Systematic review of cardiovascular disease and cardiovascular death in patients with a small abdominal aortic aneurysm

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Background: Screening for abdominal aortic aneurysm (AAA) has reduced the rate of AAA rupture. However, cardiovascular disease is still a major cause of death in men with an AAA. The aim of this study was to assess cardiovascular risk in patients with a small AAA.

Methods: Standard PRISMA guidelines were followed. Analysis was performed of studies reporting cardiovascular outcomes in patients with a small AAA (30–54 mm). Weighted metaregression was performed for cardiovascular death in patients with a small AAA, and the prevalence of cardiovascular disease was reviewed.

Results: Twenty-one articles were identified describing patients with an AAA, and the prevalence of, and death from, cardiovascular disease. Ten of these reported cardiovascular death rates in patients with a small AAA. Some 2323 patients with a small AAA were identified; 335 cardiovascular deaths occurred, of which 37 were due to AAA rupture. Metaregression demonstrated that the risk of cardiovascular death was 3.0 (95 per cent c.i. 1.7 to 4.3) per cent per year in patients with a small AAA ($R^2 = 0.902$, $P < 0.001$). The prevalence of ischaemic heart disease (44.9 per cent), myocardial infarction (26.8 per cent), heart failure (4.4 per cent) and stroke (14.0 per cent) was also high in these patients.

Conclusion: The risk of cardiovascular death in patients with a small AAA is high and increases by approximately 3 per cent each year after diagnosis. Patients with a small AAA have a high prevalence of cardiovascular disease. Patients with a small AAA should be considered for lifestyle modifications and secondary cardiovascular protection.

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Introduction

Screening programmes for abdominal aortic aneurysm (AAA) have recently been rolled out across the UK and elsewhere1, based on randomized trial evidence2,3 of clinical and cost effectiveness. Men screened for AAA have an approximately 50 per cent reduction in aneurysm-related mortality. Although screening can reduce AAA-related mortality, it has little overall effect on all-cause mortality4. The Multicentre Aneurysm Screening Study (MASS) trial3 demonstrated that cardiovascular disease was one of the main causes of death in men with AAA, regardless of intervention to treat the aneurysm3. Furthermore, data from the UK Small Aneurysm Trial5 suggested that, for every 8-mm increase in aneurysm diameter, the relative risk of cardiovascular death increased by 1.34.

In the National Health Service AAA Screening Programme6, the majority of AAs detected (over 95 per cent) are small (less than 55 mm in diameter). These small AAAs grow very slowly and it is usually many years before the threshold to consider surgical intervention is reached7. The time between detection and treatment represents an opportunity to intervene to improve the health of these patients.

Secondary cardiovascular prevention is effective at reducing cardiovascular death in high-risk groups, such as those who have had a myocardial infarction8 or patients with peripheral arterial disease9. The National Institute for Health and Care Excellence (NICE)10 currently recommends secondary prevention for individuals with a 10-year cardiovascular risk above 10 per cent. Given the high number of cardiovascular deaths observed in trial data reporting outcomes of patients with a small AAA, it may be that they should be considered for secondary cardiovascular prevention. However, there is international equipoise over the need for such intervention11.
The aim of this systematic review was to quantify the risk of cardiovascular death in patients with a small AAA, thus determining whether men with a screen-detected small AAA represent a suitable target group for secondary cardiovascular prevention.

Methods

A systematic review of the data was conducted using the Standard Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, following a formal protocol. All studies reporting cardiovascular death and morbidity in patients with a small AAA (30–54 mm) were considered for full-text review. The inclusion criteria were: studies of patients with a small AAA that published cardiovascular death rates, including myocardial infarction (MI), heart failure, cerebrovascular disease and AAA-related deaths (secondary to AAA rupture). In addition, where given, data for the prevalence of ischaemic heart disease (IHD), previous MI, heart failure and cerebrovascular disease in these patients were extracted to obtain additional descriptive information. Studies presenting non-cardiovascular mortality, and studies of large AAA (over 54 mm) were excluded.

Information sources

A literature search was undertaken using MEDLINE, Scopus and Web of Science, with grey literature search results subsequently added using the Open Grey database. Searches included all articles up to 1 February 2014 and any duplicates were removed. The search terms included ‘abdominal AND aortic AND “aneurysm” OR aneurism’ OR ‘AAA’, and were then further limited by the search terms: ‘heart failure’ OR ‘acute coronary syndrome’ OR ‘myocardial infarction OR heart attack’ OR ‘angina, stable OR angina OR angina pectoris OR angina unstable’ OR ‘coronary disease’ OR ‘myocardial ischemia OR myocardial ischaemia’ OR ‘ischaemic heart disease’ OR ‘ischaemic attack, transient OR TIA’ OR ‘stroke’ OR ‘brain infarct OR cerebral infarction OR brain infarction’ OR ‘cardiovascular mortality’ by use of an ‘AND’ statement.

Study selection

Studies were selected for inclusion in the systematic review initially by screening the abstracts for suitability by two reviewers independently, with any differences resolved by consensus. The remaining articles were then reviewed in full and those selected were included in the study. All included studies had a definition of a small AAA of 30–54 mm. Additional studies, not included in the database search, were identified by searching the reference lists of retained articles. The quality of randomized clinical trials (RCTs) included was assessed using the Jadad score, whereas a modified Newcastle–Ottawa Scale was used for non-randomized trials. A funnel plot was used to assess for potential publication bias.

Where possible, the cardiovascular death rate for each study was plotted against respective mean study follow-up with n-weighted linear regression performed to estimate the risk of cardiovascular death per year. To assess co-morbidities in this patient group, n-weighted means were produced of the prevalence of IHD, previous MI, heart failure and cerebrovascular disease in patients with a small AAA.

Results

Literature search

The results of the literature search are summarized in Fig. 1. A total of 3094 studies were identified from the search and 17 studies from additional sources. Following removal of duplicates and review of the abstracts, 79 full-text articles were selected for the study. A funnel plot suggested minimal publication bias. Of the remaining articles, 58 were excluded because they did not primarily identify patients with an AAA. From the remaining 21 articles, 11 published data on cardiovascular death in patients with a small AAA; one article could not be used for metaregression as only the relative risks were published (no reply was received with regard to absolute risks after correspondence with the author). Overall, ten articles, 15–17,21,22,24,29,30,32,34 were included in the metaregression on cardiovascular death in patients with a small AAA (Table S1, supporting information). Some 2323 patients were included from these ten studies, with a median follow-up of 5 (range 2.5–12) years. Four of these studies were RCTs that compared control groups against treatment groups; only the control arms of these trials were included here. Study quality is also shown in Table S1 (supporting information); the studies included all achieved the necessary quality scoring.

Sixteen articles were used for the secondary outcomes measures in patients with a small AAA (Table S1, supporting information). Of these, 15 articles reported prevalence of IHD, six contained prevalence of previous MI and five stated the prevalence of heart failure in their cohorts. Eleven articles stated the prevalence of any cerebrovascular disease in the study group.
Small abdominal aortic aneurysm and risk of cardiovascular death

The risk of cardiovascular death in patients with a small AAA (less than 55 mm) was entered into a metaregression analysis. Collating all available data, a total of 335 cardiovascular deaths were recorded in 2323 patients (14·4 per cent) with a small AAA (Table S1, supporting information) over a median follow-up of 5 (range 2·5–12) years. Median age at the start of the study was 71·2 years. Cardiovascular deaths were recorded in the studies as any death caused by MI, heart failure, cerebrovascular disease or AAA rupture, except in two studies in which ‘other cardiovascular disease’ or ‘cardiovascular death’ groups were not defined, yet were still included in the total deaths for the quantitative assessments.

Seven15–17,22,24,29,34 of the ten studies published AAA-specific mortality; there were 37 AAA ruptures leading to death (11·2 per cent of total cardiovascular deaths); 23 of these deaths came from the longest follow-up study, which lasted 12 years16. Only one study34 recorded the diameter at which AAA rupture occurred, stating that, of two AAA ruptures recorded, one was over 5·5 cm in diameter. Moreover, two studies16,32 stated the number of deaths after any subsequent AAA surgery; one16 reported 28 perioperative deaths from the 401 AAA operations done in the 12-year follow-up, whereas the other32 reported no perioperative deaths after 37 AAA repairs performed in the 3-year follow-up. The number of patients with cardiovascular-related death after exclusion of AAA-specific deaths was therefore 298 (12·8 per cent) of 2323; AAA rupture in this cohort with a small AAA accounted for 1·6 per cent of overall mortality, similar to the 0·96 per cent of deaths from AAA rupture recorded from the MASS trial3 control group of patients with a small AAA. Only two studies17,32 specified the proportion of patients with a small AAA who were also on a statin or aspirin; neither of these described any impact of this on cardiovascular death.

Overall, metaregression of studies publishing cardiovascular death rates suggested a strong positive correlation between follow-up duration and cardiovascular death ($R^2 = 0·902$, $P < 0·001$), and suggested that the risk of cardiovascular death increased by 3·0 (95 per cent c.i. 1·7 to 4·3) per cent each year in patients with a small AAA (Fig. 2).
Small abdominal aortic aneurysm and prevalence of cardiovascular disease

The prevalence of cardiovascular disease in patients with a small AAA was also assessed as a secondary outcome of the study; overall 16 studies reported the prevalence of IHD, previous MI, heart failure and cerebrovascular disease in patients with a small AAA (Table S1, supporting information).

Ischaemic heart disease

Fifteen studies15,17–20,23,25,26,28,31–35 reported the rate of IHD in patients with a small AAA, all showing a high prevalence of the disease. A wide variation was seen in the definitions used for IHD in these studies; most employed a history of ‘cardiac symptoms’ or intervention as their definition. The smallest study20 contained 37 patients, whereas the two largest28,31, which included 728 patients, reported a previous MI rate of 31.3 per cent. In total 1904 patients were included. A large proportion of patients with a small AAA had a history of MI, with the weighted mean(s.d.) prevalence calculated at 26.8(7.7) per cent.

Heart failure

A wide variation was seen in the definition of heart failure among the five studies15,18,20,31,34 that provided prevalence statistics, ranging from American Heart Association class III/IV to patients receiving medication for heart failure. The smallest study20 reported a prevalence of 19 per cent among the 37 patients included, whereas the largest31, containing 728 patients, showed a prevalence of 6.2 per cent. In total, 1657 patients were included and the weighted mean(s.d.) prevalence of heart failure was 4.4(2.5) per cent.

Cerebrovascular disease

The final cardiovascular disease assessed in patients with a small AAA was cerebrovascular disease. The definition in the 11 studies17,19,20,25–29,31,34,35 was previous stroke. The largest study28, which included 1136 patients, reported a prevalence of stroke in their cohort of 12.3 per cent, whereas the smallest study20 contained 37 patients and stated that the prevalence was 35 per cent. A UK-based group26 identified previous stroke in 22.8 per cent of their 206 patients with a small AAA. Overall there was a high prevalence of stroke in these patients, with a weighted mean(s.d.) rate of 14.0(3.9) per cent.

Discussion

This systematic review found a high prevalence of IHD, previous MI, stroke and heart failure in patients with a small AAA. Patients with a small AAA are at higher risk of further cardiovascular complications than the normal population. Aggregating the studies that have reported cardiovascular death in patients with a small AAA over time suggests their risk of cardiovascular death is 3 per cent each year; this is compared with the mean annual cardiovascular death rate in the general population of 65–74-year-olds from 1995 (0.78 per cent), as reported by the Office for National Statistics for England and Wales. Extrapolated to 5 years, this suggests that patients with a small AAA may have a 5-year risk of cardiovascular death of approximately 15 (95 per cent c.i. 9 to 22) per cent. Using the Framingham risk score, an algorithm used to calculate cardiovascular risk of an individual based on the Framingham Heart Study, this is equivalent to that of a 70-year-old male diabetic smoker with hyperlipidaemia and hypertension.
Current NICE guidelines\textsuperscript{38} suggest that a patient with this level of cardiovascular risk should be given basic lifestyle advice, and started on cardiovascular primary prevention. Lifestyle modifications may include smoking cessation, diet modification and weight control. Cardiovascular primary prevention includes controlling circulating cholesterol lipid and BP regulation. Recently updated NICE guidance\textsuperscript{10} states that patients with a 10 per cent risk of cardiovascular events should be placed on a statin. Data from the EUROSTAR registry\textsuperscript{39} in 2006 found that only 12.4 per cent of patients with an AAA were taking a statin; this was relatively unchanged from previous data reported in the EVAR trial\textsuperscript{10}. Data regarding the use of best medical therapy (BMT) in patients with an AAA remain variable; for example, in one study\textsuperscript{41}, 36 per cent of patients with an AAA were reported to be on statin, aspirin and antihypertensive medication. A proactive approach to managing risk factors in patients with a small AAA may help to reduce the development of, and mortality from, cardiovascular disease.

Data from Sohrabi and colleagues\textsuperscript{42} showed that the presence of a small AAA increases the levels of biomarkers for cardiovascular disease, despite the absence of any clinical cardiovascular disease. AAA is thought to be an inflammatory disease, with raised levels of inflammatory markers in patients with an AAA\textsuperscript{43,44}. However, no drugs have been able to slow or prevent the growth of small AAAs. A recent Cochrane review\textsuperscript{45} highlighted the potential use of beta-blockers, tetracyclines and statins as possible interventions to stabilize AAA growth. Smoking is the only modifiable risk factor that has been linked to the development, expansion and rupture of AAA\textsuperscript{28,46,47}, and a recent study\textsuperscript{48} demonstrated a linear relationship between AAA mortality and smoking prevalence, cholesterol levels and BP. Risk factor modification may therefore reduce AAA deaths. AAA represents a local manifestation of poor cardiovascular health and, although genetic influences are important, risk factor exposure is likely to be the dominant factor\textsuperscript{49}.

It is possible that many of these patients with an AAA will not have been prescribed any previous cardiovascular risk factor management, as not all patients in this group have concurrent cardiovascular morbidities. The prevalence data here showed that 55.1 and 73.2 per cent respectively of patients with a small AAA had no diagnosed IHD or previous MI, whereas 95.6 and 86.0 per cent respectively had no history of heart failure or stroke.

One limitation of this study is the wide range of definitions used for small AAA, yet most were within the current definition of 3–5.4 cm. Moreover, many of the studies had varying definitions for the cardiovascular diseases identified, producing potentially unreliable data. Cardiovascular death was also poorly defined in some studies. Some of the studies identified were relatively small (ranging from 16 to 662 patients); however, combining all the available studies resulted in a total of 2323 patients with a small AAA.

The present systematic review highlights the increased cardiovascular risk of patients with a small AAA. Currently there are no guidelines for this patient group, suggesting that there is a need to monitor and treat these patients for cardiovascular diseases and risk factors.

In the NHS AAA Screening Programme, men receive an appointment with a specialist nurse, who gives general lifestyle advice (including smoking cessation) and contacts the man's general practitioner to recommend antiplatelet and statin therapy. The effects of this intervention are unknown but could be expected to reduce cardiovascular morbidity and mortality.

**Disclosure**

The authors declare no conflict of interest.

**References**


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Supporting information
Additional supporting information may be found in the online version of this article:
Table S1 Included articles describing the prevalence of, and death from, cardiovascular disease in patients with a small abdominal aortic aneurysm (Word document)