The efficacy of pharmacotherapy for decreasing the expansion rate of abdominal aortic aneurysms: a systematic review and meta-analysis

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CRD summary
The growth rate of abdominal aortic aneurysms did not seem to be significantly reduced by beta-blockers, but statins and other inflammatory agents may hold promise. Further research is needed. Overall, this was a well-conducted review and the cautious conclusions and recommendation for further research are likely to be reliable, given the limitations of the included studies.

Authors' objectives
To assess the efficacy of pharmacotherapies for reducing the expansion rate of abdominal aortic aneurysms with a diameter of at least three centimetres.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception up until October 2006; the MEDLINE and EMBASE searches were also updated in July 2007. Search terms were reported; specific search filters for study design were used. In addition, reference lists of review articles and congress abstracts were checked for further studies. A search of www.ClinicalTrials.gov was also carried out.

Study selection
Randomised controlled trials (RCTs) and cohort studies comparing pharmacotherapy interventions with a control group, in patients with abdominal aortic aneurysms, were eligible for inclusion in the review. An abdominal aortic aneurysm was defined as an aneurysm of at least 3cm in diameter occurring in a vessel below the level of the renal arteries. Eligible studies had to assess abdominal aortic aneurysm size on at least two occasions, and report the mean growth rate difference in abdominal aortic aneurysm diameter expressed in millimetres per year (mm/yr) with sufficient information to calculate a standard deviation. A follow-up period of at least six months was required. Studies assessing abdominal aortic aneurysms previously treated with surgery, studies involving arteries which were not below the level of the renal arteries, infectious abdominal aortic aneurysms (e.g.mycotic) and studies assessing patients with Marfan syndrome, were excluded from the review.

Included studies assessed beta-blockers, other antihypertensive agents (diuretics, calcium channel blockers and angiotensin-converting enzyme inhibitors), antibiotics (doxycycline and roxithromycin) and other anti-inflammatory agents, including statins and non-steroidal anti-inflammatory drugs (NSAIDs). The majority of studies compared interventions with no intervention control groups, and the remainder with placebo. Abdominal aortic aneurysm diameter was usually measured using ultrasound. Follow-up ranged from at least 12 months to 87 months. Most participants were men; where reported, the mean age was 69 years. The reporting of confounding baseline characteristics was variable, but 50% of studies reported the proportion of past and current smokers (ranging from 17 to 72%).

Two reviewers independently assessed the eligibility of each study.

Assessment of study quality
Two reviewers independently assessed the validity of each RCT using the Jadad scale (randomisation, blinding and follow-up), in addition to assessing allocation concealment. Each RCT was awarded a score of between 0 and 5 points. Cohort studies were assessed using the following criteria: approach used to recruit participants; length of follow-up; and consideration of confounding variables. Both types of studies were judged on whether they had been stopped early for benefit and whether there was any a priori assessment of sample size or statistical power. Other criteria were also reported including the potential for baseline differences and the adjustment of analyses for confounding variables in RCTs.

Data extraction

Database of Abstracts of Reviews of Effects (DARE)
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The mean difference in growth rate between study groups was calculated with the standard error, which was based on the standard deviation. Where studies failed to report the standard error mean difference, standard deviation or another measure of dispersion from which a standard deviation could be calculated, standard deviations were calculated from the raw data. Study authors were contacted for missing information. Data relating to potential confounding variables including ethnicity, gender, smoking status, age, family history of abdominal aortic aneurysm and coronary artery disease, were also extracted.

Two reviewers independently extracted the study data and disagreements were resolved by a third reviewer.

Methods of synthesis
Studies were grouped according to intervention and study design. Pooled growth rate differences with 95% confidence intervals (95% CIs) were calculated using both fixed-effect and random-effects analyses. Statistical heterogeneity was assessed using the $\chi^2$ test. Publication bias was assessed using both Egger's and Begg's tests.

Results of the review
Fourteen studies (n=4,804 patients), including five RCTs and nine prospective controlled cohort studies, were included in the review. Jadad scores for the five RCTs ranged from 2 to 5, with two trials achieving maximum scores (5 points). The quality of the cohort studies was variable and most had methodological flaws.

Beta-blockers: Three RCTs (n=1,079) and five prospective cohort studies (n=658) evaluated beta-blockers. When pooled, the RCTs failed to find any significant difference between the intervention and control groups. However, the cohort studies showed a significant benefit in favour of beta-blockers (pooled growth rate difference -0.62mm/yr; 95% CI -1.00 to -0.24).

Antihypertensive agents: In the two cohort studies of other antihypertensive agents (four comparisons), all comparisons (except with diuretics) reported lower growth rates in the intervention groups in comparison with control. None of the differences were statistically significant. The studies were not pooled due to significant statistical heterogeneity.

Anti-inflammatory agents: Two RCTs of antibiotics (heterogeneity $p=0.84$), two cohort studies of statins (heterogeneity $p<0.001$) and one cohort study of non-steroidal anti-inflammatory drugs (NSAIDs) reported growth rates in favour of the intervention compared with the control group. In each case, the effects were generally larger than those reported for other types of interventions, but only the two pooled cohort studies of statins and one cohort study of NSAIDs showed a statistically significant difference in favour of the intervention.

No evidence of significant publication bias was found.

Authors' conclusions
The growth rate of abdominal aortic aneurysms did not seem to be significantly reduced by beta-blockers, but statins and other inflammatory agents may hold promise. Further research is needed.

CRD commentary
This review answered a clearly defined research question using literature searches for both published and unpublished data. Statistical tests for publication bias failed to find any evidence of significant publication bias, although these tests lacked statistical power, given the inclusion of only a limited number of studies. All of the key stages of the review process were independently checked by two reviewers to reduce the risk of reviewer errors and bias. Study quality and statistical heterogeneity were assessed. Studies were combined according to study design and intervention, using appropriate statistical methods. Study pooling was limited by the lack of studies and the differences in study design and intervention. A number of the studies also lacked methodological rigour. Overall, this was a well-conducted review and the cautious conclusions and recommendation for further research are likely to be reliable given the limitations of the included studies.

Implications of the review for practice and research
Practice: The authors stated that statins and other anti-inflammatory agents cannot be recommended as sole
Interventions without further research.

Research: The authors stated that RCTs are required to further investigate the use of pharmacotherapies in patients with abdominal aortic aneurysms, in particular the use of promising anti-inflammatory agents.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.