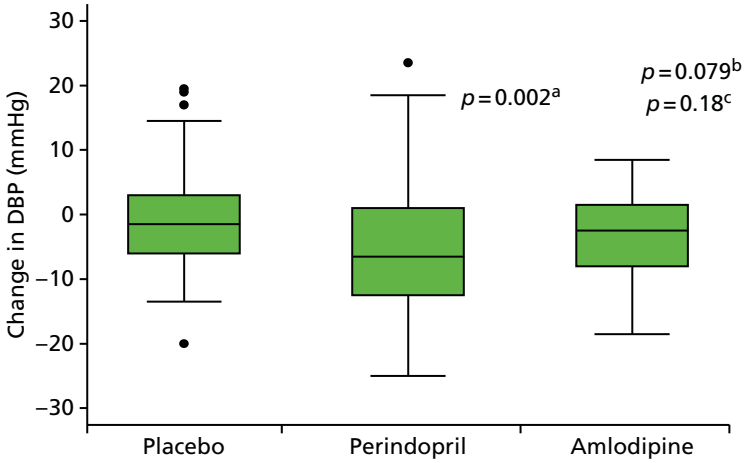


FIGURE 37 Box plot of change in DBP from baseline to month 24. *p*-value from regression of DBP at 3 months on treatment adjusted for DBP at baseline. a, perindopril vs. placebo; b, amlodipine vs. placebo; c, amlodipine vs. perindopril. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

Secondary outcomes

Time to reach an AAA diameter of 5.5 cm, being referred to or having AAA surgery, or AAA rupture

The end points for this analysis were reaching a diameter of 5.5 cm in any of the four measurements (i.e. the first visit when this happened even if the patient continued in follow-up) or having/being referred to surgery. A total of 26 patients reached an AAA diameter of 5.5 cm during the course of the trial, with the same number being referred to/having AAA surgery (*Tables 23* and *24*). There were no AAA ruptures reported. For patients who reached both end points, the date of reaching an AAA diameter of 5.5 cm was used for analysis. Two cases proceeded to surgery before an AAA diameter of 5.5 cm was recorded in-trial and for these two patients the date of surgery was used. No significant differences were found between the three treatment groups for this combined secondary end point (*Figure 38*).

TABLE 23 Numbers of patients reaching study end points by randomised group and combined

Study end point	Placebo	Perindopril	Amlodipine	Total
Reaching 5.5 cm	11	6	9	26
Being referred to or having AAA surgery	9	10	7	26
Combined end point	11	10	11	32
Surgery only	0	4	2	6

TABLE 24 Numbers of patients reaching an AAA diameter of 5.5 cm at each study visit by randomised group and combined

Visit	Placebo	Perindopril	Amlodipine	Total
Baseline	1	0	1	2
Month 3	4	0	1	5
Month 6	0	1	0	1
Month 9	1	1	2	4
Month 12	4	3	2	9
Month 15	0	1	0	1
Month 18	0	0	0	0
Month 21	0	0	1	1
Month 24	1	0	2	3
Total	11	6	9	26

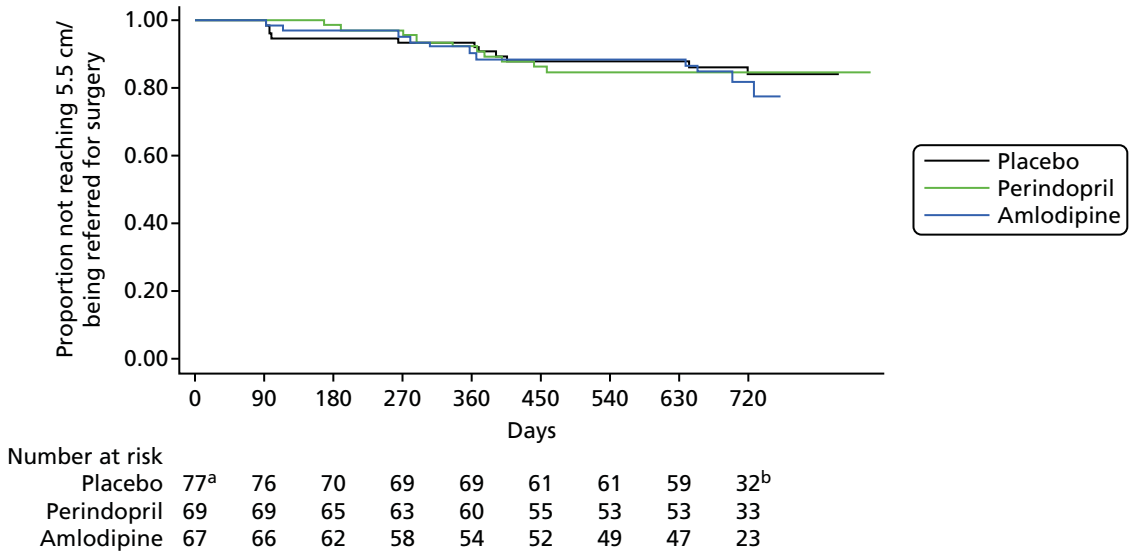


FIGURE 38 Kaplan–Meier estimates of the proportions of patients reaching secondary end points. a, 11 patients randomised are not included as they were seen only at baseline; b, apparent disparity in numbers attending their 24-month visit largely because of this visit occurring before 720 days. Reproduced from Bicknell *et al*. 2016.[95]

Quality-of-life outcomes

The overall EQ-5D scores at 12 and 24 months are shown in *Table 25* (see *Appendix 18* for the scores for each of the five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Overall, mean scores were similar across all three treatment groups at 12 months but a reduction in the mean score from 12 to 24 months was observed in the placebo group (from 71.4 to 64.0), representing a reduction in quality of life. A similar reduction in score was not observed in the perindopril or amlodipine group.

TABLE 25 Overall EQ-5D scores during follow-up by randomised group and combined

Measure	Placebo	Perindopril	Amlodipine	Total
Month 12				
n	69	59	51	179
Mean	71.4	69.6	72.7	71.2
SD	24.1	27.2	24.4	25.1
Median	80	80	80	80
IQR	25	25	20	30
Month 24				
n	56	50	45	151
Mean	64.0	70.2	71.4	68.2
SD	26.9	23.5	26.4	25.7
Median	70.5	75	80	75
IQR	33.5	20	30	25

IQR, interquartile range.

Drug compliance

Compliance was evaluated using pill count data (number dispensed minus number returned) for each time period (*Table 26*). Mean compliance combining all three groups was > 80% for each 3-month period evaluated.

Safety

Adverse events

Both active treatments were generally well tolerated, with similar numbers of patients as in the placebo group discontinuing therapy for AEs ($n = 8$, 13 and 14 for placebo, perindopril and amlodipine, respectively). *Table 27* provides a summary of AEs and SAEs occurring in the trial. Although there were more SAEs in the perindopril group, none of these SAEs was deemed to be related to the study IMP by the PI of the relevant site.

TABLE 26 Compliance (%) based on pill count for each 3-month study period by randomised group and combined

Study period	*n*	Mean	SD	Median	P25	P75	Minimum	Maximum
Placebo								
Baseline to month 3	60	80	15	82	76	88	14	100
Month 3 to month 6	65	75	25	85	71	90	0	100
Month 6 to month 9	61	80	19	85	73	96	26	100
Month 9 to month 12	60	77	20	84	69	90	10	100
Month 12 to month 15	58	81	21	87	78	92	0	100
Month 15 to month 18	47	82	21	88	80	95	1	100
Month 18 to month 21	45	80	26	87	77	96	0	100
Month 21 to month 24	40	82	20	89	76	94	6	100
Perindopril								
Baseline to month 3	56	76	20	80	74	85	0	100
Month 3 to month 6	59	84	16	86	81	96	4	100
Month 6 to month 9	51	82	18	88	73	96	4	100
Month 9 to month 12	45	78	22	85	75	91	20	100
Month 12 to month 15	44	79	25	87	78	94	12	100
Month 15 to month 18	38	76	27	87	75	91	0	99
Month 18 to month 21	37	85	14	89	78	94	26	100
Month 21 to month 24	32	84	20	90	81	94	12	100
Amlodipine								
Baseline to month 3	60	75	19	77	71	84	1	100
Month 3 to month 6	59	80	18	81	74	91	0	100
Month 6 to month 9	50	75	22	81	71	89	12	100
Month 9 to month 12	48	72	25	82	70	89	0	96
Month 12 to month 15	43	73	30	84	75	90	3	100
Month 15 to month 18	40	84	11	85	77	93	58	100
Month 18 to month 21	37	82	20	89	84	93	3	100
Month 21 to month 24	31	81	23	89	75	94	0	100
Total								
Baseline to month 3	176	77	18	80	74	86	0	100
Month 3 to month 6	183	80	20	85	74	92	0	100
Month 6 to month 9	162	79	20	84	73	93	4	100
Month 9 to month 12	153	75	22	83	71	90	0	100
Month 12 to month 15	145	78	25	86	77	92	0	100
Month 15 to month 18	125	81	21	87	77	92	0	100
Month 18 to month 21	119	82	21	88	78	94	0	100
Month 21 to month 24	103	82	21	89	78	94	0	100

P25, 25th percentile; P75, 75th percentile.

TABLE 27 Summary of AEs

	Events				Patients[a]				Patients[b]			
AEs and SAEs	Placebo	Perindopril	Amlodipine	Total	Placebo	Perindopril	Amlodipine	Total	Placebo	Perindopril	Amlodipine	Total
Number of AEs	175	137	103	415	54	55	36	145	54	55	36	145
Number permanently discontinued	8	13	14	35	8	9	9	26	8	9	9	26
Number of SAEs	23	33	17	73	16	19	12	47	16	19	12	47
SAEs related to study (definite or probable)	0	0	2	2	0	0	2	2	0	0	2	2
Reason defined as a SAE												
Death	3	2	2	7	3	2	2	7	3	2	2	7
Life-threatening	1	0	1	2	1	0	1	2	1	0	1	2
Hospitalisation required	17	28	11	56	11	17	8	36	10	16	7	33
Other important medical events	2	3	3	8	2	3	3	8	2	1	2	5

a Subjects are shown only once in each category but may have AEs in more than one category.
b Subjects are shown only once for their 'worst' category.

Serum creatinine

Table 28 and *Figure 39* show the distribution of serum creatinine levels at 3, 12 and 24 months for the three treatment arms and combined. *Table 29* shows the serum creatinine differences between each of the study visits and screening. As expected, there was little difference in mean serum creatinine levels in the placebo and amlodipine groups across the duration of the trial but a small increase was observed in the perindopril group (6% at 3 months). However, this increase was not statistically significant and no patients were withdrawn from the trial because of concerns regarding renal function.

TABLE 28 Serum creatinine levels (μmol/l) at screening and 3, 12 and 24 months by randomised group and combined

Visit	*n*	Mean	SD	Median	P25	P75	Minimum	Maximum
Placebo								
Screening	73	86.6	20.5	79	73	96	56	154
Month 3	72	87.5	19.7	84	72	100	56	153
Month 12	63	88.2	19.8	85	73	99	55	154
Month 24	52	85.5	16.5	83	74	97	58	126
Perindopril								
Screening	69	87.0	18.7	86	75	95	54	156
Month 3	66	92.1	19.1	88	78	101	66	169
Month 12	54	93.0	21.9	89	75	105	64	161
Month 24	49	90.3	20.7	86	75	101	53	137
Amlodipine								
Screening	67	90.0	20.0	87	78	96	55	178
Month 3	64	90.0	20.3	88	74	100	61	161
Month 12	50	90.3	18.8	87	78	96	54	136
Month 24	43	89.8	18.7	89	75	95	65	143
Total								
Screening	209	87.8	19.7	86	75	96	54	178
Month 3	202	89.8	19.7	87	76	100	56	169
Month 12	167	90.4	20.2	87	77	100	54	161
Month 24	144	88.4	18.7	85	75	98	53	143

P25, 25th percentile; P75, 75th percentile.

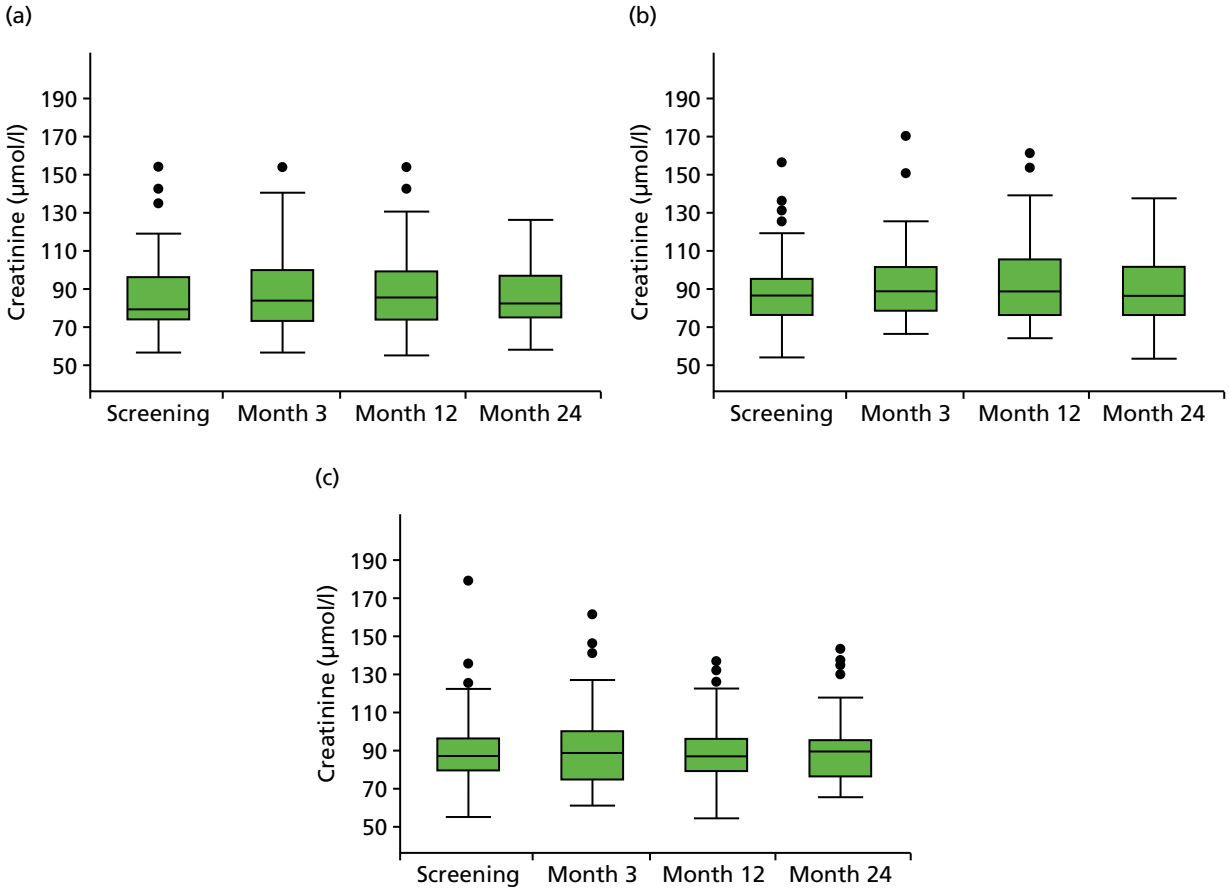


FIGURE 39 Median serum creatinine levels at screening and 3, 12 and 24 months by randomised group. (a) Placebo; (b) perindopril; and (c) amlopidine. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

TABLE 29 Differences in mean serum creatinine levels (µmol/l) by randomised group at 3, 12 and 24 months compared with screening levels

Study period	*n*	Mean	SD	Median	P25	P75	Minimum	Maximum
Placebo								
Month 3 – screening	67	0.6	12.9	0	–4	5	–64	49
Month 12 – screening	61	0.5	14.6	1	–5	6	–61	30
Month 24 – screening	50	–0.4	13.4	–1	–7	8	–51	31
Perindopril								
Month 3 – screening	62	5.6	10.4	4	–1	11	–9	54
Month 12 – screening	51	4.8	10.6	4	–2	10	–19	37
Month 24 – screening	47	3.8	11.2	1	–4	11	–17	44
Amlodipine								
Month 3 – screening	60	–0.3	10.3	–1	–7	6	–23	35
Month 12 – screening	46	1.7	11.5	1	–4	6	–21	49
Month 24 – screening	41	–0.1	8.2	–2	–5	6	–18	18

P25, 25th percentile; P75, 75th percentile.

Chapter 5 Discussion

The AARDVARK trial was designed to evaluate whether or not ACE inhibition induces a beneficial effect on the growth of small AAAs. This trial has shown that 2 years of daily ingestion of the ACE-I perindopril has no impact on the growth rate of small AAAs (the primary end point of the trial) compared with that observed among those randomised to the CCB amlodipine or placebo.

In keeping with this lack of any differential effect on AAA growth among the three randomised treatment arms of the trial, there was also no difference between the groups in the numbers of trial participants whose AAA reached a diameter of 5.5 cm and/or who were referred for/received surgical intervention for their AAA (26 patients), which was a secondary end point of the trial. No ruptures were reported in the study, confirming the safety of a policy of ultrasound surveillance for small AAAs.

Taking into account various sources of data collated during the trial, including three QA events at which trial sonographers and AAA patient volunteers attended, it was clear that, as expected, AAA measurements collected in the longitudinal plane were more repeatable than those collected in the transverse plane and that, overall, OTO measurements were superior to ITI measurements in terms of interobserver repeatability. Hence, for the primary analyses of this trial, OTO measurements in the longitudinal plane were used.

Serum creatinine levels as well as other potential AEs were monitored closely in the study. Although a small and expected increase in creatinine levels was seen in the perindopril group, trial withdrawals because of study drug-related AEs were similar among the three groups. As expected, no suspected unexpected serious adverse reactions were reported during the trial, consistent with the established safety profiles of ACE-Is and CCBs. Compliance with therapy was excellent in all three treatment arms.

The trial was designed to generate equivalent BP reduction in the two actively treated groups, based on previously published data[73–75] and the knowledge that ACE-Is tend to be less effective than CCBs in terms of BP lowering among the older age group included in the trial.[45]

Both actively treated groups had lower in-trial BPs than those on placebo; however, somewhat surprisingly, BP lowering was greater among those randomised to perindopril than among those receiving amlodipine. Nevertheless, had there been a BP-related benefit in terms of AAA growth rather than a drug class-related effect, such a BP-related effect could have been detected in this trial. However, no differential effects on AAA growth were apparent across the three groups, BP related or otherwise.

Although data are inconsistent, ACE-Is have been associated with a reduced incidence of AAA rupture in analyses of administrative databases.[6,70] Evidence for the benefit of other antihypertensive agents has been lacking,[6] suggesting that ACE-Is may act through a BP-independent mechanism; however, it is important to note that analyses of administrative databases are subject to the caveats and shortcomings of observational data.

Meanwhile, evidence implicating the RAS in aortic aneurysm formation and growth in animal models has been reported.[67,68,96,97] For example, infusion of angiotensin II induces suprarenal post-dissection aneurysm formation in animal models and continued infusion has been shown to cause pathological changes in the aneurysmal tissue including infiltration of macrophages and disruption of elastin in the medial layer.[98] The discrepancies between animal and human studies may reflect the challenges of conducting RCTs in AAA patients, including accurately measuring AAA growth and bias in patient recruitment, but may more likely reflect differential associations and physiology across species or differences in the pathology of these aneurysms between humans and artificial animal models.

Strengths

To our knowledge this study is unique in being the only placebo-controlled RCT to have completed an evaluation of the impact of ACE-Is on the growth rate of small AAAs. However, two other RCTs of the ARBs valsartan (NCT01904981) and telmisartan[99] are currently in progress. Interestingly, the large Canadian case–control study[6] that reported the protective effects of ACE-Is on the rupture of AAAs did not show similar benefits for ARBs.

Although a significant proportion of trial participants did not complete 2 years of follow-up in the AARDVARK trial because of reaching a censoring trial end point (e.g. referral for surgical intervention or death), the great majority continued regular follow-up and the overall attrition rate was only 6% (which was less than the target attrition rate of 10% used in power calculations). Hence, 94% of patients did contribute at least two sequential AAA measurements to facilitate an evaluation of growth.

Drug compliance among attendees was excellent as evaluated by pill counts and data collection was efficient with only a small number of key measurements or investigations (e.g. BP levels) missing in the trial overall.

The trial included a system for quality control. The standardised procedures used for AAA measurements as outlined in the scanning protocol were designed to reduce measurement variability associated with using 19 sonographers from 11 sites. This protocol was taught at specifically designed QA days. Image quality was also robustly assessed and sites with poor-quality scans were reassessed. Lastly, the measurements taken for all time points were audited by the trial senior clinical vascular scientist and, when obvious differences between measurements in the same subject at the same time point existed, a review took place.

Limitations

The profile of the trial participants – largely white men aged ≥ 55 years with a heavy smoking history – is typical of that for UK patients with an AAA but this should be set in the context of those ineligible for the trial or who did not take part (see *Figures 11* and *12*). Indeed, the limitations of the AARDVARK trial include the potentially restricted generalisability of the trial recruits. Trial inclusion and exclusion criteria predetermined that, although the overall profile of the recruits might at first sight be considered typical of patients from the UK with an AAA, the age range was limited to ≥ 55 years and SBP had to be < 150 mmHg.

Furthermore, it is clear from *Figure 11* that most patients considered for the trial were already taking an antihypertensive agent that made them ineligible. Allied with the other reasons why patients declined to join the trial (see *Figure 12*), it is reasonable to assume that the trial population may not be representative of the true AAA population in the UK as a whole. This conclusion is supported by the mean SBP and DBP levels recorded in other AAA studies (see *Table 2*), with SBP levels ranging from 143 to 157 mmHg and DBP levels ranging from 81 to 91 mmHg. These levels appear to be significantly higher than the mean BPs found at baseline in all three treatment arms in the AARDVARK trial (131.7/77.9 mmHg, 130.9/76.7 mmHg and 131.9/78.0 mmHg for placebo, perindopril and amlodipine, respectively).

At a more global level, the findings of a study predominantly including UK-based white men may clearly not be generalisable to non-UK populations, women or those of different ethnicities.

The doses of ACE-I and CCB chosen for the trial were expected to cause similar reductions in BP;[73–75] however, this was not found to be the case. Although both treatments were effective in lowering BP, the mean differences in SBP from baseline to 24 months in the perindopril and amlodipine groups were –5.0 (SD 16.3) mmHg and –2.8 (SD 11.7) mmHg, respectively, compared with 2.5 (SD 16.5) mmHg in the

placebo group. With similar withdrawal rates observed among the three treatment groups and no differences in relation to compliance, the reason for the difference in BP reduction between the perindopril group and the amlodipine group remains unclear. Although ACE-Is are known to be particularly effective in treating hypertension in patients with renal artery stenosis, patients with known renal artery stenosis of > 50% were excluded from the trial. However, no further investigations were undertaken to explore or exclude lesser degrees of renal artery stenosis in the trial population, making it difficult to draw any further conclusions about the observed BP differences in relation to the role of renal artery stenosis.

A potentially crucial limitation of the AARDVARK trial relates to the statistical power. To calculate the sample size of the trial we estimated that the trial would have 90% power at the 5% level to detect a 38% (1-mm) difference in growth rate between those receiving perindopril and those on placebo. This was based on an estimated annual growth in AAA diameter of 2.6 (SD 1.8) mm, as reported in the UKSAT trial.[22] However, given the actual average annual growth rate observed of 1.7 (SD 3.0) mm, 190 patients per group would have been required to detect a 1-mm difference in growth with a power of 90%. Based on the actual sample size (75 per group), we had 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). However, our estimated difference in the slopes of regression between perindopril and placebo was 0.08 mm with a 95% CI of –0.50 mm to 0.65 mm, which statistically excludes a likely reduction of 1 mm. This implies that an important clinical difference in growth rate of small AAAs is unlikely to occur in this population in association with the use of perindopril compared with placebo.

Given the very small changes in AAA size that were expected over the 2-year follow-up period, numerous quality control measures were put in place to obtain accurate AAA measurements. Furthermore, sites were requested to have the same observer scanning the same patient on the same machine for the duration of the study. All sites reported that they adhered to this request to the greatest extent possible, bearing in mind clinical service pressures and staffing changes. Despite this, the mean (range) intrasonographer repeatability coefficient was 0.33 (0.21–0.45) cm for OTO measurements. Although ultrasonography is a cost-effective tool for the identification of AAAs and sufficient to direct clinical management of patients, the accuracy of measurements made in a RCT becomes critical because of its high operator dependence. During the site initiation visits for the trial it became clear that the routine methods for taking ultrasound measurements varied among sites. Despite the protocol and training that were provided for the trial, unfamiliarity with taking some of the AAA measurements required by the trial may explain the greater than expected range in measurement variability.

The greater than expected intra- and inter-observer variability and measurement error add uncertainty to the interpretation of the results. For future studies involving observers at multiple sites it would be pertinent to undertake detailed and practical training sessions prior to the recruitment of patients. Furthermore, measurement variability might be reduced by using more accurate methods of obtaining images, such as performing an electrocardiogram simultaneously with recording ultrasound videos, allowing for electrocardiogram gating in the reading process.[100,101]

Chapter 6 Conclusions

We were unable to demonstrate any impact of an ACE-I compared with placebo or a CCB on the growth rate of small AAAs over a 2-year period. Furthermore, a decrease in BP achieved among those allocated to active BP-lowering therapy was not associated with a reduction in AAA growth rate compared with those allocated to placebo. However, because of the small AAA growth rates observed, as well as the greater than expected AAA measurement variability (including measurement error), the trial had only 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). Nevertheless, our estimated difference in slope between those receiving perindopril and those receiving placebo was 0.08 mm, with a 95% CI of –0.50 mm to 0.65 mm, which statistically excludes a likely reduction of 1 mm. Hence, at least in this type of population with relatively well-controlled BP, modest BP reduction with a CCB or an ACE-I offers no obvious benefits in terms of reducing the growth of small AAAs and this trial was unable to show any indication of any BP-independent beneficial effect on the growth of small AAAs of an ACE-I over placebo or a CCB or a combination of placebo and a CCB.

Implications for health care

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

Recommendations for future research

The results of this pilot trial do not provide strong support for a larger trial to evaluate the effects of ACE-Is on small AAA growth rate.

Other than the apparently negative findings of the trial (albeit with some caveats around the issue of power), the large and increasing numbers of elderly patients with an AAA already receiving some form of RAS blockade (the most common cause of ineligibility for this trial) would make randomisation to an ACE-I or an ARB significantly more difficult, with associated concerns about the generalisability of the findings of any such trial. Nevertheless, patients recruited through the NAAASP were less likely to be already receiving a RAS blocker than those already in a vascular database and could therefore offset some of those concerns.

Patients considered unfit for surgery but with an AAA of larger diameter than those included in the AARDVARK trial may, by virtue of their larger AAA growth rates, provide a further source of eligible patients for a more powerful evaluation of medical interventions with regard to AAA size and/or rupture.

Importantly, whichever groups of patients are included in future trials of AAA, strict protocols around ultrasound measurements and training of trial staff are critical if AAA measurements are key outcomes.

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

- Further work related to the data already collected in the AARDVARK trial:
  - A multivariate analysis of determinants of AAA growth in the AARDVARK trial.
  - Potential differences were observed between the three treatment groups in relation to the number 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 BPs and BP variability with regard to AAA growth rates.

- Further work potentially arising from the AARDVARK trial:
  - An evaluation of currently available data regarding AAA growth rates in those with SBP of < 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 are 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.

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Ms Gaia Kiru (Trial Manager) contributed to the design of the study, the day-to-day management and delivery of the trial and interpretation of the results, and was the principal author responsible for the writing and delivery of the final report.

Mr Colin Bicknell (Vascular Surgeon and coinvestigator) contributed his expertise to the design of the study, recruitment, interpretation of the trial findings, and writing and delivery of the final report.

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Professor Neil Poulter (Professor of Preventative Cardiovascular Medicine and chief investigator) contributed his expertise to the design of the study, recruitment, interpretation of the trial findings and writing and delivery of the final report, and held overall oversight and responsibility for the study.

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Data sharing statement

Requests for available data can be made by contacting the corresponding author.

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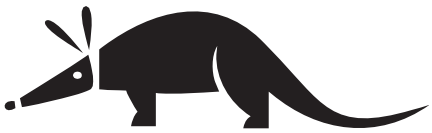
Appendix 1 Patient information sheet and informed consent form

PATIENT INFORMATION SHEET AND CONSENT FORM

An evaluation of the effect of an angiotensin-converting enzyme (ACE) inhibitor on the growth rate of small abdominal aortic aneurysms	Eudract number **:** 2010-020226-17 Ethics ref : 10/H0711/80 Sponsors ref : CRO 1644



AARDVARK

Aortic Aneurysm Regression of Dilation: Value of ACE inhibitors on RisK

This patient information sheet is in two parts. **Part A** is a summary of the AARDVARK study. **Part B** gives more detailed information on the study and administration issues. Please read both sections before making your final decision.

PART A

Invitation

You are being invited to take part in a research trial. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it if you wish with family, friends or your doctor. Do ask the research doctor or nurse if there is anything that is not clear or if you would like more information. Take as much time as you need to decide whether or not you wish to take part. Thank you for reading this.

If you agree to take part, you will be asked to fill out, sign and date this information sheet and consent form and to keep it as a useful reference on trial details and personal contacts

WHAT IS THE PURPOSE OF THE TRIAL?

You have a condition known as an abdominal aortic aneurysm**.** An abdominal aortic aneurysm is a balloon-like swelling of the main blood vessel of the body (the aorta) as it runs through the abdomen. The normal diameter of the abdominal aorta is approximately 1.8cm or about three quarters of an inch in diameter. Small aneurysms grow slowly and do not appear to cause problems until the diameter exceeds 2-3 times the diameter of the normal aorta (about 5.5cm or more than 2 inches in size).

When the aneurysm is small it is safer to monitor using regular ultrasound scanning - an ultrasound scan is a painless test that uses sound waves to create images of organs and structures inside your body. If the aneurysm reaches a large size (usually over 5.5cm), repair with an operation is recommended to avoid the serious problem of bursting: Causing significant internal bleeding (aneurysm rupture).

It is important to find treatments that help prevent an aneurysm enlarging.

One trial has shown that the use of a specific type of drug, angiotensin converting enzyme (ACE) inhibitors, which are usually used to treat high blood pressure, may reduce the risk of bursting (rupture) of large aneurysms. Therefore it has been suggested that ACE inhibitors also might slow the growth of small aneurysms. It is not clear whether these drugs, ACE inhibitors, would have their effect by reducing blood pressure or by acting directly on the aneurysm or both.

This trial will assess whether an ACE inhibitor drug called perindopril will reduce the growth rate of small aneurysms. It will also assess whether a small reduction in blood pressure levels with any drug also could reduce the growth rate of these aneurysms.

WHY HAVE I BEEN CHOSEN?

You have been asked to take part in this trial as you have an aortic aneurysm of a small size that is currently being monitored using ultrasound scans.

DO I HAVE TO TAKE PART?

It is up to you to decide if you want to take part in the research or not.

If you decide to take part you are still free to stop being in the trial and withdraw your consent at any time. In this case, your research doctor may ask you why you want to withdraw but you do not have to give a reason. You may also decide at any time that you no longer want to take the trial tablet. In such case, you can stop taking the trial drug but continue in the trial and the trial team will collect information on your health until the end of the trial.

If you agree to take part, your GP will be told that you have agreed to take part in the trial and, with your permission, will be told about the trial and the treatments you may be taking. He/she will be asked for some additional medical details about you. We may also need to contact other doctors or specialists who look after your medical care.

If you decide not to take part, the care you receive will not be affected in any way.

WHAT WILL HAPPEN TO ME IF I TAKE PART? / WHAT DO I HAVE TO DO?

Each patient in this trial must take part for a 2-year period. There are likely to be 225 patients similar to you in this trial.

You will first undergo a screening visit. At this visit we will check whether you are suitable for the study. If your blood pressure is found to be raised, we will suggest some treatment for this. We will then invite you back after 6 weeks to check if your blood pressure has lowered.

If you proceed into the study, you will be asked to take half a tablet for the first two weeks (you will be provided with a pill-cutter) and one tablet each day from then onwards.

This tablet could contain the ACE inhibitor called perindopril (10mg), or another drug used to treat blood pressure called amlodipine (5mgs) or a placebo (dummy) pill.

It will be decided randomly (like the toss of a coin) if you receive the placebo or one of the blood pressure medicines so you have a one in three chance or receiving each of the medications.

This is a blinded trial which means you will not know which treatment you are receiving, although, if your research doctor needs to find out, he/she can quickly do so. Neither the trial doctor nor you may choose which treatment you receive.

To assess the effects of these drugs we will:

- Monitor your aneurysm growth by a series of ultrasound scans at either 3 or 6monthly intervals. Please speak to your study team in regards to the frequency of your visits.
- At least once a year your scans will be performed by a specialist scanner
- Measure your blood pressure at every visit.
- Collect blood samples at screening, 3 month, 12 month and 24 month visits. These samples are to check that your kidney function is normal. Approximately 1 teaspoon of blood will be collected these visits.
- Ask you to complete questionnaires to assess quality of life and other health care resources used (for conditions unrelated to your aneurysm) at the end of each year.

Each follow up visit to the hospital (every 3 or 6 months) will take approximately 30 minutes although your initial visit could take up to one hour. After this first visit you will be informed of the aneurysm size and blood pressure from your visit. There will be no need for you to attend your GP for extra visits unless any of our tests show that you may need other treatment or tests.

Reasonable travel expenses for attending a trial visit will be paid to you and you should discuss this with the trial team.

All the costs of the trial (medicines, visits and tests) will be provided for by the trial funder. Your research doctor will be compensated for his/her time and resources given to the trial however, your research doctor will not be paid for his/her involvement in the trial.

So long as you continue to take part, you will be required to:

- Attend the scheduled visits organised by your research doctor and nurses.
- You should take the trial drug as instructed by your trial doctor or research staff.
- At each visit you should bring all unused medicines and any empty medicine boxes with you.
- Bring a written list of all your medications to each visit.
- You will not have to limit your normal lifestyle or activities while you are part of the trial.
- Your GP will continue looking after you in the usual way. It is important that you tell your research doctor about any other medicine you are taking before starting the trial, because some of them may prevent you from joining the trial.
- Should you start taking a new medicine during the trial, you must tell your research doctor or nurse straight away in order to check if it can be taken safely with the trial treatment. This includes any medicines prescribed by your GP or specialist or those you may have bought yourself even herbal products or food supplements.
- You should tell your trial doctor or trial staff about any medical problems, doctor visits, hospital visits, or medical procedures that you have while you are in the trial.
- It would be a good idea to mark in your diary card details of any hospital or GP appointments with notes of any medication changes.
- You will be given a contact card with details of the trial. You should carry this card with you at all times and should you need to be admitted to hospital make sure that the hospital is aware that you are taking part in this trial so that they may contact your

trial team. If you experience any serious health problems such as a heart attack or a stroke, your trial doctor must be informed immediately.

- You should not take part in any other research trial whilst you are in this trial

POSSIBLE BENEFITS OF TAKING PART IN THE TRIAL

Your part in the trial may provide important information and allow doctors to learn more about the trial drugs and treating abdominal aortic aneurysms. During this trial you will get physical exams and your health

will be monitored. If this trial demonstrates a decreased growth rate of aneurysms for patients taking ACE inhibitor drugs, patients that have the same condition as you may significantly benefit from this trial after the resulted have been determined and made public.

For patients with very small aneurysms less than 4.5 cm (or 1.8 inches) in diameter there will be an increased frequency of ultrasound examinations over and above what is normally offered in the NHS, but benefits of more regular scans may include earlier detection of rapidly growing aneurysms or detection of aneurysms that have reached a size that requires treatment.

ARE THERE ANY SIDE EFFECTS FROM THE DRUGS USED IN THIS TRIAL?

The active drugs in this trial are small doses, expected to lower the blood pressure by a small amount (about 6mm of mercury). They should not cause any untoward effects, but in the case of side effects you should contact the trial centre or other medical help as soon as possible for advice.

Common side effects (ie. those that are experienced in 1-10% of patients) specific to each drug that may be experienced are noted below. A full list of the side effects is available in the appendix of this information sheet. Investigation of any of symptoms you experience may be discussed with the study medical team.

Drug	Side Effects
Perindopril (ACE inhibitor)	• Cough - If the cough is intolerable you will be told to stop the drug and you will be switched to another blood pressure drug called losartan which has a lower incidence of cough. You can continue on the trial receiving this drug. • Hypotension (low blood pressure) • Gastro-intestinal problems (nausea, vomiting, indigestion, diarrhoea, constipation, abdominal pain)

	• Allergic symptoms – rash, runny nose, nasal congestion, sore throat • Headaches • Muscle cramps • Vision disturbance • Tinnitus (ringing in the ears)
Amlodipine (Calcium channel blocker)	• Headache • Ankle swelling • Dizziness • Abdominal pain • Nausea • Tiredness • Flushing
Losartan	• Dizziness • Vertigo • High potassium levels in the blood

ALTERNATIVE TREATMENTS

At present there are no treatments used routinely to try to prevent the enlargement of aneurysms. However, it is thought however that stopping smoking and treating high blood pressure and raised blood fats are all beneficial. We will contact your GP so he may give you treatment to lower your cholesterol (blood fats). This is likely to be with a medication called a statin.

ARE THERE ANY SIDE EFFECTS FROM REGULAR ULTRASOUND SCANS?

The ultrasound examinations do not cause any harm. Ultrasound scans are simple, pain-free, non-invasive tests that can image the aneurysm and measure the size and, by comparing to previous scans, measure the growth rate. The test is very quick and will take 10-20 minutes. We will ask you to eat a small meal only before the scan, as large meals can lead to excess gas in the gut and obscure the aneurysm from view.

It is likely that you will have had an ultrasound scan previously for the diagnosis or monitoring of your aneurysm. This ultrasound examination will not be noticeably different to previous scans.

We will ask you, as part of this trial to undergo ultrasound scans at 3 or 6monthly intervals (slightly more frequently than many hospitals ask the majority of patients to undergo scans). Following this scan we will give you the results and you will have the chance to ask any questions.

BLOOD TESTS may sometimes cause some bruising and discomfort.

WHAT WILL HAPPEN IF MY ANEURYSM GROWS TO A SIZE THAT NEEDS INTERVENTION?

Your GP and vascular surgeon will be informed immediately and options for aneurysm repair will be discussed with you. If you proceed to have an aneurysm repair, we will not ask you to attend any further appointments as part of this trial and the drug treatment may be stopped.

PART B

WHO IS THE SPONSOR OF THE TRIAL?

This research is funded by the National Institute of Health Research. There is no funding from any industrial or pharmaceutical company. The research is organised and sponsored by the Imperial College. Your local hospital will be compensated for the work performed and services used at your local hospital. This trial will be co-ordinated from the Imperial College Clinical Trials Unit, London, and take place at hospitals and AAA screening centres in and around London and Coventry.

WHAT HAPPENS WHEN THE RESEARCH TRIAL STOPS?

At the end of the trial you will be informed which of the treatment arms you were assigned to. Further drug treatment will not be available from the trial centre but your GP will be notified and you may request to continue the medication. We shall tell you the results of the trial as soon as possible. Regular examination of your aneurysm will continue at your local aneurysm follow up clinic.

WHAT IF NEW RELEVANT INFORMATION BECOMES AVAILABLE?

Sometimes we get new information about the treatment being studied. If this happens, your trial doctor will tell you and discuss whether you should continue in the trial. If you decide not to carry on, your trial doctor will make arrangements for your care to continue (aneurysm surveillance). If you decide to continue in the trial he may ask you to sign an agreement outlining the discussion. If the trial is stopped for any other reason, we will tell you and arrange your continuing care (aneurysm surveillance).

WILL MY GENERAL PRACTITIONER BE INFORMED?

Your GP (or other health care practitioner) will be notified of your participation. We will seek consent for this. We will, in turn, notify your GP (or other health care practitioner) of any other problems that occur as a

result of this trial. You will be informed of the measurements of blood pressure and aneurysm size after each visit. If the aneurysm grows to a significant size during the trial period, your GP (and vascular surgeon) will be notified urgently.

WHO HAS REVIEWED THE TRIAL?

The trial has been reviewed by the Imperial Clinical Trials Unit at Imperial College and by the Health Technology Assessment group of the National Institute of Health Research. All human research is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This trial has been reviewed and received favourable opinion by a Research Ethics Committee.

WITHDRAWING CONSENT FROM THE TRIAL

Your participation in this trial is voluntary. You can choose at any time to ***withdraw*** your consent for this trial (take yourself out of this trial). Your decision will not affect your ability to receive medical care for your disease. You will not lose any rights or benefits to which you are otherwise entitled.

For the purpose of this trial, the sponsor and its agents and representatives (including the trial doctor, institution and its representatives) reserves the right to verify your survival status by way of your medical records, public records or contacting your physician or the named alternate contact person(s) if the law permits.

WHAT IF THERE IS A PROBLEM?

Imperial College London holds insurance policies which apply to this study. If you experience serious and enduring harm or injury as a result of taking part in this study, you may be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator (Insert name and contact details). The normal National Health Service complaint complaints mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial AHSC Joint Research Office.

WILL MY TAKING PART IN THE TRIAL BE KEPT CONFIDENTIAL?

If you agree to take part in the research, all personal information collected during the trial will be kept strictly confidential. It will be used only for the research and for submission to Regulatory Authorities in a way so they will not be able to identify you.

Your medical records and other personal information created during the trial may be looked at by representatives of the sponsor, people working on behalf of the sponsor such as monitors of the trial, members of the ethics committee, and from regulatory authorities and auditors to check the research is being carried out correctly.

Any information from your medical records will always be kept strictly confidential.

All information about you which leaves your research doctor's site will not be able to be traced back to you. Any transfer of this information will be done according to the rules and regulations protecting personal information.

With your agreement, your research doctor will inform your general practitioner or other medical practitioners who may be treating you of your participation in the trial

You will be allowed to have a look at your personal information to check it is correct. If you wish to do so, you should ask your research doctor**.**

You will only be told details of which specific medicine you had been taking once the trial is over and when the results are ready.

If you decide to leave the trial early, any information collected on you up to that point will still be used.

You have the right to check the accuracy of data held about you and correct any errors.

Procedures for handling, processing, storage and destruction of information about you are compliant with the Data Protection Act 1998.

Information about you will be kept for 15 years after the end of the trial, and will be disposed of securely after this time.

THE RESULTS OF THE TRIAL

The results from this trial may be published in medical journals or used in scientific reports, but your name or any other confidential information will never appear.

You may have a copy of the results should you wish. You will need to speak to your research doctor about this at the time.

Finally, you will be told which type of medicine you have been taking.

You should note that you would not be identified in any report/publication unless you have given your written consent.

THE ETHICS COMMITTEE BELOW HAS APPROVED THE PROTOCOL

The Ethics Committee of West London REC 2 has given a favourable opinion to the trial on 14th February 2011

CONTACTS AT SITE

Should you have questions about the trial or the trial products, or in the case of an emergency please contact:

Research Doctor	
Research Nurse	
Address and telephone	
Emergency contact number	

Full list of side effects

Drug	Side effects
Perindopril (ACE inhibitor)	Common (affecting 1- 10% of people who take this drug) : • Cough - If the cough is intolerable you will be told to stop the drug and you will be switched to another blood pressure drug called losartan which has a lower incidence of cough. You can continue on the trial receiving this drug. • Hypotension (low blood pressure) • Gastro-intestinal problems (nausea, vomiting, indigestion, diarrhoea, constipation, abdominal pain) • Allergic symptoms – rash, runny nose, nasal congestion, sore throat • Headaches and dizziness • Muscle cramps • Vision disturbance • Tinnitus (ringing in the ears) Less common (affecting less than 1% of people): Mood or sleep disturbances. Acute swelling of the throat and face. Inflammation of the pancreas which could cause pain in your abdomen. Inflammation of the liver and jaundice have been reported. Altered blood levels of liver tests, other chemicals in the blood, lowering of white cells and anaemia have occurred in patients taking this group of drugs.
Amlodipine (Calcium channel blocker)	Common (affecting 1- 10% of people who take this drug): • Headache • Ankle swelling • Dizziness • Abdominal pain

	• Nausea • Tiredness • Flushing Less common (affecting less than 1% of people): Gastro-intestinal disturbances, dry mouth, taste disturbances, low blood pressure, faintness, chest pain, shortness of breath, rhinitis, mood changes, general weakness, tremor, pins and needles, disturbances when passing urine, impotence, breast swelling, weight changes, muscle pains and cramps, back pain, joint pain, visual disturbances, ringing in the ears, skin irritation, rashes, sweating, hair loss and skin discolouration.
Losartan	Common (affecting 1- 10% of people who take this drug): • Dizziness • Vertigo • High potassium levels in the blood Less common (affecting less than 1% of people): Gastro-intestinal disturbances, chest pain, palpitation, general swelling, shortness of breath, headache, sleep disorders, skin rash with irritation and swelling.

Study Title	**An evaluation of the effect of an angiotensin-converting enzyme (ACE) inhibitor on the growth rate of small abdominal aortic aneurysms**		
Subject #		*Site #*	
Name of Research Doctor			

Please **initial** box if you agree with the following:

I, ***(forename and surname)***

freely agree to take part in the study. ☐

- I have been given the Patient Information Final 8 dated 01/07/2012 to read as well as a full explanation by . . . . . of the aims, the procedures and possible risks of the study. I was able to ask him / her questions regarding all areas of the study and these questions have been answered to my satisfaction. I have been given the name of a person to contact if I have any questions during the study. ☐
- I have had sufficient time to think about taking part and I agree to cooperate with the research team. I will inform them immediately if I have any problems. ☐
- I understand that I am free to leave the study at any time, if I want to without having to give a reason and that my decision will not affect the standard of care I receive. ☐
- I understand my identity will never be disclosed and any information collected will remain confidential. I agree that my medical records and other personal data generated during the study may be examined by representatives of the sponsor and by people working on behalf of the sponsor, members of the Ethics Committee and by representatives of regulatory authorities. I agree that I will not seek to restrict the use to which the results of the study may be put. ☐
- I agree to my GP being informed of my participation in the study ☐

Participant/Legal Representative	**Person responsible for collecting the informed consent**
Date:	*Date:*
Signature:	*Signature:*

Name:	*Name:*

Give one signed original information and consent form to the participant and keep the other signed original in the study file.

Study Title	**An evaluation of the effect of an angiotensin-converting enzyme (ACE) inhibitor on the growth rate of small abdominal aortic aneurysms**		
Subject #		*Site #*	
Name of Research Doctor			

Please **initial** box if you agree with the following:

I, ***(forename and surname)***

freely agree to take part in the study. ☐

- I have been given the Patient Information Final 8 dated 01/07/2012 to read as well as a full explanation by . . . . . of the aims, the procedures and possible risks of the study. I was able to ask him / her questions regarding all areas of the study and these questions have been answered to my satisfaction. I have been given the name of a person to contact if I have any questions during the study. ☐
- I have had sufficient time to think about taking part and I agree to cooperate with the research team. I will inform them immediately if I have any problems. ☐
- I understand that I am free to leave the study at any time, if I want to without having to give a reason and that my decision will not affect the standard of care I receive. ☐
- I understand my identity will never be disclosed and any information collected will remain confidential. I agree that my medical records and other personal data generated during the study may be examined by representatives of the sponsor and by people working on behalf of the sponsor, members of the Ethics Committee and by representatives of regulatory authorities. I agree that I will not seek to restrict the use to which the results of the study may be put. ☐
- I agree to my GP being informed of my participation in the study ☐

Participant/Legal Representative	**Person responsible for collecting the informed consent**

Date: *Signature:* *Name:*	*Date:* *Signature:* *Name:*

Give one signed original information and consent form to the participant and keep the other signed original in the study file.

Appendix 2 The European Quality of Life-5 Dimensions questionnaire

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

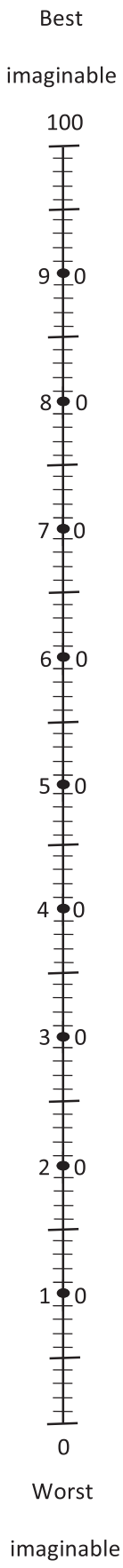
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state



Appendix 3 Health resource use questionnaire

QUESTIONNAIRE ON USE OF HEALTH SERVICES DURING THE AARDVARK TRIAL

We would be grateful if you would take a few minutes to answer the following questions about services you may have used since you enrolled in the AARDVARK trial on

Please insert date of enrolment here and where requested on each page. ☐☐ ☐☐ ☐☐

Please only provide information since this date.

☐☐ ☐☐ ☐☐

Section A (Questions 1-5) is about services you may have used because of your aneurysm.

Section B (Questions 6) is about services you may have used for other health reasons.

Date of completion: ☐☐ ☐☐ ☐☐

HOW TO FILL IN THE QUESTIONNAIRE

Most questions can be answered by ticking the box next to the answer that applies to you. Please tick one box only for each question.

Example:

Since you enrolled in the AARDVARK trial for have you had further hospital treatment of your aneurysm, by either a doctor or nurse?

Yes ☑ No ☐

If **yes**, where was this?

Name of Hospital: e.g. West Middlesex

If **yes**, did you an operation?

Yes ☐ No ☑

Example:

How many appointments have you had with the doctor or nurse at an outpatient's department because of your aneurysm?

	Who?	**How many times?**	**OR if you can't remember the exact number of times tick one of the following boxes**
1	A doctor		**1 or 2** ☐ **3 or 4** ☐ **5 or more** ☐
2	A nurse or similar		**1 or 2** ☐ **3 or 4** ☐ **5 or more** ☐

Services used since your enrolment in the AARDVARK trial on

☐☐ ☐☐ ☐☐

Section A: Service use for reasons related to your aneurysm

1.1 Have you had further hospital treatment of your aneurysm?

Yes ☐ No ☐

(If no, go to question 1.3)

1.2A If **yes**, where was this? Name of Hospital: _____

1.2B If **yes**, did you have a different type of scan (not ultrasound) to image your aneurysm?

Yes ☐ No ☐

1.2C If **yes**, did you have an operation?

Yes ☐ No ☐

1.2D How many appointments have you had with the doctor or nurse at an outpatients department because of your aneurysm?

	Who?	How many times?	OR if you can't remember the exact number of times tick one of the following boxes		
1	**A doctor**		**0** ☐	**1 or 2** ☐	**3 or more** ☐
2	**A nurse or similar**		**0** ☐	**1 or 2** ☐	**3 or more** ☐

1.3 Have you seen your GP because of your aneurysm?

Yes ☐ No ☐ (if no go to question 2 about Social Services)

1.4 If **yes**, how many times have you seen the GP?

Exact number of times	**OR if you can't remember the exact number of times tick one of the following boxes**
____time(s)	**1 or 2** ☐ **3 or 4** ☐ **5 or more** ☐

2 Use of social services

2.1 Have you seen a social worker for reasons related to your aneurysm since

☐☐ ☐☐ ☐☐

(enrolment)

Yes ☐ No ☐

2.2 If **yes**, how many times?

Exact number of times	**OR if you can't remember the exact number of times tick one of the following boxes**
____time(s)	**1 or 2** ☐ **3 or 4** ☐ **5 or more** ☐

2.3 Has a home carer (someone from social services who comes to assist with cleaning and feeding) visited you since

☐☐ ☐☐ ☐☐

*<please relevant insert date here >

Yes ☐ No ☐

2.4 If **yes**, how often have has the home carer visited you?

Once a day ☐ 1 – 2 times a week ☐

Once a month ☐ Other (please specify) _____

2.5 For how many weeks have you had a home carer?

Exact number of weeks	**OR if you can't remember exactly how many weeks tick one of the following boxes**
____weeks	**1-3 weeks** ☐ **4-7 weeks** ☐ **8-12 weeks** ☐

2.6 Did you have a home carer before *<please relevant insert date here >?

Yes ☐ No ☐

3 Input from patients and carers

3.1 Have you had to leave paid employment because of your aneurysm?

Yes ☐ No ☐

3.2 Have you had to take time off work because of your aneurysm?

Yes ☐ No ☐

3.3 If **yes**, how many days?

Exact number of days	**OR if you can't remember the exact number of days tick one of the following boxes**
_____days	**1-5 days** ☐ **6-10 days** ☐ **more than 10 days** ☐

3.4 Have any of your friends or relatives had to have time off work for reasons relating to your aneurysm?

Yes ☐ No ☐

3.5 If **yes**, how many days?

Exact number of days	**OR if you can't remember the exact number of days tick one of the following boxes**
____days	**1-5 days** ☐ **5-10 days** ☐ **more than 10 days** ☐

3.6 Do any of your family or friends help you with feeding, washing or dressing?

Yes ☐ No ☐

3.7 If **yes**, on average for how many hours a day?

Exact number of hours	**OR if you can't remember the exact number of hours tick one of the following boxes**
____hours	**2 hours or less** ☐ **3 to 5 hours** ☐ **More than 5 hours** ☐

Section B: Service use for reasons *not related* to your aneurysm

4.1 Have you had hospital treatment by either a **doctor or nurse** for **anything other** than your aneurysm (examples might include breathing problems, skin rashes, chest pain, constipation etc) since

date of enrollment ? ☐☐ ☐☐ ☐☐

Yes ☐ No ☐

4.2 If **yes**, where was this?

Name of Hospital:_____

4.3 If **yes**, what was the treatment for?

_____

4.4 How many appointments have you had with the doctor or nurse at an outpatients department for reasons *unrelated* to your aneurysm?

Who?	**How many times?**	**OR if you can't remember the exact number of times tick one of the following boxes**
A doctor		**1 or 2** ☐ **3 or 4** ☐ **5 or more** ☐
A nurse		**1 or 2** ☐ **3 or 4** ☐ **5 or more** ☐

4.5 Have you seen your GP for reasons *unrelated* to your aneurysm?

Yes ☐ No ☐

4.6 If yes, how many times have you seen the GP for reasons *unrelated* to your aneurysm?

Exact number of times	**OR if you can't remember the exact number of times tick one of the following boxes**
____times	**1 or 2** ☐ **3 or 4** ☐ **5 or more** ☐

Many thanks for your help.

Appendix 4 Data collection forms

AARDVARK: Screening Visit Worksheet

Screening ID: _____

Date of visit: _____

Informed consent form completed? Yes ☐ No ☐

(If No, please ensure that the patient has consented to the trial/completed a consent form before continuing with the screening visit)

Inclusion/Exclusion Checklist

Inclusion	
Is the patient willing and able to give written informed consent?	Yes ☐ No ☐
Is the patient aged at least 55 years?	Yes ☐ No ☐
Does the patient have an AAA 3 to 5.4 cm in diameter by internal or external measurement according to ultrasound?	Yes ☐ No ☐
Does the patient have a systolic BP <150mmHg?	Yes ☐ No ☐
Exclusion	
Is the patients already required to take either an ACE-inhibitor or a calcium channel blocker or Angiotensin II blocker (ARB) and cannot be converted to diuretic therapy and/or a 5mg dose of amlodipine for control (i.e. SBP < 150mmHg) of their BP?	Yes ☐ No ☐
Does the patient have known renal artery stenosis (>50%), or with a serum creatinine of >180µmol/L	Yes ☐ No ☐
Is the patient unable to give informed consent	Yes ☐ No ☐
Is the patient too frail to travel for 3-monthly surveillance?	Yes ☐ No ☐
Does the patient have any clinically significant medical condition which, in the opinion of the investigator, may interfere with the study results and or reduce life expectancy to < 2 years	Yes ☐ No ☐
Has the patient participated in another trial of an investigational product or device within the previous 30 days?	Yes ☐ No ☐

Does the patient have a known allergy or sensitivity to perindopril or amlodipine?	Yes ☐	No ☐
Is the patient unable or unwilling to comply with the requirements of the study, in the opinion of the investigator?	Yes ☐	No ☐

Completed by: _____ _____

Name **Signature**

Vital Signs & AAA measurement

BP machine used: Omron ☐ (please photocopy the printout of the BP results)

Pulsecor ☐ (please save the measurements onto a computer)

Time	Pulse	BP measurement 1 (mmHg)	BP measurement 2 (mmHg)	BP measurement 3 (mmHg)
		/	/	/

Is the patient receiving statins?	Yes ☐	No ☐
Has the patient been prescribed indapamide at this visit?	Yes ☐	No ☐
Does this patient require referral to GP for hypertension?	Yes ☐	No ☐
Will this patient be attending a 6wk rescreening?	Yes ☐	No ☐
AAA LONGDITUDINAL internal diameter		cm
AAA LONGDITUDINAL external diameter		cm
AAA TRANSVERSE internal diameter		cm
AAA TRANSVERSE external diameter		cm

Note - Please record the AAA measurements from the previous clinical scan above rather than the AAA measurements obtained for the baseline visit. At least one of these measurements must be entered.

6 week re-screen **N/A** ☐

Date:_____

Time	BP measurement 1 (mmHg)	BP measurement 2 (mmHg)	BP measurement 3 (mmHg)
	/	/	/
Is the patient suitable to continue in the trial based on their BP? (systolic BP < 150mmHg)			Yes ☐ No ☐

Screening ID: _____

General Medical History

Does subject have any clinically relevant past or current medical history conditions? Yes ☐
No ☐

If yes, please complete table below:

Diagnosis	Date of diagnosis (dd/mm/yyyy)	Status (if past, please record end date)	End date (dd/mm/yyyy)
		☐ Ongoing ☐ Past	
		☐ Ongoing ☐ Past	
		☐ Ongoing ☐ Past	
		☐ Ongoing ☐ Past	
		☐ Ongoing ☐ Past	
		☐ Ongoing ☐ Past	
		☐ Ongoing ☐ Past	
		☐ Ongoing	

		☐ Past	
		☐ Ongoing ☐ Past	

Smoking and Alcohol History

Current smoker	Yes ☐ No ☐ If yes, no. of cigarettes per day: _____ If yes, no. of years smoking: _____
Past smoker	Yes ☐ No ☐ If yes, approx. date of stopping : _____ If yes, no. of cigarettes per day: _____ If yes, no. of years smoking: _____
Units of alcohol per week	

Screening ID: _____

Height and Weight

Date of measurements: _____

Time of measurements: _____

Weight (kg)	Height (cm)

Demographics

Date of birth: _____

Age:_____

Ethnicity:	☐ White ☐ Black or Black British specify: _____ ☐ Asian or Asian British specify: _____ ☐ Other, specify: _____

Blood Sample

Date: _____

Was sample taken for **creatinine?**

Yes ☐ Result: _____umol/L No ☐ Reason:
_____

Was sample taken for **electrolytes?**

Yes ☐ No ☐ Reason:
_____

ALL results **signed** and dated by doctor? Yes ☐ No ☐

Concomitant Medication

Does the patient currently take any concomitant medication? Yes ☐ No ☐

(If Yes, please complete the concomitant medication log)

Screening completed by:

_____ _____ _____

Name **Signature** **Date**

AARDVARK Worksheet : Randomisation Visit (Month 0)

Patient ID: _____

Date of visit: _____

Inclusion/Exclusion criteria reviewed: Yes ☐ No ☐ Reason:

_____

Informed consent reviewed: Yes ☐ No ☐ Reason:

_____

Current medical therapies reviewed: Yes ☐ No ☐ Reason:

_____

Screening bloods reviewed: Yes ☐ No ☐ Reason:

_____

Vital Signs & AAA measurement

Time	Pulse	BP measurement 1 (mmHg)	BP measurement 2 (mmHg)	BP measurement 3 (mmHg)
		/	/	/

AAA LONGDITUDINAL internal diameter	cm
AAA LONGDITUDINAL external diameter	cm
AAA TRANSVERSE internal diameter	cm
AAA TRANSVERSE external diameter	cm

Patient randomised via InForm to bottle: _____

(attach print screen to this page)

Patient seen by: _____

Signature: _____

AARDVARK Worksheet : Month 3

Patient ID: _____

Date of visit: _____

Has the patient experienced any adverse events? Yes ☐ No ☐

If yes, please complete an adverse event form.

Has there been any change to the patient's concomitant medications? Yes ☐ No ☐

If yes, please update the concomitant medications form.

Vital Signs & AAA measurement

Time	Pulse	BP measurement 1 (mmHg)	BP measurement 2 (mmHg)	BP measurement 3 (mmHg)
		/	/	/

AAA LONGDITUDINAL internal diameter	cm
AAA LONGDITUDINAL external diameter	cm
AAA TRANSVERSE internal diameter	cm
AAA TRANSVERSE external diameter	cm

Blood Sample

Was sample taken for creatinine & electrolytes?

Yes ☐ Time: _____ No ☐ Reason: _____

Results reviewed and signed by doctor? Yes ☐ No ☐

Confirmation of bottle dispensed: _____

Visit conducted by: _____

Signature: _____

AARDVARK Worksheet : Months 6, 9, 15, 18, 21

Patient ID: _____

Date of visit: _____

Which month is this? : 6 ☐ 9 ☐ 15 ☐ 18 ☐ 21 ☐

Has the patient experienced any adverse events? Yes ☐ No ☐

If yes, please complete an adverse event form

Has there been any change to the patient's concomitant medications? Yes ☐

No ☐

If yes, please update the concomitant medications form

Vital Signs & AAA measurement

Time	Pulse	BP measurement 1 (mmHg)	BP measurement 2 (mmHg)	BP measurement 3 (mmHg)
		/	/	/

AAA LONGDITUDINAL internal diameter	cm
AAA LONGDITUDINAL external diameter	cm
AAA TRANSVERSE internal diameter	cm
AAA TRANSVERSE external diameter	cm

Confirmation of bottle dispensed: _____

Visit conducted by: _____

Signature: _____

AARDVARK Worksheet : Months 12 & 24

Patient ID: _____

Date of visit: _____

Which month is this? : 12 ☐ 24 ☐

Has the patient experienced any adverse events? Yes ☐ No ☐

If yes, please complete an adverse event form

Has there been any change to the patient's concomitant medications? Yes ☐ No ☐

If yes, please update the concomitant medications form

Vital Signs & AAA measurement

Time	Pulse	BP measurement 1 (mmHg)	BP measurement 2 (mmHg)	BP measurement 3 (mmHg)
		/	/	/

AAA LONGDITUDINAL internal diameter	cm
AAA LONGDITUDINAL external diameter	cm
AAA TRANSVERSE internal diameter	cm
AAA TRANSVERSE external diameter	cm

Blood Sample

Was sample taken for creatinine & electrolytes?

Yes ☐ Time: _____ No ☐ Reason: _____

Results reviewed and signed by doctor? Yes ☐ No ☐

Weight (kg)

Questionnaires

Was the EuroQoL questionnaire completed by the patient? Yes ☐ No ☐

If No, reason: _____

Was the Health Resources questionnaire completed by the patient? Yes ☐ No ☐

If No, reason: _____

Confirmation of bottle dispensed: _____ **(12 MONTH VISIT ONLY)**

Visit conducted by: _____

Signature: _____

Appendix 5 Transverse abdominal aortic aneurysm diameter tables

TABLE 30 Abdominal aortic aneurysm diameter in the transverse plane: summary data by randomised group and combined at each trial visit

	Transverse internal diameter (cm)					Transverse external diameter (cm)				
Visit	*n*	Mean	SD	Minimum	Maximum	*n*	Mean	SD	Minimum	Maximum
Placebo										
Baseline	78	3.65	0.69	2.29	5.28	79	4.05	0.68	3.00	5.64
Month 3	74	3.74	0.72	2.52	5.40	74	4.12	0.72	3.03	6.07
Month 6	68	3.80	0.66	2.63	5.50	67	4.17	0.64	3.07	5.80
Month 9	62	3.77	0.68	2.59	5.30	62	4.12	0.67	3.08	5.60
Month 12	69	3.78	0.64	2.66	5.46	68	4.15	0.65	3.00	5.55
Month 15	57	3.80	0.68	2.47	5.41	57	4.14	0.68	3.06	5.90
Month 18	60	3.84	0.64	2.56	5.28	60	4.19	0.66	3.07	5.72
Month 21	52	3.85	0.63	2.75	5.28	52	4.18	0.67	3.03	5.95
Month 24	56	3.80	0.63	2.52	5.38	56	4.13	0.62	3.07	5.57
Perindopril										
Baseline	71	3.68	0.68	2.39	5.17	73	4.09	0.65	3.08	5.39
Month 3	65	3.67	0.66	2.20	4.99	65	4.09	0.66	3.05	5.41
Month 6	61	3.70	0.70	2.43	5.23	61	4.12	0.73	3.05	5.90
Month 9	56	3.72	0.69	2.29	5.29	56	4.10	0.67	3.07	5.64
Month 12	60	3.80	0.70	2.50	5.47	60	4.14	0.72	3.03	6.07
Month 15	47	3.73	0.69	2.46	5.42	47	4.09	0.67	3.06	5.74
Month 18	49	3.77	0.61	2.59	5.50	49	4.10	0.64	3.03	5.83
Month 21	44	3.78	0.65	2.42	5.73	43	4.09	0.70	3.09	6.03
Month 24	52	3.73	0.58	2.42	5.13	52	4.04	0.58	3.03	5.42
Amlodipine										
Baseline	69	3.61	0.70	2.20	4.92	72	4.04	0.67	3.00	5.35
Month 3	65	3.71	0.68	2.18	5.12	65	4.08	0.66	3.02	5.52
Month 6	60	3.79	0.75	2.14	5.30	60	4.13	0.72	3.00	5.60
Month 9	54	3.87	0.72	2.08	5.26	54	4.22	0.66	3.05	5.66
Month 12	52	3.85	0.70	2.39	5.21	52	4.20	0.69	3.01	5.76
Month 15	44	3.85	0.69	2.33	5.22	44	4.20	0.66	3.04	5.63
Month 18	47	3.90	0.71	2.78	5.50	47	4.18	0.70	3.03	5.88
Month 21	47	3.89	0.76	2.58	5.46	47	4.22	0.70	3.02	5.80
Month 24	48	3.85	0.72	2.59	5.45	47	4.18	0.67	3.03	5.67

TABLE 30 Abdominal aortic aneurysm diameter in the transverse plane: summary data by randomised group and combined at each trial visit (*continued*)

	Transverse internal diameter (cm)					Transverse external diameter (cm)				
Visit	*n*	Mean	SD	Minimum	Maximum	*n*	Mean	SD	Minimum	Maximum
Total										
Baseline	218	3.65	0.69	2.20	5.28	224	4.06	0.67	3.00	5.64
Month 3	204	3.71	0.69	2.18	5.40	204	4.10	0.68	3.02	6.07
Month 6	189	3.77	0.70	2.14	5.50	188	4.14	0.69	3.00	5.90
Month 9	172	3.78	0.69	2.08	5.30	172	4.14	0.67	3.05	5.66
Month 12	181	3.81	0.67	2.39	5.47	180	4.16	0.68	3.00	6.07
Month 15	148	3.80	0.68	2.33	5.42	148	4.14	0.67	3.04	5.90
Month 18	156	3.84	0.65	2.56	5.50	156	4.16	0.66	3.03	5.88
Month 21	143	3.84	0.68	2.42	5.73	142	4.16	0.69	3.02	6.03
Month 24	156	3.79	0.64	2.42	5.45	155	4.12	0.62	3.03	5.67

TABLE 31 Differences in transverse AAA diameter compared with baseline by randomised group and combined

	Transverse internal diameter (cm)					Transverse external diameter (cm)				
Study period	*n*	Mean	SD	Minimum	Maximum	*n*	Mean	SD	Minimum	Maximum
Placebo										
Month 3 – baseline	73	0.12	0.31	–0.5	1.48	74	0.09	0.24	–0.64	0.83
Month 6 – baseline	67	0.19	0.29	–0.32	1.44	67	0.12	0.27	–0.47	0.89
Month 12 – baseline	68	0.24	0.34	–0.67	1.49	68	0.18	0.29	–0.51	0.91
Month 18 – baseline	59	0.33	0.38	–0.41	1.67	60	0.26	0.27	–0.28	1.36
Month 24 – baseline	55	0.37	0.37	–0.28	1.62	56	0.30	0.31	–0.34	1.12
Perindopril										
Month 3 – baseline	64	0.02	0.28	–0.68	0.70	65	0.06	0.22	–0.69	0.78
Month 6 – baseline	60	0.07	0.21	–0.37	0.77	61	0.10	0.22	–0.47	0.73
Month 12 – baseline	59	0.24	0.28	–0.29	1.27	60	0.19	0.27	–0.52	1.14
Month 18 – baseline	48	0.26	0.22	–0.13	0.83	49	0.21	0.27	–0.53	1.15
Month 24 – baseline	51	0.28	0.22	–0.15	0.89	52	0.21	0.26	–0.53	0.76
Amlodipine										
Month 3 – baseline	62	0.08	0.29	–0.68	1.19	65	0.04	0.21	–0.57	0.74
Month 6 – baseline	57	0.19	0.43	–0.65	2.38	60	0.10	0.26	–0.75	0.76
Month 12 – baseline	49	0.31	0.49	–0.65	2.68	52	0.23	0.27	–0.44	0.86
Month 18 – baseline	44	0.37	0.37	–0.3	1.57	47	0.27	0.28	–0.25	0.85
Month 24 – baseline	45	0.37	0.42	–0.66	1.42	47	0.32	0.33	–0.63	0.95
Total										
Month 3 – baseline	199	0.07	0.30	–0.68	1.48	204	0.06	0.23	–0.69	0.83
Month 6 – baseline	184	0.15	0.32	–0.65	2.38	188	0.11	0.25	–0.75	0.89
Month 12 – baseline	176	0.26	0.37	–0.67	2.68	180	0.20	0.28	–0.52	1.14
Month 18 – baseline	151	0.32	0.34	–0.41	1.67	156	0.25	0.27	–0.53	1.36
Month 24 – baseline	151	0.34	0.34	–0.66	1.62	155	0.27	0.30	–0.63	1.12

Appendix 6 Histograms of change in abdominal aortic aneurysm longitudinal external measurements (6 and 18 months)

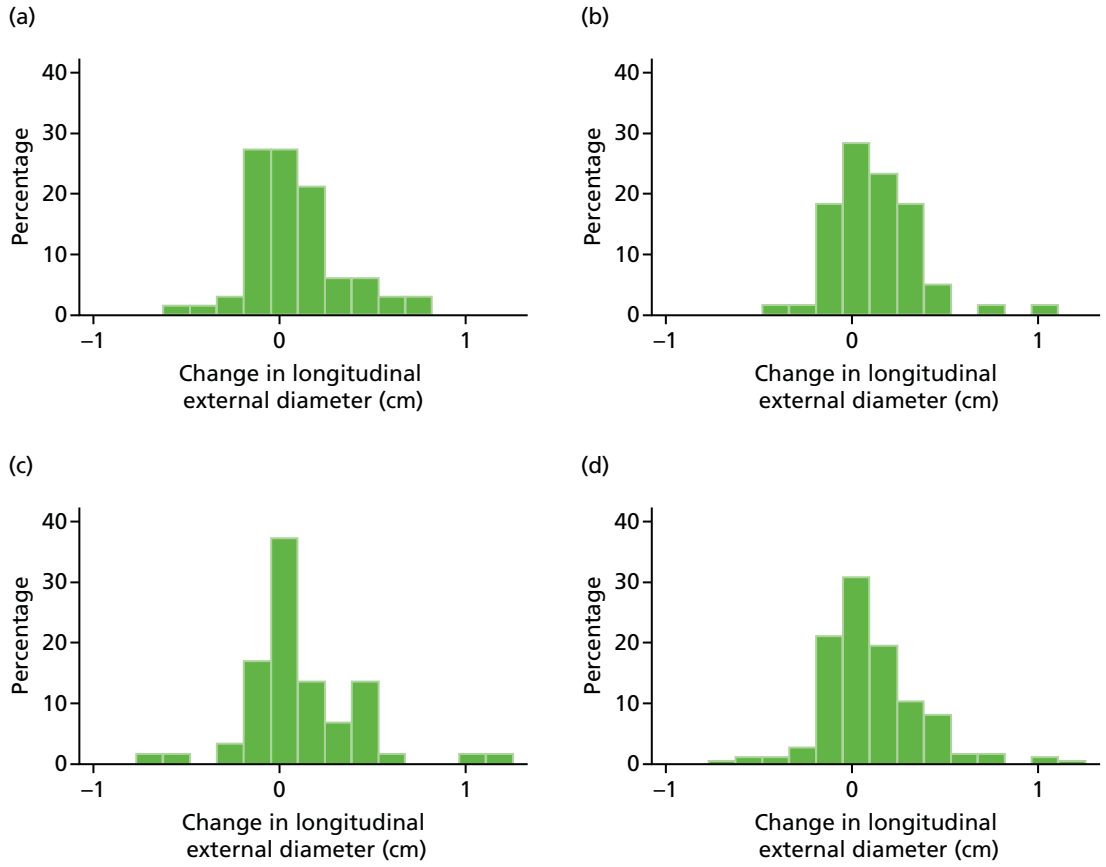


FIGURE 40 Histograms of change in AAA longitudinal external diameter from baseline to month 6. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

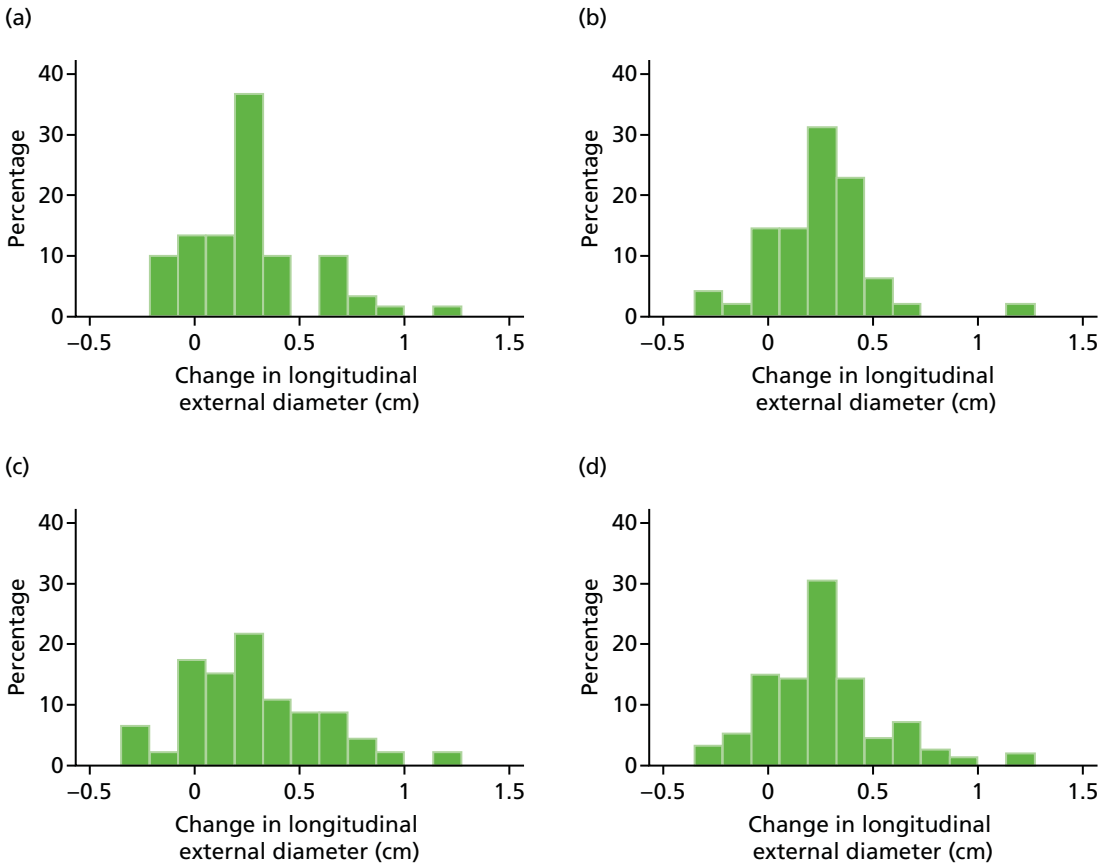


FIGURE 41 Histograms of change in AAA longitudinal external diameter from baseline to month 18. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

Appendix 7 Box plots of change in abdominal aortic aneurysm longitudinal external measurements (6 and 18 months)

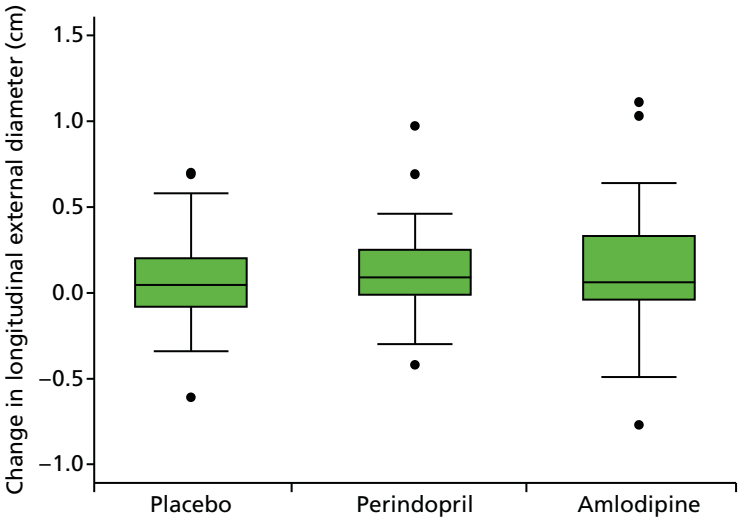


FIGURE 42 Box plot of change in AAA longitudinal external diameter from baseline to month 6. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

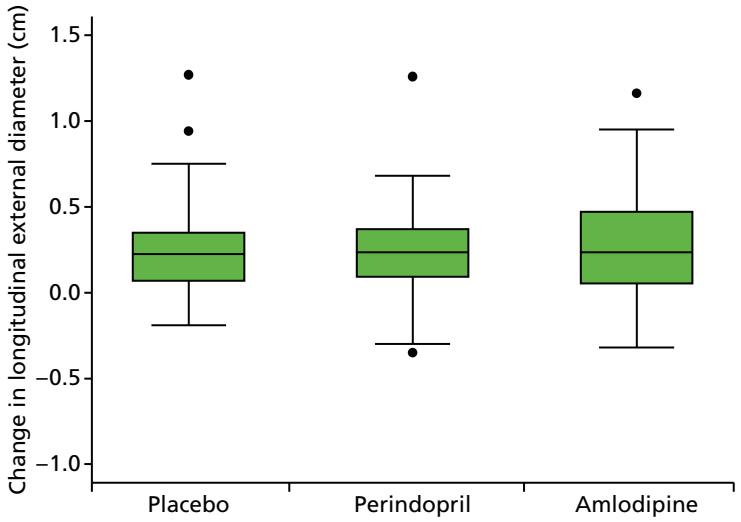


FIGURE 43 Box plot of change in AAA longitudinal external diameter from baseline to month 18. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

Appendix 8 Histograms of change in abdominal aortic aneurysm longitudinal internal measurements

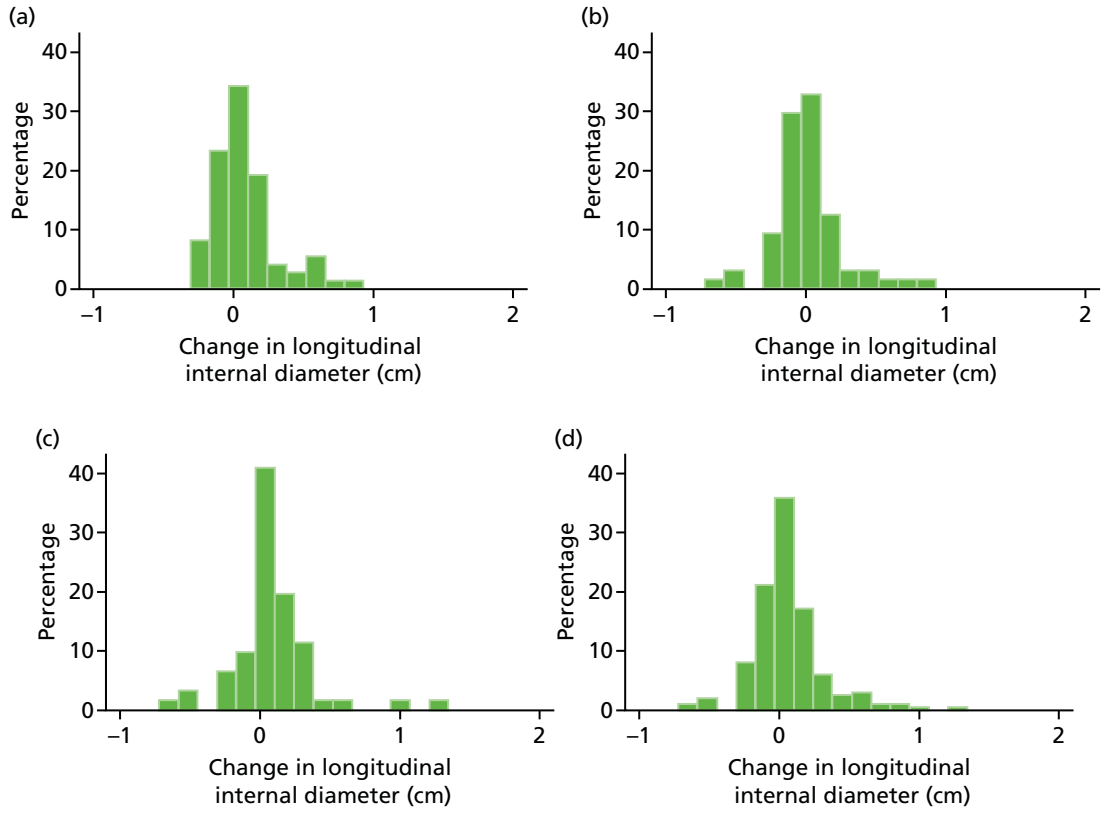


FIGURE 44 Histograms of change in AAA longitudinal internal diameter from baseline to month 3. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

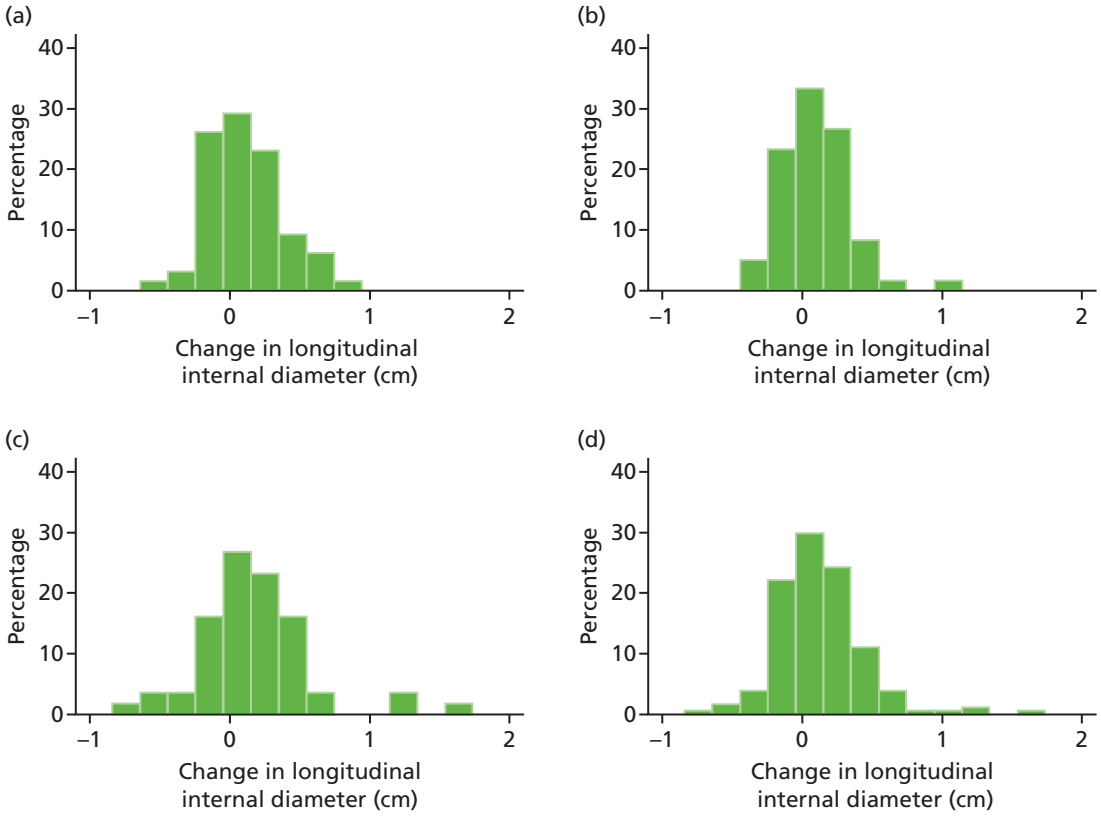


FIGURE 45 Histograms of change in AAA longitudinal internal diameter from baseline to month 6. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

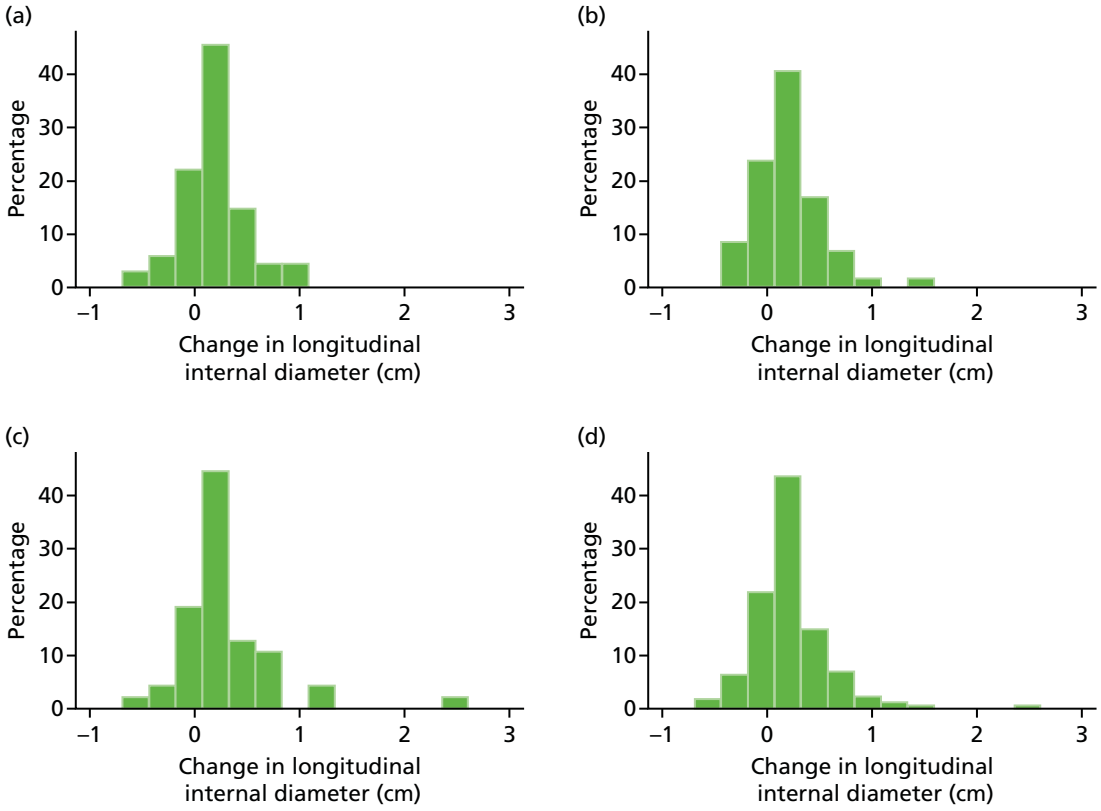


FIGURE 46 Histograms of change in AAA longitudinal internal diameter from baseline to month 12. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

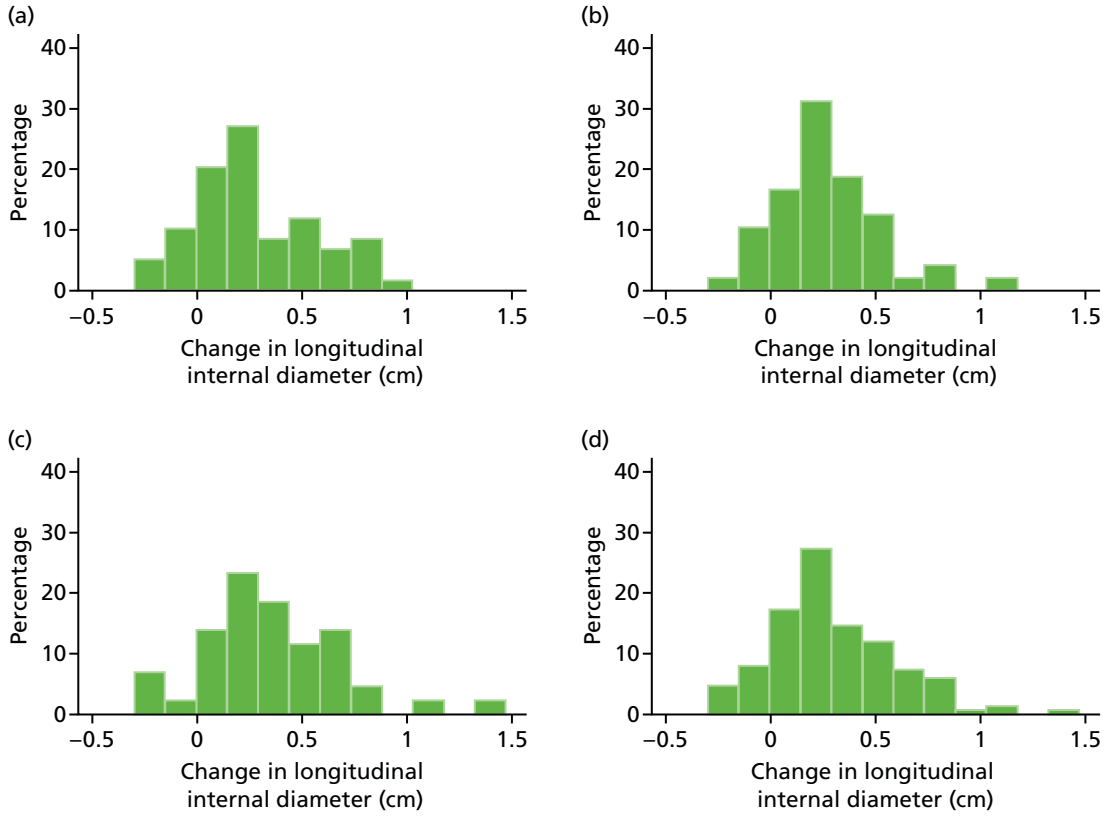


FIGURE 47 Histograms of change in AAA longitudinal internal diameter from baseline to month 18. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

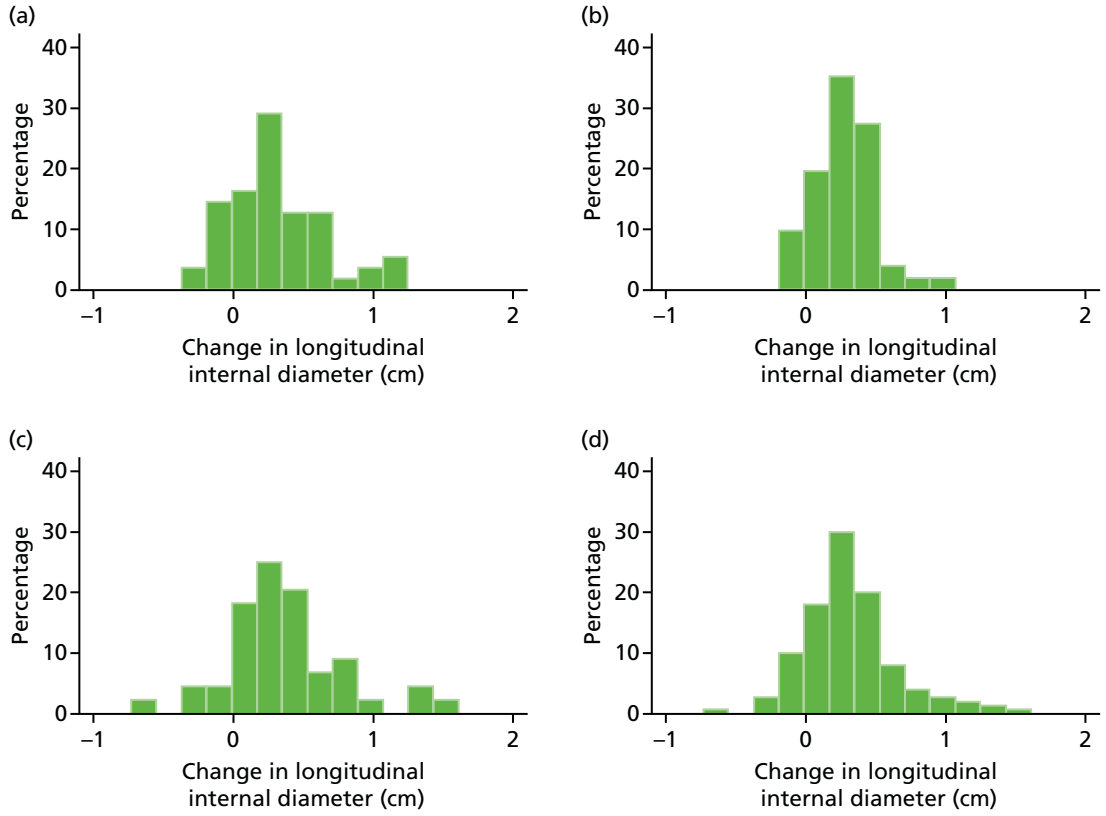


FIGURE 48 Histograms of change in AAA longitudinal internal diameter from baseline to month 24. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

Appendix 9 Box plots of change in abdominal aortic aneurysm longitudinal internal measurements

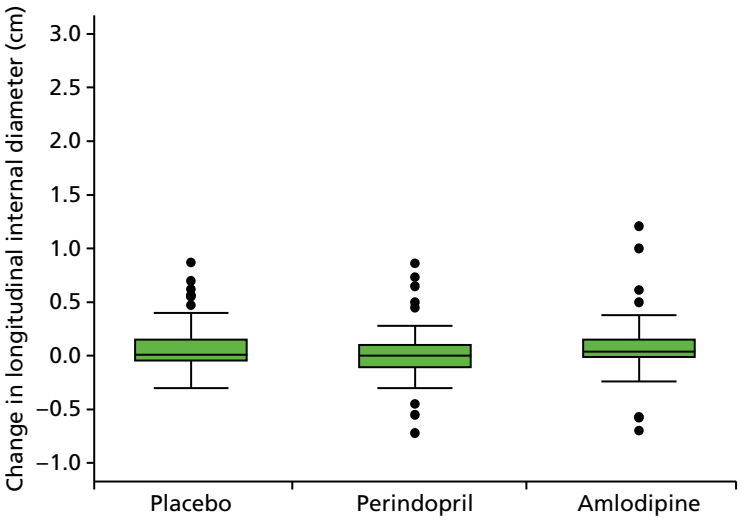


FIGURE 49 Box plot of change in AAA longitudinal internal diameter from baseline to month 3. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

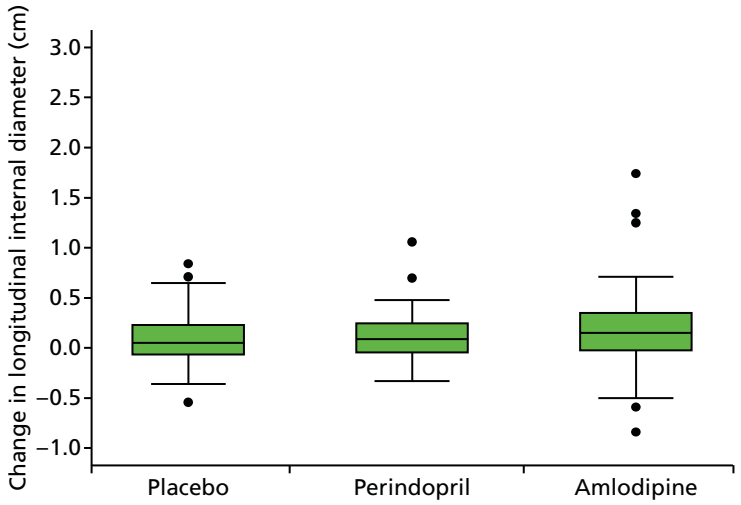


FIGURE 50 Box plot of change in AAA longitudinal internal diameter from baseline to month 6. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

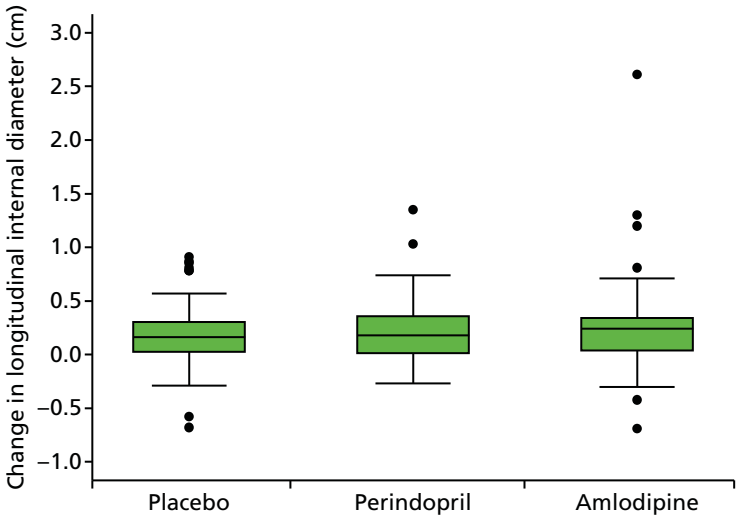


FIGURE 51 Box plot of change in AAA longitudinal internal diameter from baseline to month 12. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

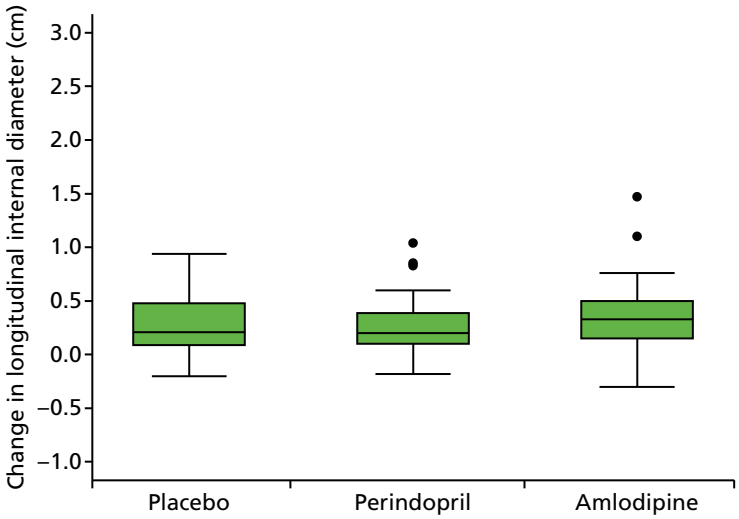


FIGURE 52 Box plot of change in AAA longitudinal internal diameter from baseline to month 18. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

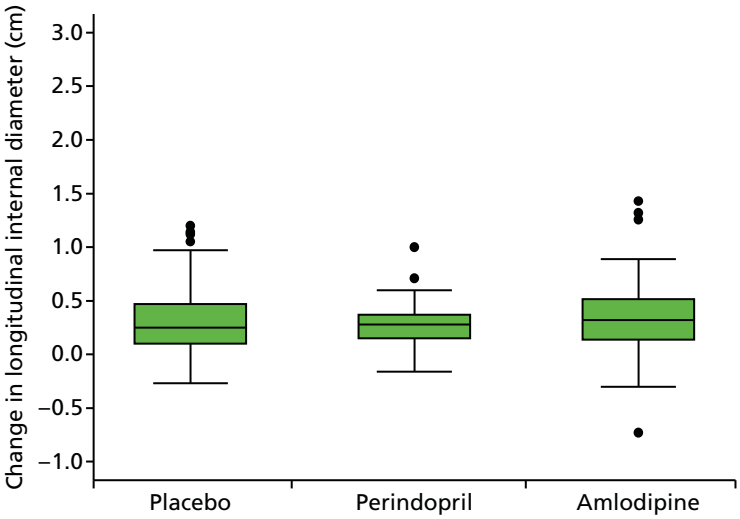


FIGURE 53 Box plot of change in AAA longitudinal internal diameter from baseline to month 24. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

Appendix 10 Histograms of change in abdominal aortic aneurysm transverse external measurements

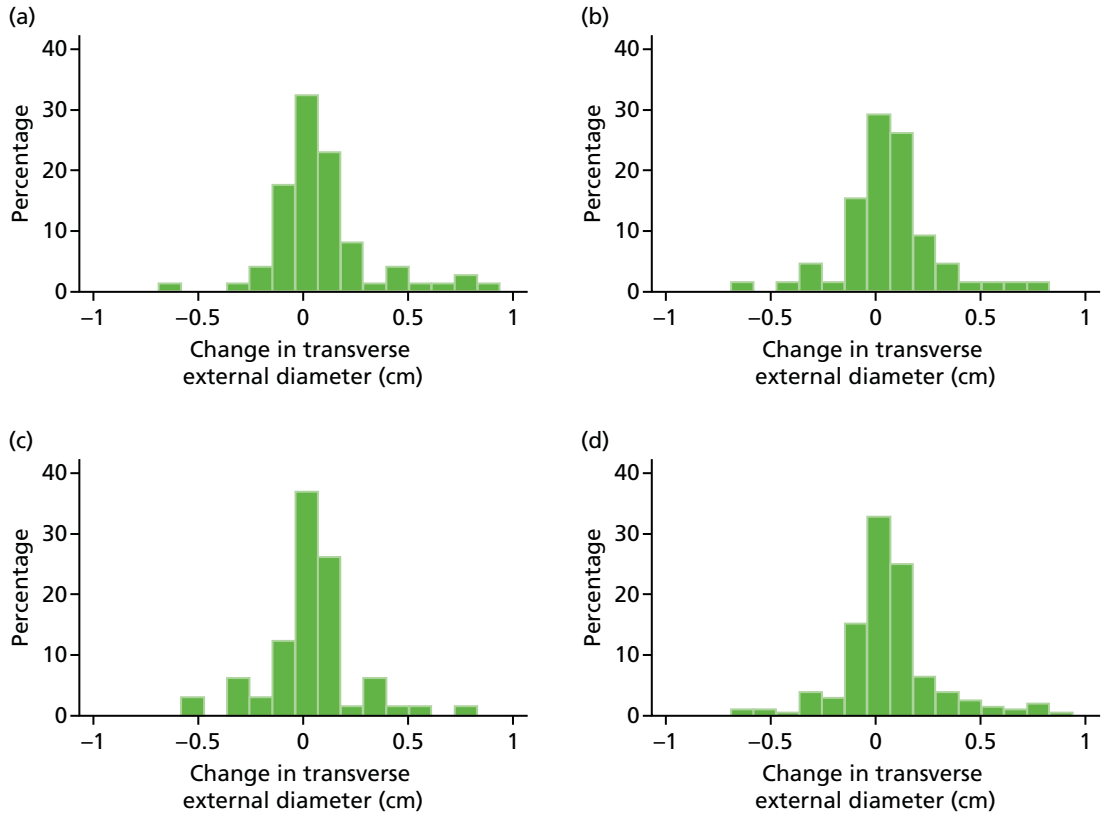


FIGURE 54 Histograms of change in AAA transverse external diameter from baseline to month 3. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

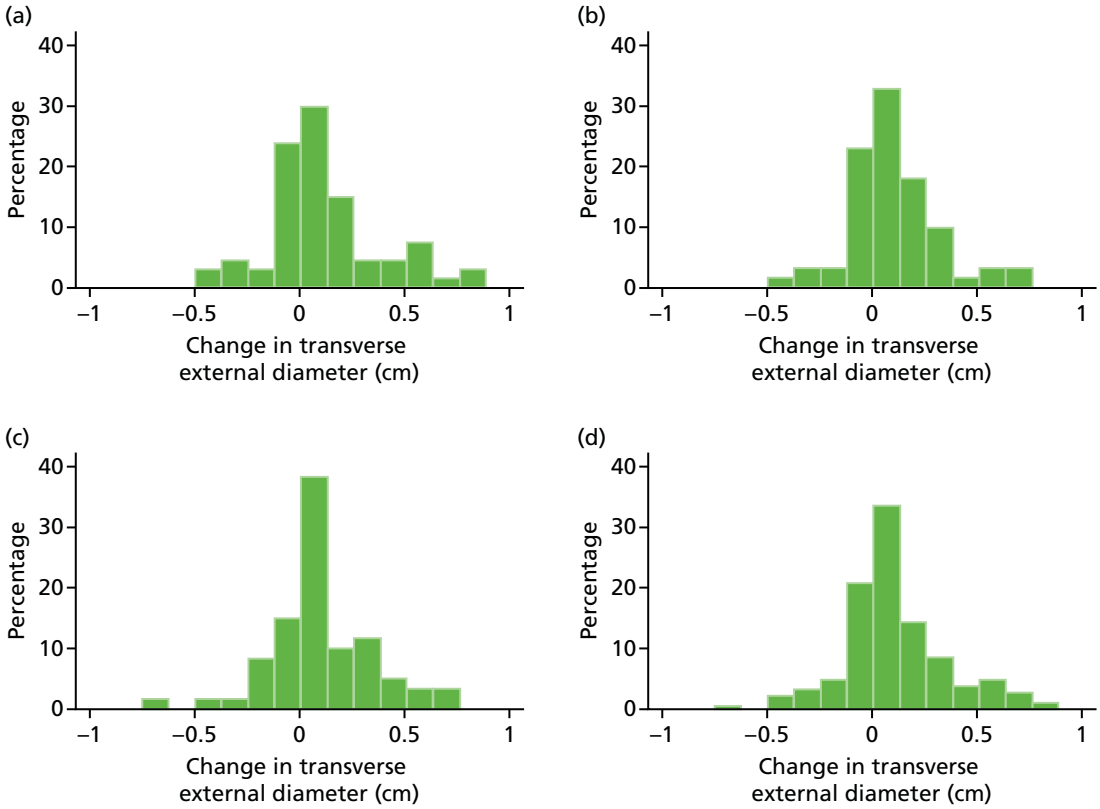


FIGURE 55 Histograms of change in AAA transverse external diameter from baseline to month 6. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

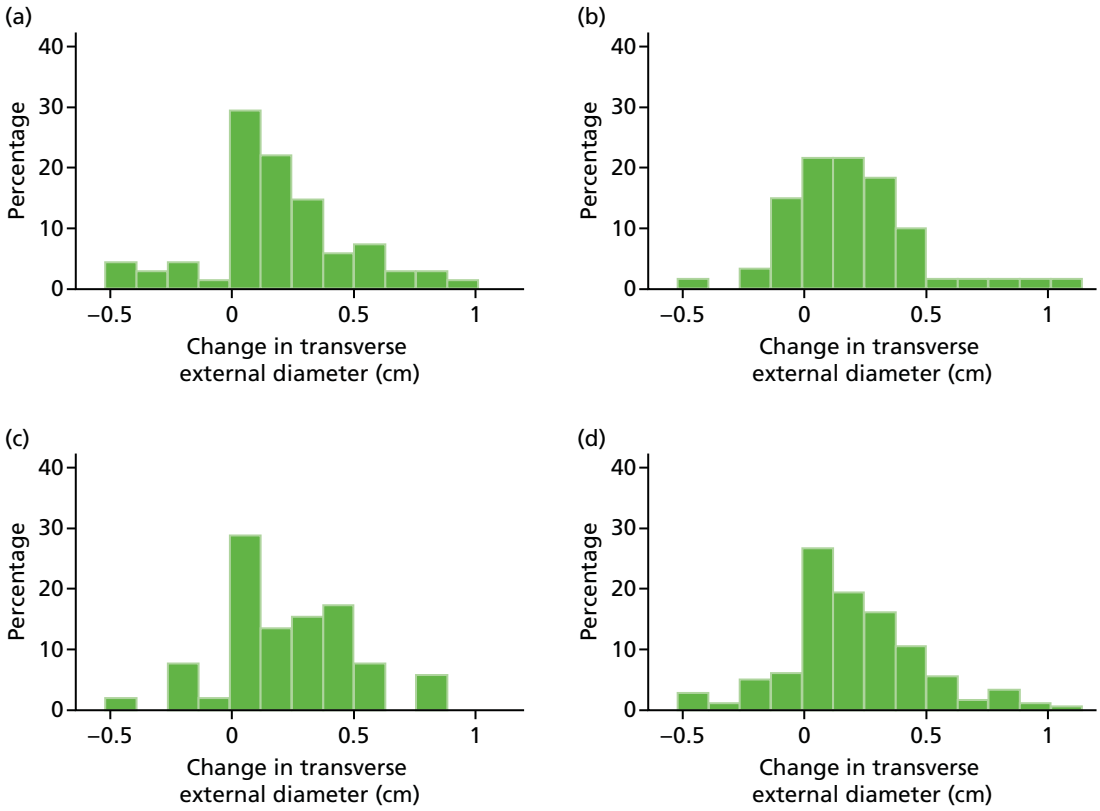


FIGURE 56 Histograms of change in AAA transverse external diameter from baseline to month 12. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

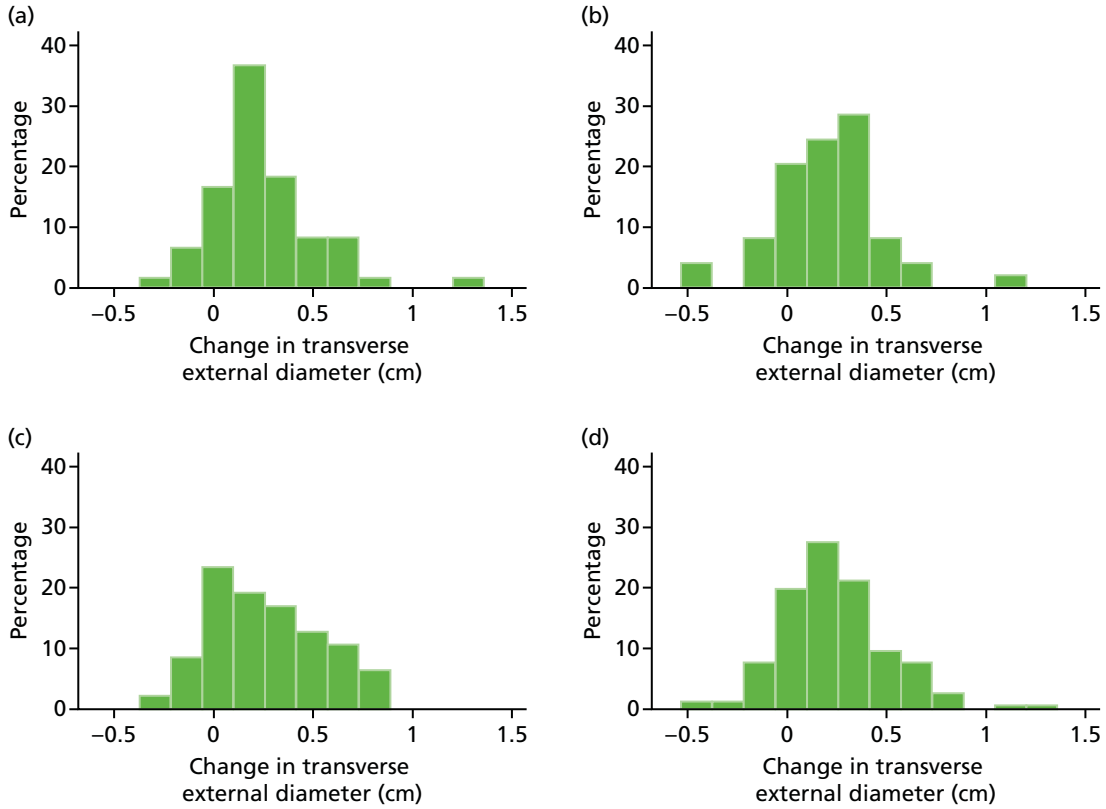


FIGURE 57 Histograms of change in AAA transverse external diameter from baseline to month 18. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

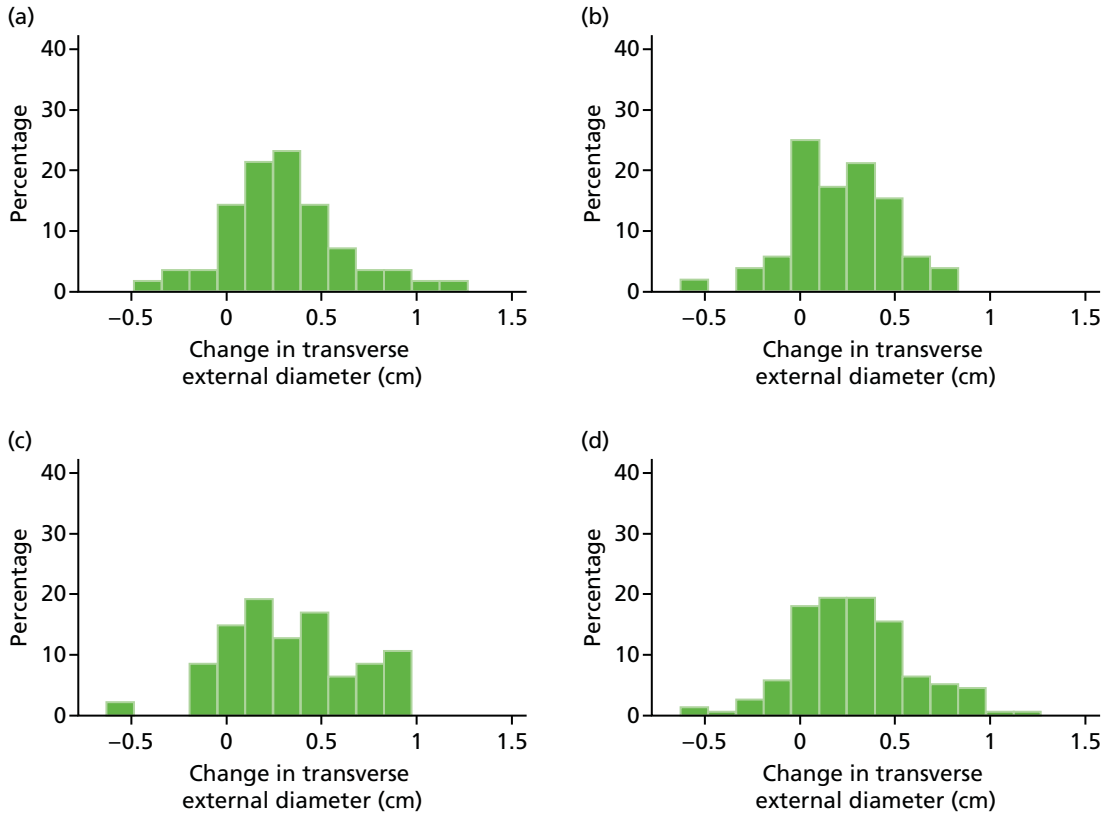


FIGURE 58 Histograms of change in AAA transverse external diameter from baseline to month 24. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

Appendix 11 Box plots of change in abdominal aortic aneurysm transverse external measurements

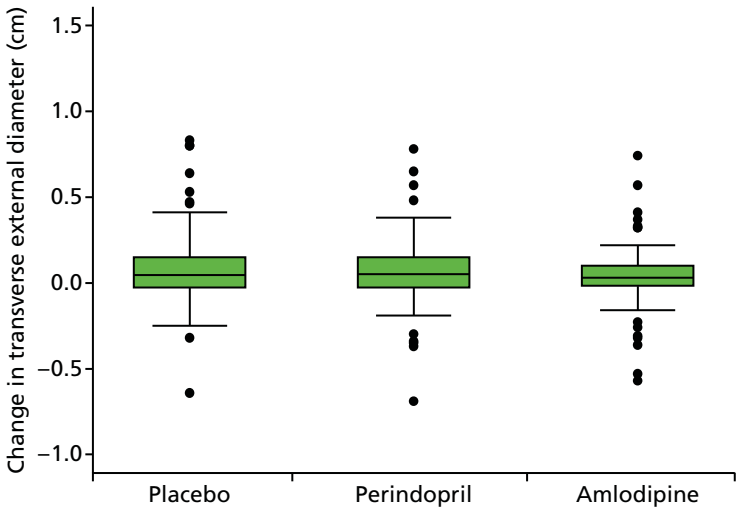


FIGURE 59 Box plot of change in AAA transverse external diameter from baseline to month 3. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

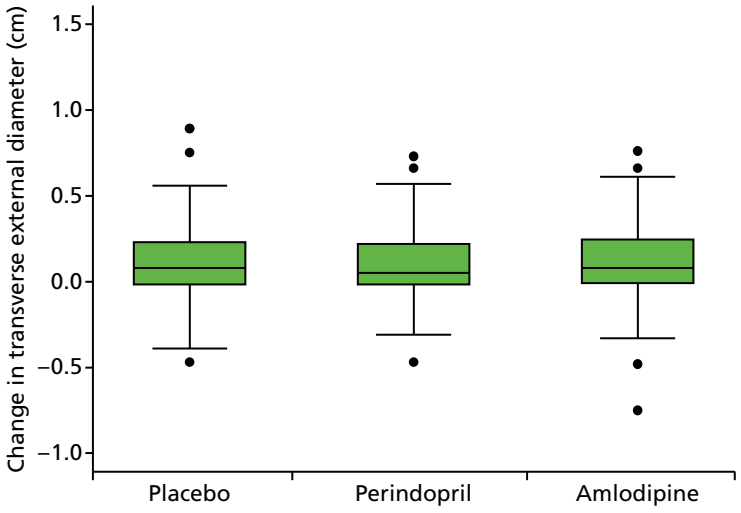


FIGURE 60 Box plot of change in AAA transverse external diameter from baseline to month 6. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

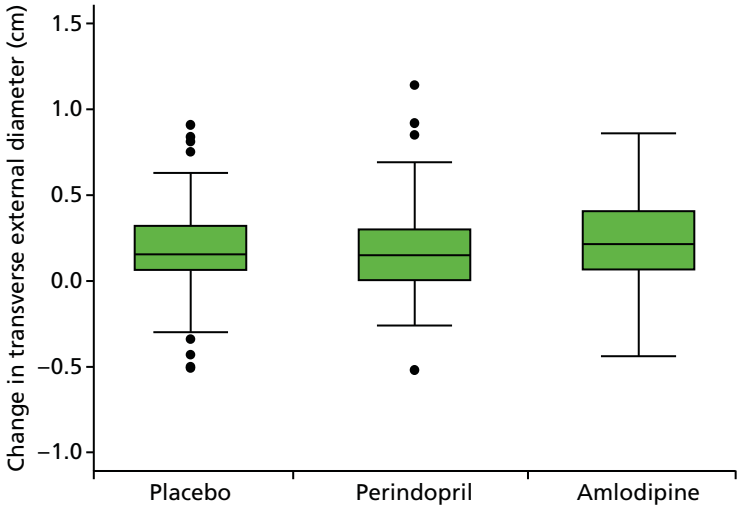


FIGURE 61 Box plot of change in AAA transverse external diameter from baseline to month 12. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

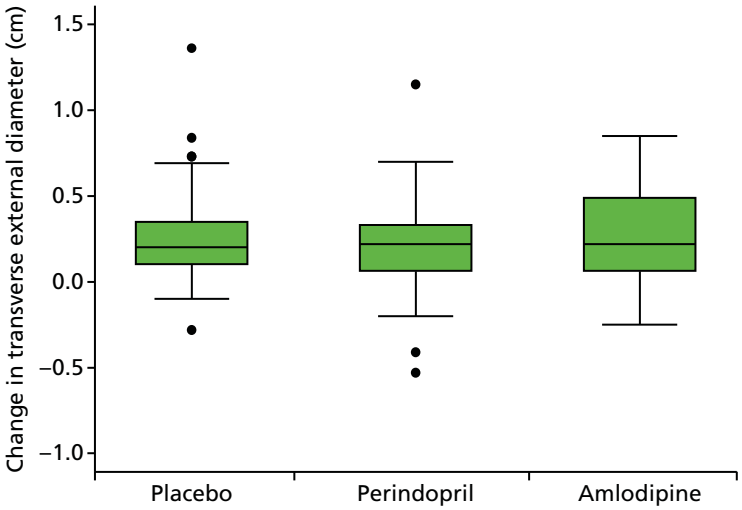


FIGURE 62 Box plot of change in AAA transverse external diameter from baseline to month 18. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

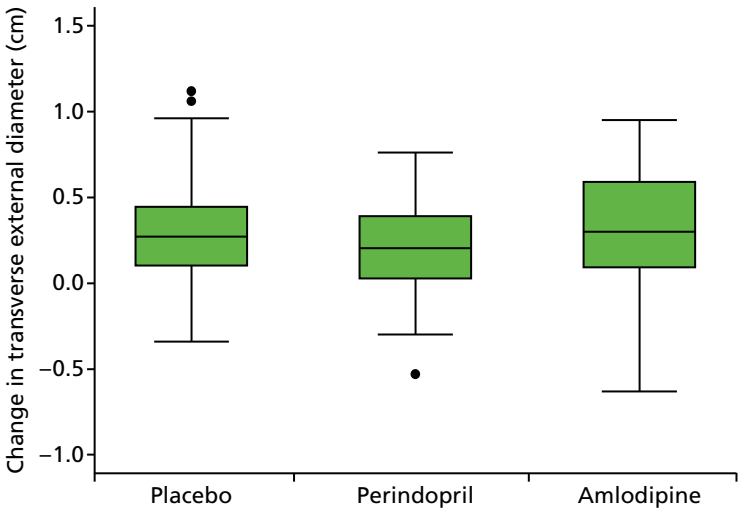


FIGURE 63 Box plot of change in AAA transverse external diameter from baseline to month 24. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

Appendix 12 Histograms of change in abdominal aortic aneurysm transverse internal measurements

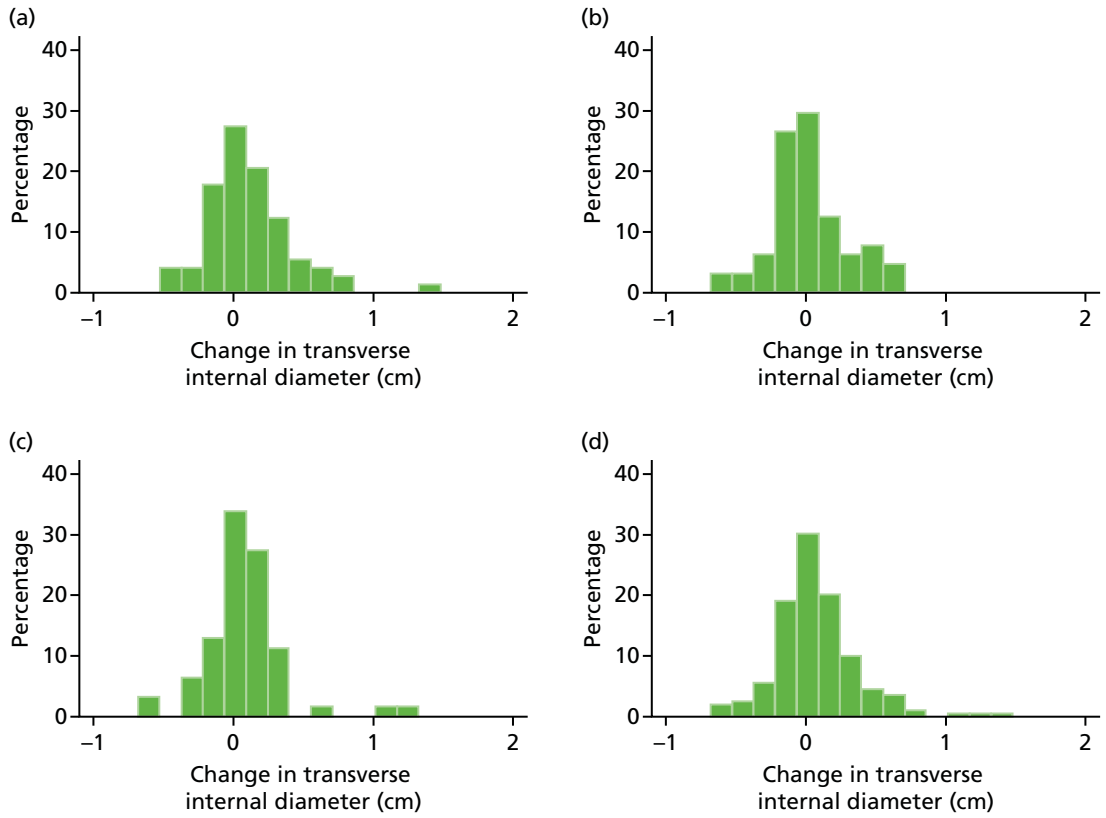


FIGURE 64 Histograms of change in AAA transverse internal diameter from baseline to month 3. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

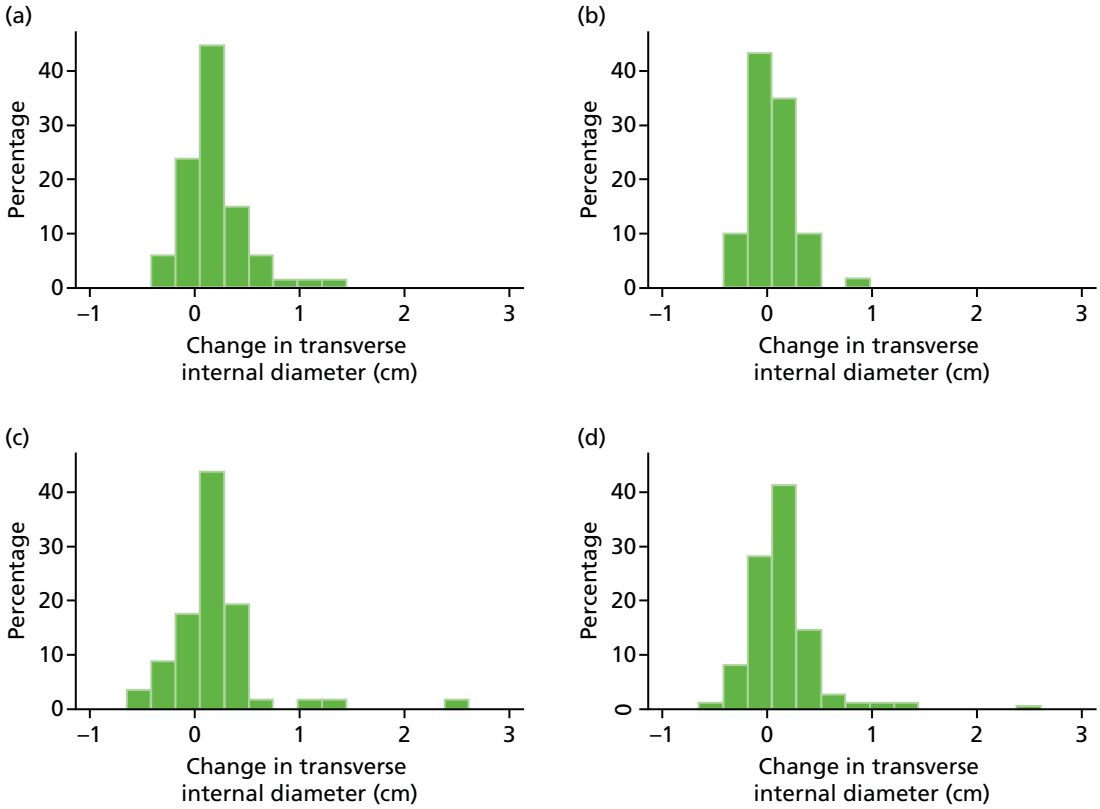


FIGURE 65 Histograms of change in AAA transverse internal diameter from baseline to month 6. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

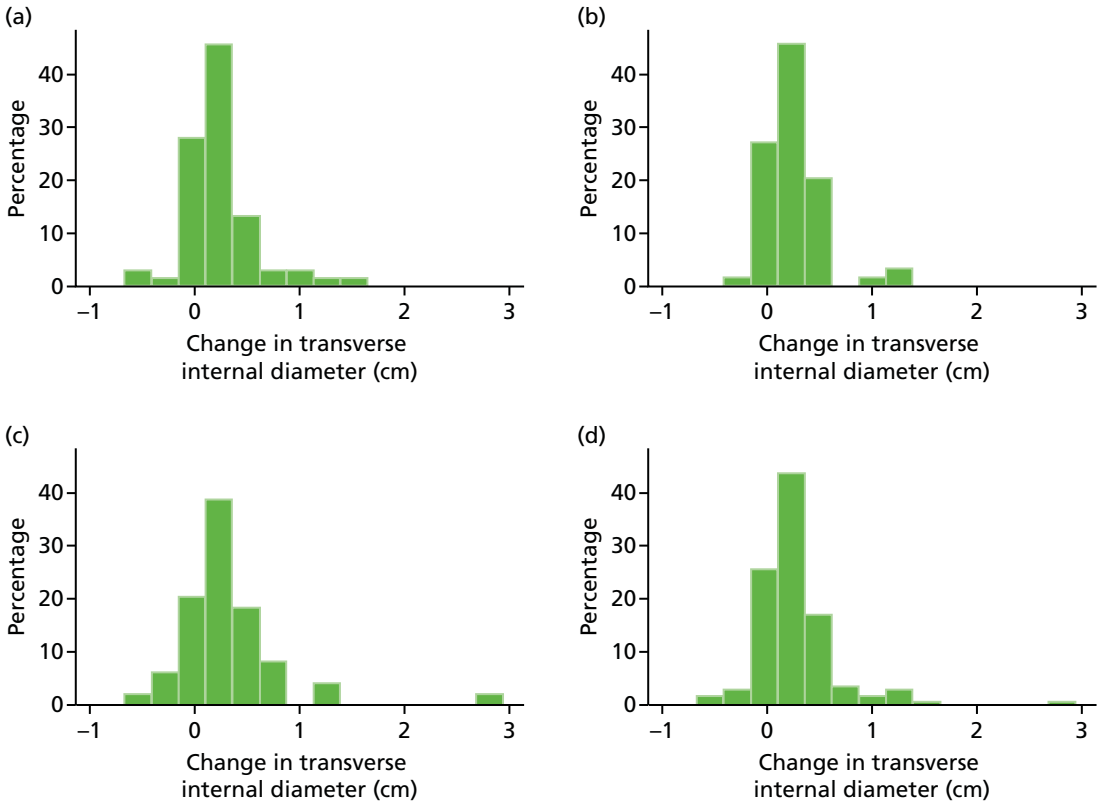


FIGURE 66 Histograms of change in AAA transverse internal diameter from baseline to month 12. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

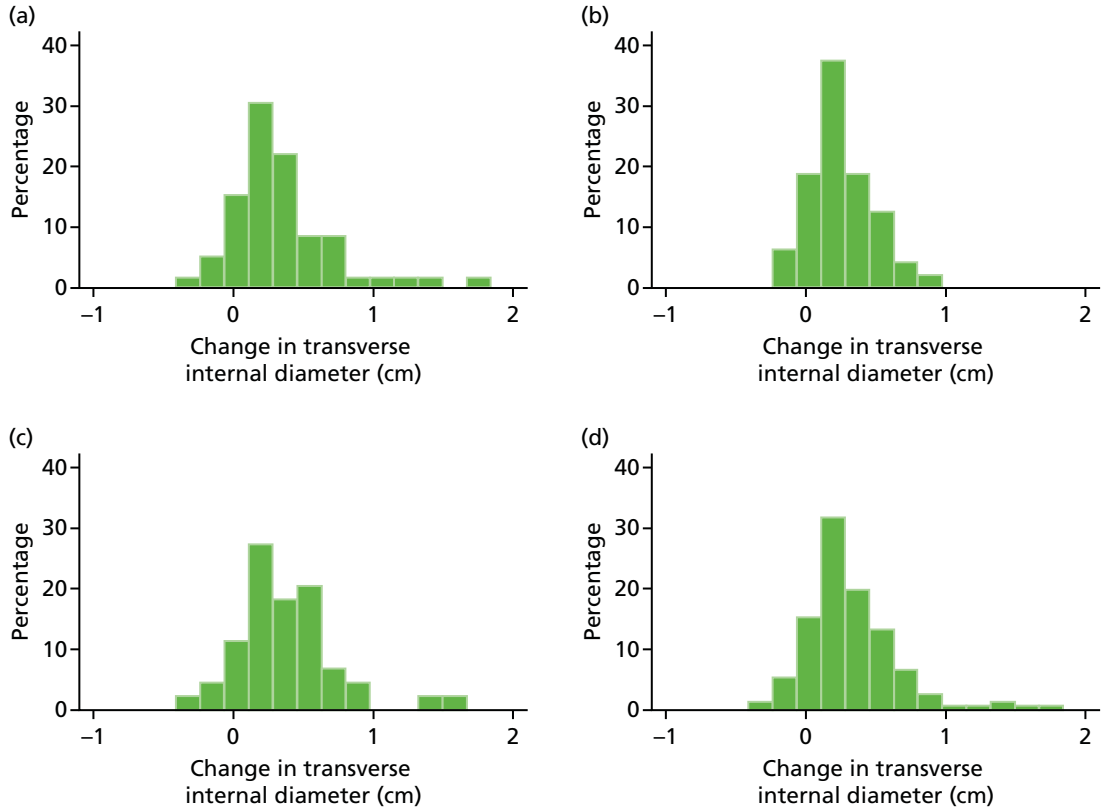


FIGURE 67 Histograms of change in AAA transverse internal diameter from baseline to month 18. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

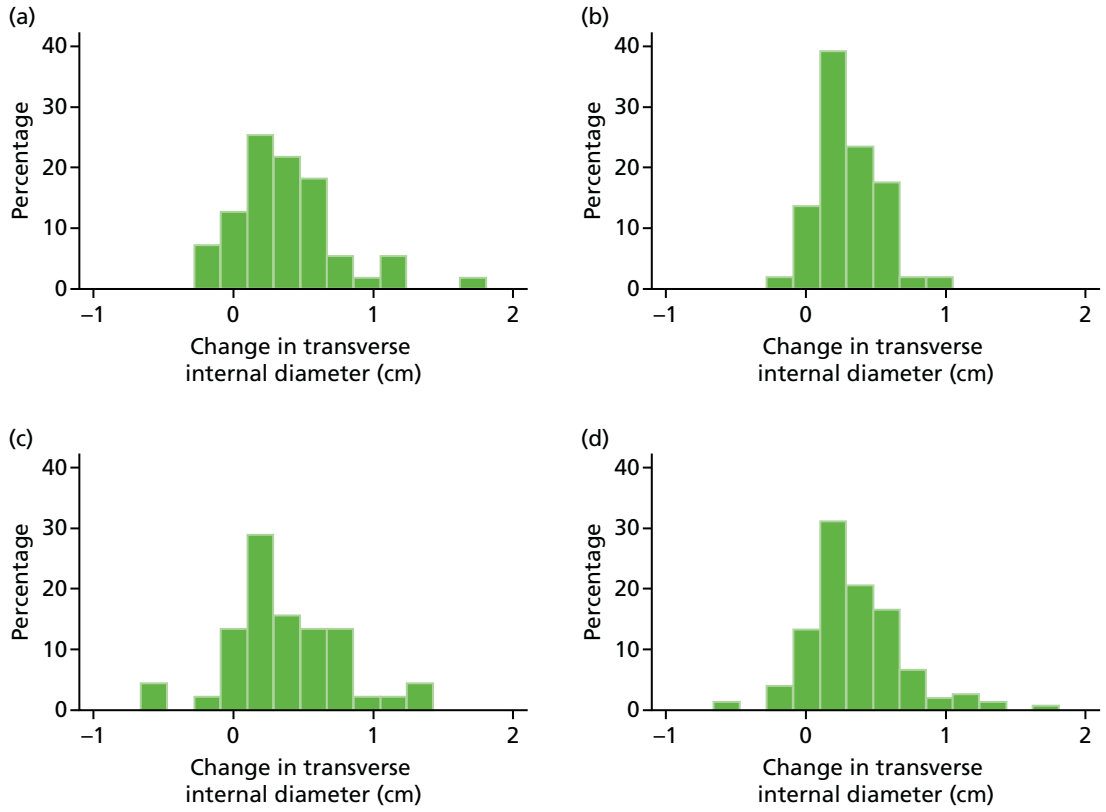


FIGURE 68 Histograms of change in AAA transverse internal diameter from baseline to month 24. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

Appendix 13 Box plots of change in abdominal aortic aneurysm transverse internal measurements

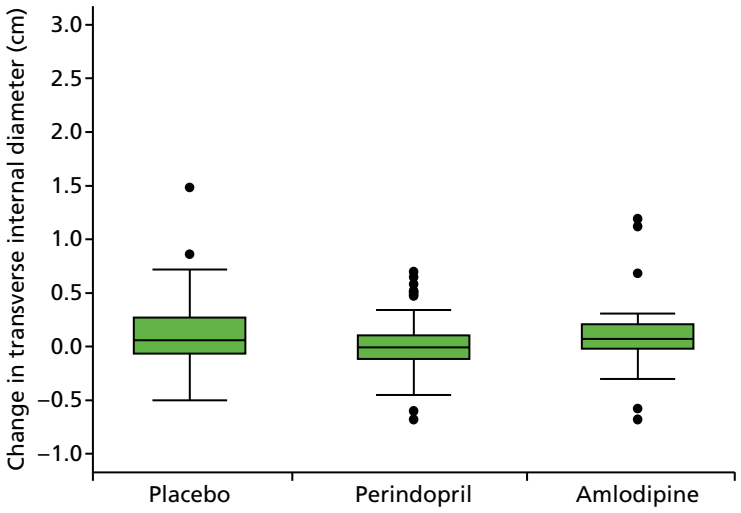


FIGURE 69 Box plot of change in AAA transverse internal diameter from baseline to month 3. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

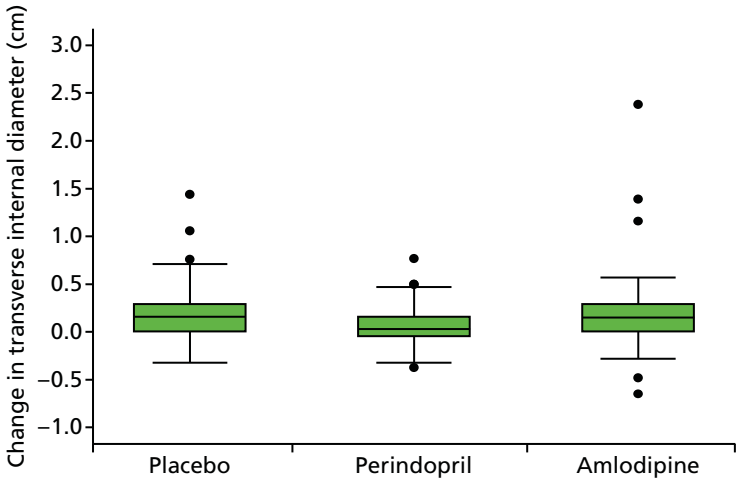


FIGURE 70 Box plot of change in AAA transverse internal diameter from baseline to month 6. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

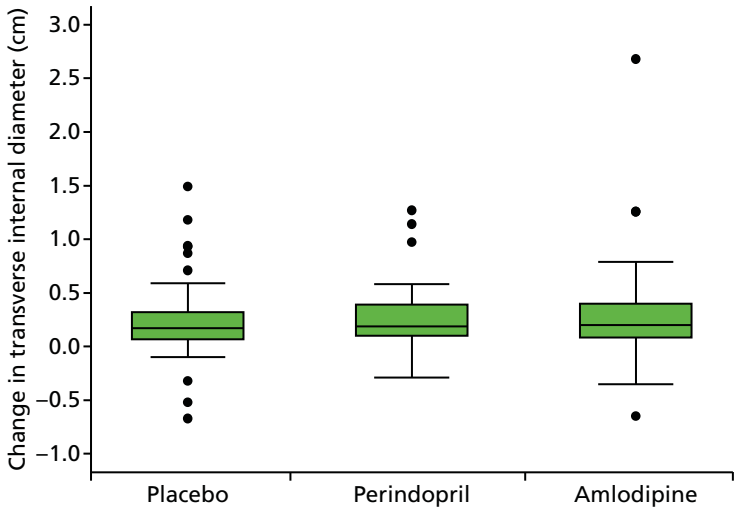


FIGURE 71 Box plot of change in AAA transverse internal diameter from baseline to month 12. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

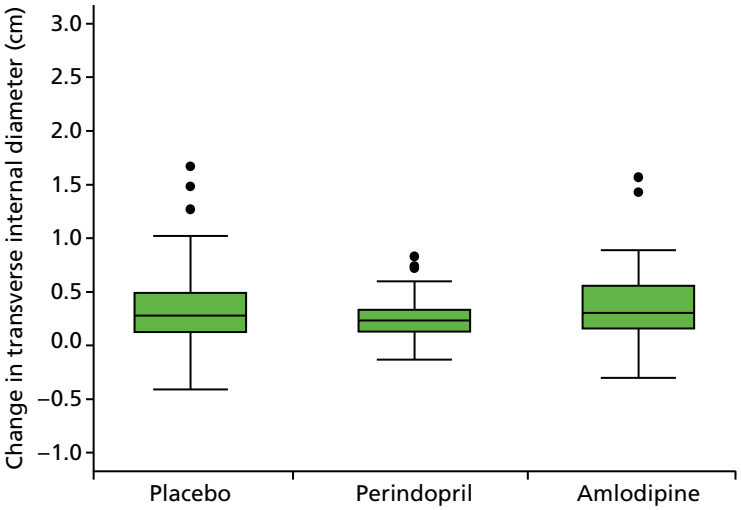


FIGURE 72 Box plot of change in AAA transverse internal diameter from baseline to month 18. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

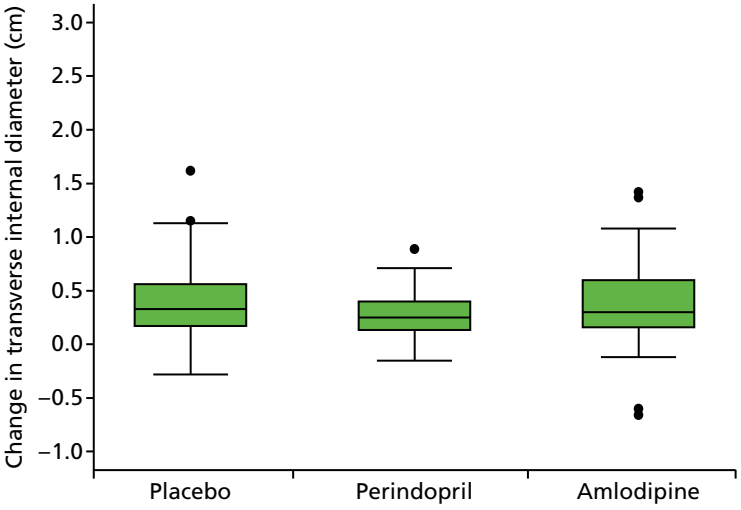


FIGURE 73 Box plot of change in AAA transverse internal diameter from baseline to month 24. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

Appendix 14 Histograms of change in systolic blood pressure (6 and 18 months)

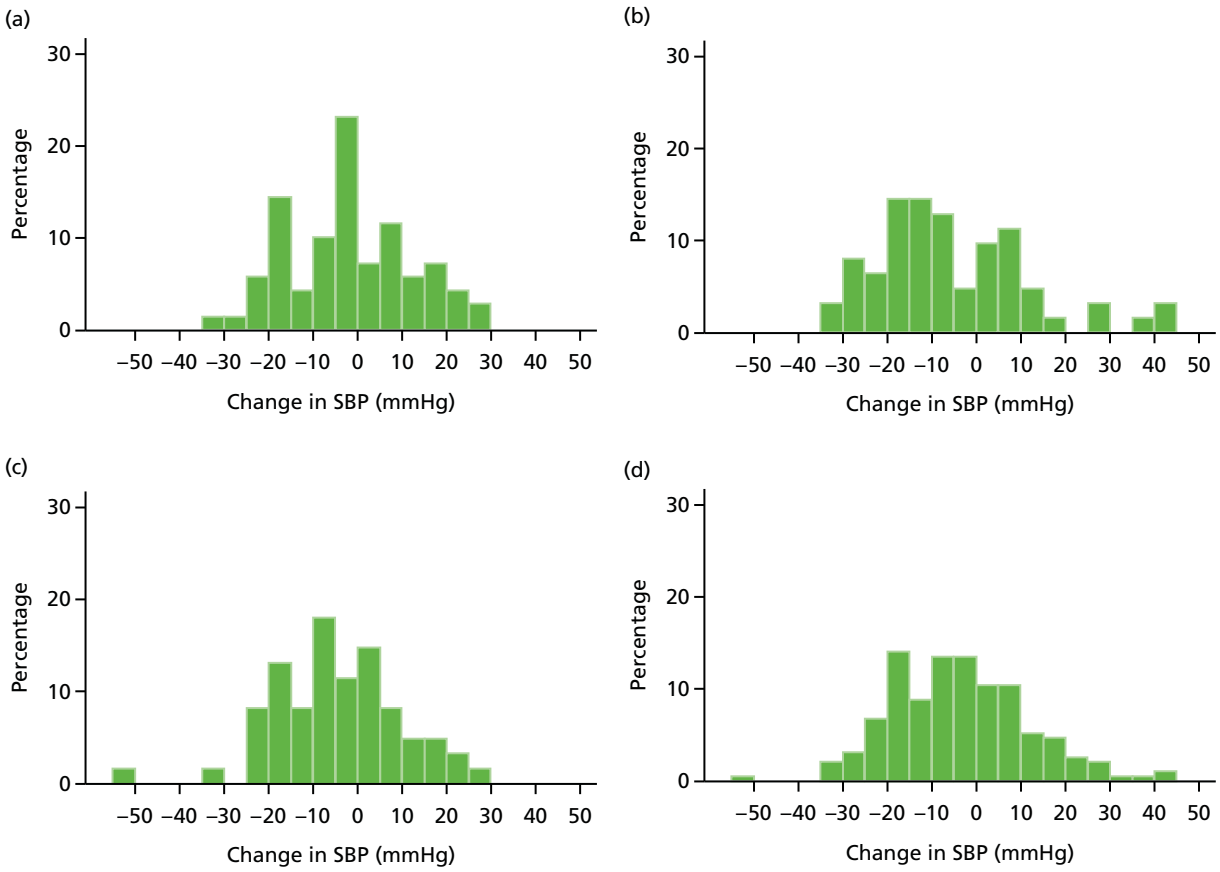


FIGURE 74 Histograms of change in SBP from baseline to month 6. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

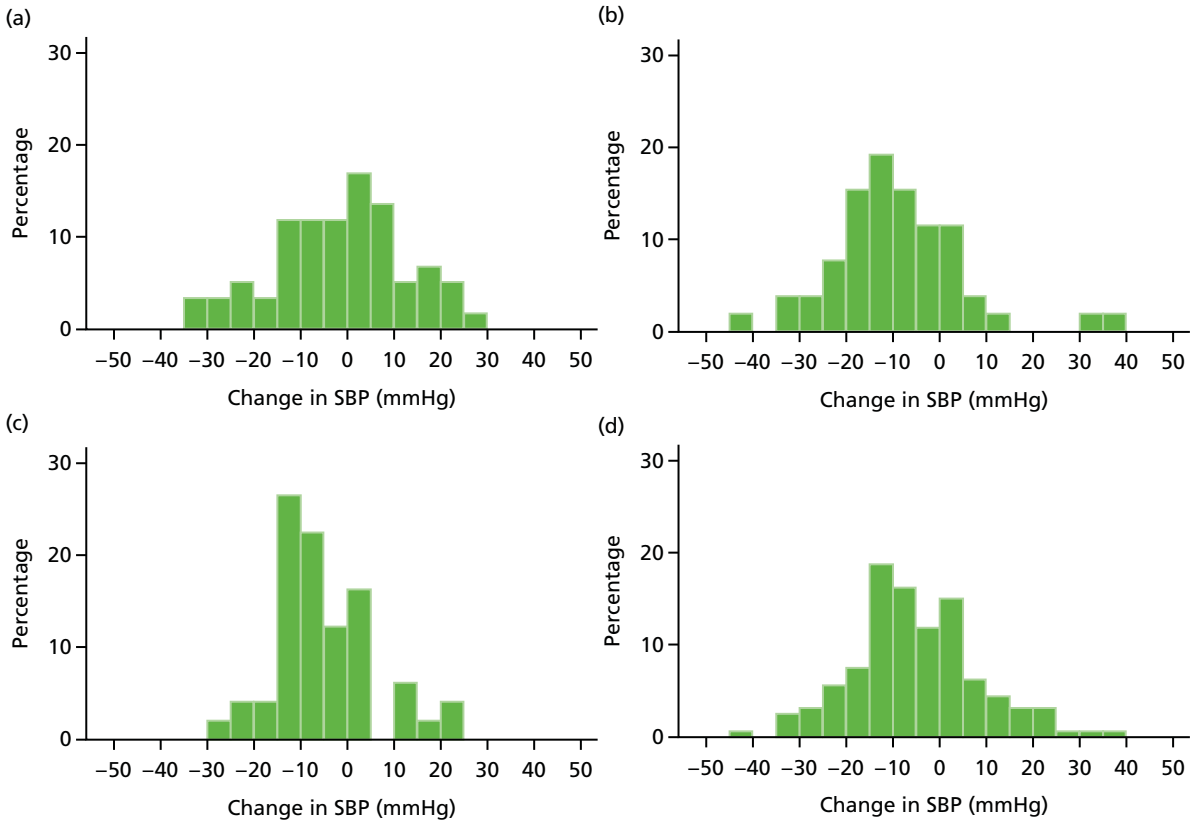


FIGURE 75 Histograms of change in SBP from baseline to month 18. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

Appendix 15 Box plots of change in systolic blood pressure (6 and 18 months)

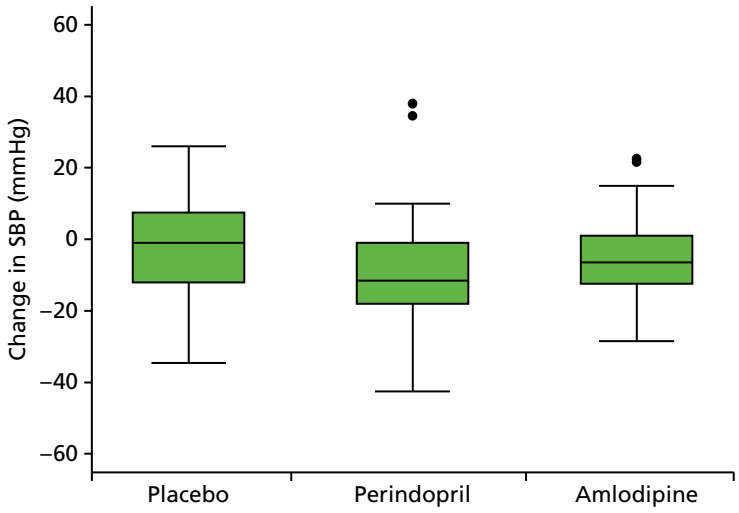


FIGURE 76 Box plot of change in SBP from baseline to month 6. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

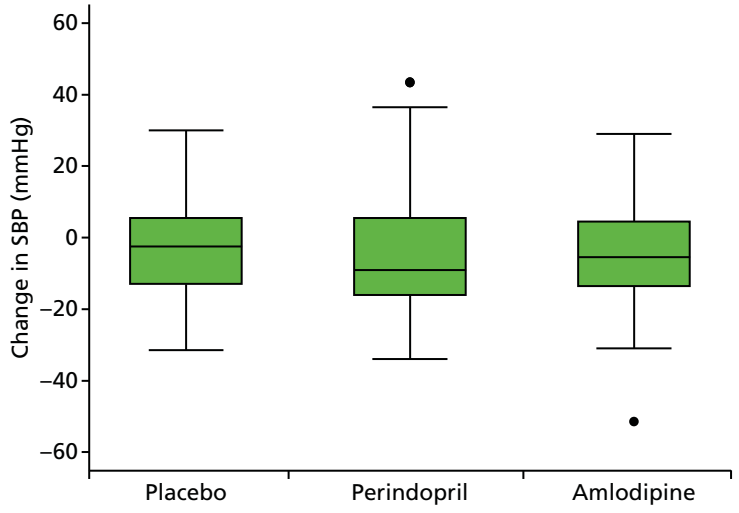


FIGURE 77 Box plot of change in SBP from baseline to month 18. Circles are outside values. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

Appendix 16 Histograms of change in diastolic blood pressure (6 and 18 months)

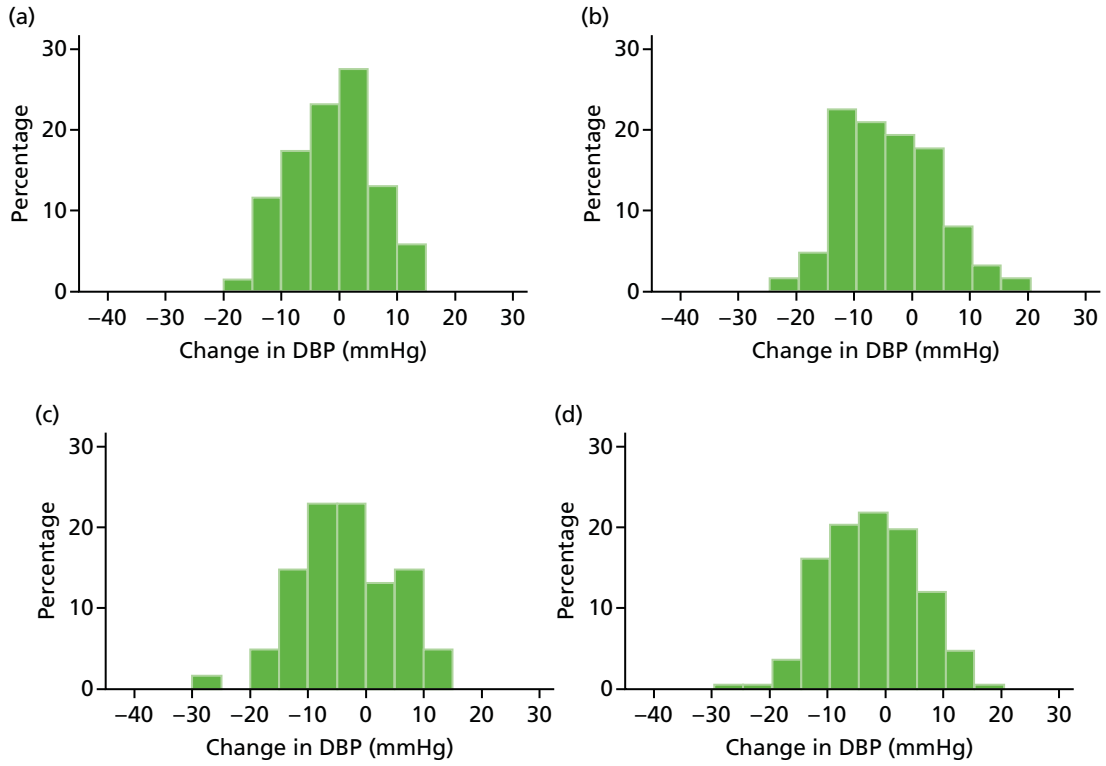


FIGURE 78 Histograms of change in DBP from baseline to month 6. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

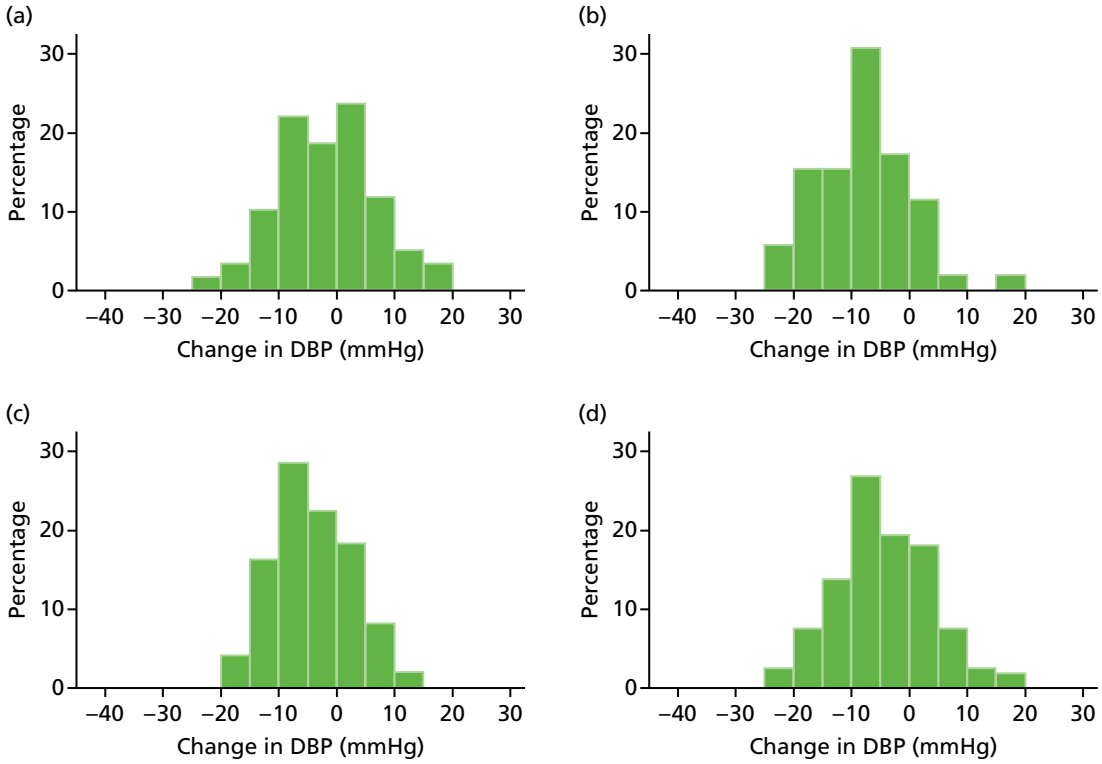


FIGURE 79 Histograms of change in DBP from baseline to month 18. (a) Placebo; (b) perindopril; (c) amlodipine; and (d) total.

Appendix 17 Box plots of change in diastolic blood pressure (6 and 18 months)

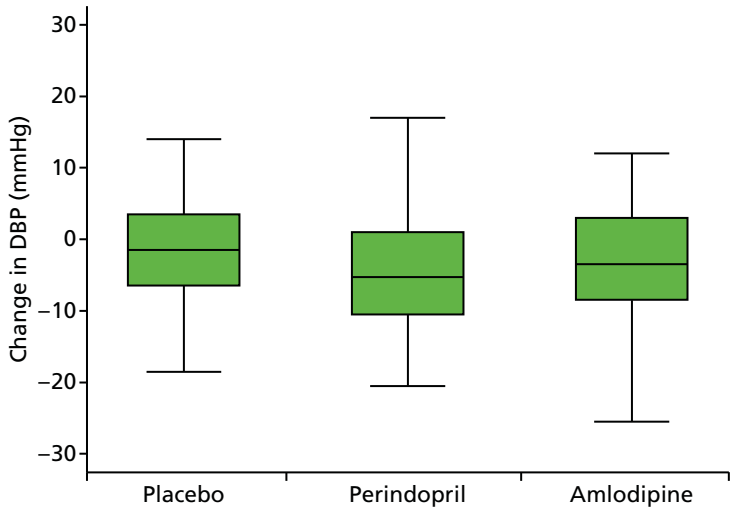


FIGURE 80 Box plot of change in DBP from baseline to month 6. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

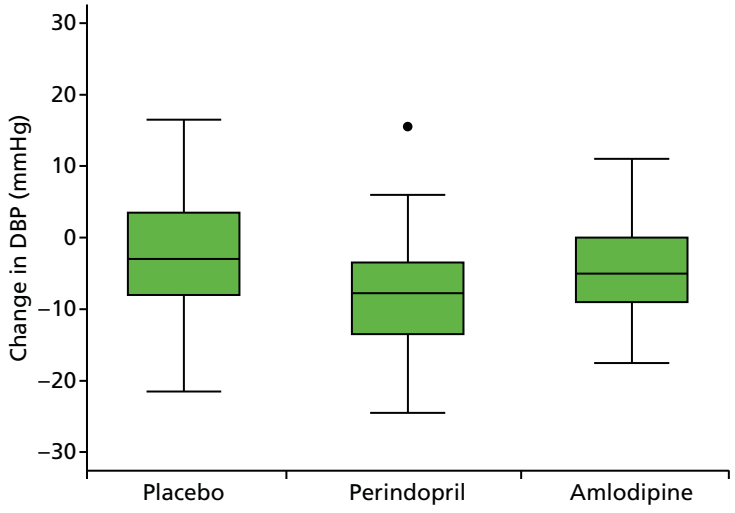


FIGURE 81 Box plot of change in DBP from baseline to month 18. Circle is an outside value. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

Appendix 18 Breakdown of European Quality of Life-5 Dimensions scores by domain

Domain	Placebo		Perindopril		Amlodipine		Total	
	n	%	*n*	%	*n*	%	*n*	%
Mobility *Month 12*								
I have no problems in walking about	34	48.6	37	61.7	33	63.5	104	57.1
I have some problems in walking about	35	50	23	38.3	19	36.5	77	42.3
Missing	1	1.4	0	0	0	0	1	0.5
Month 24								
I have no problems in walking about	31	55.4	32	61.5	32	69.6	95	61.7
I have some problems in walking about	25	44.6	20	38.5	14	30.4	59	38.3
I am confined to bed	0	0	0	0	0	0	0	0
Self-care *Month 12*								
I am unable to wash or dress myself	0	0	1	1.7	0	0	1	0.5
I have no problems with self-care	63	90.0	53	88.3	48	92.3	164	90.1
I have some problems washing or dressing myself	6	8.6	6	10	4	7.7	16	8.8
Missing	1	1.4	0	0	0	0	1	0.5
Month 24								
I am unable to wash or dress myself	0	0	0	0	0	0	0	0
I have no problems with self-care	50	89.3	46	88.5	42	91.3	138	89.6
I have some problems washing or dressing myself	6	10.7	6	11.5	4	8.7	16	10.4
Usual activities *Month 12*								
I am unable to perform my usual activities	2	2.9	0	0	2	3.8	4	2.2
I have no problems performing my usual activities	44	62.9	44	73.3	43	82.7	131	72.0
I have some problems with performing my usual activities	23	32.9	16	26.7	7	13.5	46	25.3
Missing	1	1.4	0	0	0	0	1	0.5
Month 24								
I am unable to perform my usual activities	1	1.8	0	0	1	2.2	2	1.3
I have no problems performing my usual activities	38	67.9	37	71.2	34	73.9	109	70.8
I have some problems with performing my usual activities	17	30.4	15	28.8	11	23.9	43	27.9

Domain	Placebo		Perindopril		Amlodipine		Total	
	n	%	*n*	%	*n*	%	*n*	%
Pain/discomfort *Month 12*								
I have extreme pain or discomfort	5	7.1	4	6.7	2	3.8	11	6.0
I have moderate pain or discomfort	36	51.4	27	45.0	18	34.6	81	44.5
I have no pain or discomfort	28	40.0	29	48.3	32	61.5	89	48.9
Missing	1	1.4	0	0	0	0	1	0.5
Month 24								
I have extreme pain or discomfort	4	7.1	4	7.7	1	2.2	9	5.8
I have moderate pain or discomfort	25	44.6	29	55.8	16	34.8	70	45.5
I have no pain or discomfort	27	48.2	19	36.5	29	63.0	75	48.7
Anxiety/depression *Month 12*								
I am extremely anxious or depressed	1	1.4	0	0	0	0	1	0.5
I am moderately anxious or depressed	20	28.6	9	15.0	7	13.5	36	19.8
I am not anxious or depressed	48	68.6	51	85.0	45	86.5	144	79.1
Missing	1	1.4	0	0	0	0	1	0.5
Month 24								
I am extremely anxious or depressed	2	3.6	1	1.9	0	0	3	1.9
I am moderately anxious or depressed	13	23.2	10	19.2	4	8.7	27	17.5
I am not anxious or depressed	41	73.2	41	78.8	42	91.3	124	80.5

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