A Multicentre Observational Study of the Outcomes of Screening Detected Sub-aneurysmal Aortic Dilatation CME ☆

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WHAT THIS PAPER ADDS?

This observational study combines several small AAA surveillance programmes in order to determine what the outcomes of patients with sub-aneurysmal aortic dilatation, 25 mm—29 mm diameter, are. Using time to event analysis we determined that at 10 years of follow up 26.2% had developed an AAA of greater than 54 mm.

Objectives: Currently most abdominal aortic aneurysm screening programmes discharge patients with aortic diameter of less than 30 mm. However, sub-aneurysmal aortic dilatation (25 mm—29 mm) does not represent a normal aortic diameter. This observational study aimed to determine the outcomes of patients with screening detected sub aneurysmal aortic dilatation.

Design and methods: Individual patient data was obtained from 8 screening programmes that had performed long term follow up of patients with sub aneurysmal aortic dilatation. Outcome measures recorded were the progression to true aneurysmal dilatation (aortic diameter 30 mm or greater), progression to size threshold for surgical intervention (55 mm) and aneurysm rupture.

Results: Aortic measurements for 1696 men and women (median age 66 years at initial scan) with sub-aneurysmal aortae were obtained, median period of follow up was 4.0 years (range 0.1—19.0 years). Following Kaplan Meier and life table analysis 67.7% of patients with 5 complete years of surveillance reached an aortic diameter of 30 mm or greater however 0.9% had an aortic diameter of 54 mm. A total of 26.2% of patients with 10 complete years of follow up had an AAA of greater that 54 mm.

Conclusion: Patients with sub-aneurysmal aortic dilatation are likely to progress and develop an AAA, although few will rupture or require surgical intervention.

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INTRODUCTION

Abdominal aortic aneurysms (AAA) are associated with high mortality when they rupture (RAAA). The Multi-centre Aneurysm Screening Study (MASS) demonstrated that screening asymptomatic males aged 65—74 reduces aneurysm related mortality.[1] This, and additional evidence from other studies of AAA screening have led to the adoption of AAA screening programmes in many countries.[2,3] In most screening programmes, a policy of regular ultrasound scan surveillance is adopted for men with infra-renal aortic diameters between 30 mm and 54 mm with referral for elective aneurysm repair for those with AAAs above 54 mm (either at detection or whilst under surveillance). Patients with aortic diameters of less than 30 mm are usually

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discharged as it is perceived that there is no risk of aortic rupture in these patients.[4]

However, many authors consider aortic diameters between 25 mm and 29 mm as being not normal and there have been reports of such patients with sub-aneurysmal aortic dilatation progressing to develop true AAA and even rupture.[5,6] Sub-aneurysmal aortic dilatation has been reported to have a prevalence of 2.1% in 65 year old males[5] and for screening programmes, this patient group is therefore likely to represent a similar number of patients as those detected to have AAAs. Recent evidence indicates that patients with an aortic diameter of between 25 mm and 29 mm have significantly higher rates of all cause mortality when compared to those with an aortic diameter of less the 24 mm.[7]

This study aims to determine the long-term outcomes of patients with sub-aneurysmal aortic dilatation through the combination of individual patient level data from community surveillance.

METHODS

This article was completed in accordance with the STROBE statement. Individual patient data from 8 community screening and surveillance studies was obtained. Datasets for inclusion were identified by contacting authors of publications that had reported the outcomes of such patients previously and via personal communication with individuals known to have such datasets. Datasets were included in the study if they contained serial ultrasound measurements of aortic size in patients found to have an infra-renal aortic diameter between 25 mm and 29 mm at the time of screening. The time to referral for repair and/or AAA rupture were obtained where available from each centre. A pragmatic definition of rupture was adopted whereby individual contributing centres reported this outcome based upon their local policies. This may have been from post mortem examination or admission due to RAAA however there was no formal system of reporting adopted.

The methodology of determining the aortic diameter was not uniform between the centres. Measurement of aortic diameter was always taken in the antero-posterior orientation, however, some groups recorded the diameter from the anterior outermost aortic wall to the posterior outermost wall (OTO) and some groups used the anterior innermost wall to the posterior innermost wall (ITI). Since it is known that there are discrepancies between the two methods[8,9] the method used in each contributing dataset was recorded. The effect of method of measurement, ITI or OTO, was subsequently analysed.

Ethical approval was not considered necessary as this was a non interventional, retrospective observational study.

Datasets from individual centres were combined into one single dataset for analysis using standard time-to-event techniques without using meta-analytical statistical combination.[10] Statistical analysis was performed using SPSS v18 (IBM 2010) Kaplan—Meier analysis was used to estimate time-to-event results. Cox regression analysis was used to determine the influence of how the diameter was measured on progression of aortic diameter and a sensitivity analysis was conducted according to sample size of the study, comparing larger and smaller studies.

RESULTS

A total of 1696 individuals (66 female) with initial aortic diameters between 25 mm and 29 mm with long-term surveillance data were included in this study. These data were obtained from 8 centres across Europe (6 UK, 1 Finland, and 1 Denmark). The characteristics of the contributed datasets are shown in Table 1. All studies utilised ultrasound to determine the diameter of the aorta. The period of follow up varied between centres, as did recall interval (Table 1). Data regarding RAAA and related mortality was available in 7 of the datasets. Median period of follow up was 4.0 years (range 0.1—19.0 years).

The first outcome assessed was the progression of sub-aneurysmal aortic dilatation to true aneurysmal dilatation (diameter greater than 29 mm). A total of 1011 of the 1696 subjects (59.6%) developed true aneurysms at a mean time of 4.7 years (95% confidence interval 4.5 years—5.0 years), the median time was 4.0 years (range 0.1 years—16.3 years) (Fig. 1). At the 5 year point there were 774 aneurysms detected and 369 patients were still under surveillance, therefore 67.7% of patients had developed an aneurysm by 5 years, 96% by 10 years (983 aneurysms and 41 still in surveillance). The median age at first scan was 66 years old (range 56 years—71 years).

Secondly, we determined the number of patients with sub-aneurysmal aortic dilatation who developed large aneurysms (aortic diameter greater than 54 mm). Only 140 of the 1696 patients (8.3%) with sub-aneurysmal aortic dilatation developed large AAA at a mean time of 13.2 years (95% confidence interval 12.6 years—13.7 years) (Fig. 2) the median time was 12.6 years (range 1.2 years—19.5 years). Of those patients who developed large AAA, 4.3% had done so by 5 years and 47.7% by 10 years. An alternative method of interpreting these results is that a total of 189 patients had 10 years or more of surveillance and 67 patients had reached 55 mm by this time, therefore 26.1% of patients with 10 years follow-up reached the threshold for surgery. Although a diameter of 54 mm represents the current threshold for referral from screening for consideration of repair, certain groups utilised a diameter of 50 mm as the threshold for referral. Therefore analysis of the data for patients progressing to an aortic diameter of greater than 50 mm was conducted (195 of the 1696 patients, 11.5%, reached this diameter). The mean time for an ectatic aorta to reach this size was 11.9 years (95% confidence interval 11.4 years—12.4 years) (Fig. 3) the median time was 11.1 years (range 0.8 years—18.5 years). Of those patients reaching an aortic diameter of 50 mm, 6.7% had done so by 5 years of surveillance, 60.1% by 10 years and 96.4% by 15 years.

Our final endpoint was progression to aortic rupture. Data was available from 7 sites (1631 patients) however as

Table 1. The participants in the sub aneurysmal aortic dilation study.

Country and Region	No of patients (no. female)	Median age at first scan in years	Mean baseline aortic diameter	Frequency of follow up (Duration of programme)	Period of Follow-up in years (Range)	Mean No. of scans per person	Method of measurement	Previously published
Finland, Oulu	8 (1)	70	27.0 mm	Mixed (1991–2000)	8.2 (5.1–10.5)	2.0	Outer to outer	Biancari et al.[11]
Denmark, Viborg	127 (0)	66	26.5 mm	Annual (1994–2005)	5.7 (2.7–11.0)	2.4	Outer to outer	Lindholt et al.[6,a]
UK, Bournemouth	92 (22)	70	27.1 mm	Varied (1993–2010)	4.0 (10.5–13.0)	6.3	Outer to outer	Parvin[12]
UK, Chichester	128 (0)	65	27.0 mm	Alternate years (2004–2011)	3.9 (1.9–7.4)	4.9	Inner to inner	Hafez et al.[13,a]
UK, Gloucester	924 (0)	65	27.1 mm	Varied (1990–2011)	5.5 (0.1–19.5)	6.7	Inner to inner	McCarthy et al.[5,a]
UK, Leicester	309 (1)	66	27.2 mm	Alternate Years (1996–2010)	4.8 (0.6–14.)	6.1	Outer to outer	Gibbs et al.[14,a]
UK, Manchester	43 (16)	66	28.0 mm	Annual (2001–2011)	3.5 (0.5–10.1)	3.8	Outer to outer	McCollum-personal communication
UK, Stirling	65 (26)	68	26.7 mm	Alternate years (1994–2011)	4.6 (0.1–15.5)	2.5	Not stated	Holdsworth-personal communication

[a] Dataset has been updated from published data.

Figure 1. Proportion of patients progressing from sub-aneurysmal aortic dilatation to an aortic diameter of >30 mm. Mean time to event 4.75 years (95% Confidence Interval 4.54–4.96) SE 0.11, median time to event 4.00 years (95% Confidence Interval 3.90–4.10) SE 0.49.

Figure 2. Proportion of patients progressing from sub-aneurysmal aortic dilatation to an aortic diameter of >54 mm. Mean time to event 13.15 years (95% Confidence Interval 12.57–13.74) SE 0.30. Median 11.12 years, median time to event 12.61 (95% Confidence Interval 11.66–13.56) SE 0.48.

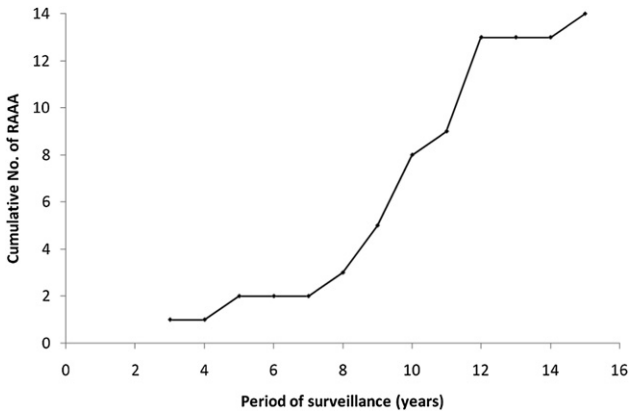

Figure 3. Cumulative number of RAAA following entry in to surveillance.

there was no formal system of defining an aortic rupture we believe RAAA may be under-reported. Additionally the rupture rate will be influenced by patients under surveillance being referred for surgical correction of their aneurysm. Of the 14 ruptures known to have occurred the mean time from presentation to rupture was 18.7 years (95% confidence interval 18.3 years—19.1 years) (Fig. 3). Median aortic diameter at presentation of the patients that went on to rupture was 26 mm (range 25—29) and median age at presentation was 65 years old (range 64 years—72 years). Survival table analysis revealed at five years 0.3% of patients remaining under surveillance had ruptured (2 ruptures, 711 individuals in surveillance) at 10 years follow-up this was 3.1% (7 ruptures, 222 individuals in surveillance). 10 RAAA patients died, 71.4% (95% CI 45.4%—88.3%). The median age at rupture was 76 years (range 68 years—84 years).

The use of either ITI or OTO measurement to determine the aortic diameter is contentious; therefore we compared the mean time from initial scan to an event based upon the method of measurement.[8,9] Two sites utilised ITI measurement, 5 utilised OTO and one site did not specify the method by which the aortic diameter was determined. In terms of progression to true aneurysmal dilatation (30 mm aortic diameter) there was little difference in comparison of the methods of measurement, with a mean time of 4.6 years in the ITI group and 4.7 years in the OTO group (Table 2) and formal statistical comparison revealed no significant difference between the ITI and OTO groups (hazard ratio for OTO group 0.91 (95% confidence interval 0.80 to 1.04, $P = 0.17$). The group that did not specify method of aortic measurement had a mean time to true aneurysmal dilatation of 6.6 years, a sizeable deviation from the results of other groups. In terms of progression to an aortic diameter of 55 mm, there was again little difference in comparison of the methods of measurement, mean time to event was 12.9 years in the ITI group, 14.6 years in the OTO group and 13.6 years in the group that did not specify their method of assessment (Table 2) (hazard ratio for OTO group 1.56 (95% confidence interval 0.94 to 2.60, $P = 0.08$) Cox Regression). Finally, when comparing the progression to aneurysm ruptures the mean time to event was 18.9 years in the ITI group and 16.3 years in the OTO group (hazard ratio for OTO group 2.85 (95% confidence interval 0.89 to 2.85, $P = 0.08$) Cox Regression).

We performed a sensitivity analysis to determine whether the results presented above were influenced by any measures of study quality. The only robust measure available was study size and we therefore compared the results from the data contributed by the four studies in the lower half of the range of study sizes (less than 100 patients) with all others. Very little difference was observed for all outcomes between the aggregated low volume studies and the aggregated high volume studies (Table 3). The mean time for progression to true aneurysm aortic diameter (30 mm) in larger studies was 4.7 years and in smaller studies it was 5.0 years (Table 3). The mean time for progression to large aneurysm (>54 mm) in larger studies (127 or more patients), was 13.1 years and in smaller studies, it was 14.6 years (Table 3). Comparison of the mean time to aneurysm rupture was not possible as no ruptures were reported in the groups with less than 100 patients.

DISCUSSION

This study shows that the majority of patients with sub-aneurysmal aortic dilatation progress to true aneurysmal aortic dilatation, with almost half of these doing so within 5 years of follow-up. Furthermore, the study also shows that within 10 years of detection, a smaller proportion (approximately 4%) will progress to an aortic diameter that would be considered at or above the threshold for surgical intervention. The proportion of patients with sub-aneurysmal aortic dilatation who progress to true aneurysmal dilatation or develop large AAA is similar irrespective of the method of ultrasound measurement used (ITI or OTO), as demonstrated in the sensitivity analysis.

The principle strength of this study is the large combined sample size available for analysis. The results from most of the individual cohorts that contributed to this study have

Table 2. Total numbers of patients that progressed to aortic diameters of greater than 29 mm and greater than 54 mm by 5 and 10 years, stratified by method of measuring aortic diameter. ITI = Inner wall to inner wall aortic measurement, OTO = Outer wall to outer wall aortic measurement.

Method of measurement	*n*	Progression to ≥30 mm			Progression to ≥54 mm		
		5 years (%)	10 years (%)	Mean time to 30 mm (95% CI)	5 years (%)	10 years (%)	Mean time to 55 mm (95% CI)
ITI	1052	484 (71.0)	617 (96.4)	4.6 years (4.3—4.8)	4 (0.95)	54 (28.3)	12.9 years (12.3—13.5)
OTO	579	272 (64.9)	333 (75.0)	4.7 years (4.3—5.0)	2 (1.1))	6 (15.7)	14.6 years (12.6—16.7)
Not Specified	65	18 (42.9)	34 (85.0)	6.6 years (5.4—7.7)	1 (5.6)	2 (25.0)	13.6 years (11.9—15.3)

Table 3. Total numbers of patients that progressed to aortic diameters of greater than 29 mm and greater than 54 mm by 5 and 10 years, stratified by cohort size. Large cohorts were defined as the top 4 cohorts contributing to the study in terms of size (127, 128, 309 and 924 patients) with all other cohorts being classified as small (8, 43, 65 and 92 patients).

Cohort size	*n*	Progression to 30 mm			Progression to 55 mm		
		5 years (%)	10 years (%)	Mean time to 30 mm (95% CI)	5 years (%)	10 years (%)	Mean time to 55 mm (95% CI)
Large	1487	687 (68.6)	859 (96.5)	4.7 years (4.5—4.9)	6 (1.0)	60 (25.6)	13.1 (12.5—13.7)
Small	209	87 (61.3)	124 (92.5)	5.0 years (4.4—5.6)	1 (1.9)	7 (31.8)	14.6 (12.3—16.8)

been published in part previously[5,6,11—14] with a variety of conclusions drawn regarding the benefit of continued surveillance in patients with sub-aneurysmal aortic dilatation. Unsurprisingly, these studies have all shown similar findings to this combined analysis. However, similar results have been observed in small datasets that were not included in this analysis.[15,16] The sensitivity analysis presented demonstrates that when considering the results from the group of patients drawn from smaller cohorts, similar results are seen when compared to the results from the larger cohorts. This, taken together with the fact that other small studies have found similar results, suggests that the analysis of small cohorts remains valuable. This may be particularly useful for the determination of covariate effects on the progression of sub-aneurysmal dilatation providing sample sizes allow at least 100 patients in each covariate sub-group. Additionally as our analysis utilises time to event data we are able to allow for patients who fail to participate in full screening without adversely effecting our data. The follow-up regime varied greatly between the programmes that contributed data to this analysis. Annual rescanning was completed in Viborg, Manchester and Gloucester, alternate yearly scans were offered in Chichester, Stirling and Leicester, 3—6 monthly scanning was conducted in Oulu whilst a varied rescan interval was performed in Bournemouth. As the landmarks used in aneurysm measurement also varied between study centres, we have examined this effect within our sensitivity analysis. It has been previously demonstrated that ITI measurement is superior to OTO in terms of reproducibility,[8] however some centres also use a method of measuring the aneurysm leading edge to leading edge, as these structures are more clearly defined in ultrasound imaging.[3] As the aortic wall may contribute up to 4 mm of the total diameter it is important to understand the potentially wide variation in an ITI and OTO measurement, despite the definition for a sub-aneurysmal aortae being the same for both. Therefore the use of these 2 forms of measurement is a limitation of this study, which we have attempted to correct for. Sensitivity analysis comparing ITI and OTO methodology revealed no significant difference in terms of size progression, ensuring that combining these methods of surveillance is reliable. None of these centres included inter and intra-observer variability analyses. It is also unknown how many patients were lost to follow up due to either a change in location, mortality, or termination of their surveillance either due to a non-progressing aortic diameter or co-morbidities.

To accurately evaluate the impact of possessing a sub-aneurysmal aorta, comparison of this data to a cohort of patients with normal aortic diameters would be ideal. Although this has not been undertaken within this study, the risk of future AAA development requiring intervention beyond this point is negligible, with Crow et al.[17] observing that 1.8% of patients developed an aneurysm diameter >30 mm after 12 years of follow up.

This study was unable to assess the effect of environmental or patient-related factors on the progression of sub-aneurysmal aortic dilatation to true aneurysmal dilatation because of a lack of consistently defined covariate data in the contributing cohorts. The main effect of this deficiency is that limited clinical recommendations can be made on the basis of this study alone. However, large datasets examining the effect of covariate data on the progression of small AAA are becoming available[18] and since the majority of patients with sub-aneurysmal dilatation progress to true aneurysmal dilatation, clinical recommendations for the management of patients with small AAA are also likely to be applicable to patients with sub-aneurysmal dilatation. Similarly, additional outcomes such as the proportion of patients referred for surgery and the outcomes of surgery in these patients could not be assessed because of a lack of robust data in the contributing cohorts but these are again, likely to be similar to those observed in cohorts of patients with small AAA.

The known rate of ruptured AAA in this study was low (0.9% over a median period of follow up of 4.0 years). Since each individual in this study was not followed up clinically, nor were causes of death established for every individual in the study, we cannot be certain that this is the true rate of rupture. In addition, all subjects in this study were in surveillance programmes, and many of those who would have ruptured without surveillance will have been referred for surgical repair thus preventing rupture (or in cases where patients were turned down for surgical repair, further surveillance terminated). It is likely that the true rupture rate of patients with sub-aneurysmal aortic dilatation is higher than that observed here but to what extent cannot be determined. As the length of time from initial scan to rupture is 18.7 years the time interval prior to rescanning should clearly be less than this, however as the true rate of rupture outside of surveillance in this subgroup of patients is not known, the exact time of rescanning cannot be determined. In addition, two patients ruptured following less than 5 years follow up, which is the time interval for rescanning sub-aneurysmal aortae in several Swedish counties.

In the UK 300,000 men per year are offered aneurysm screening, with 2.1% of these patients measuring 25—29 mm.

If routine surveillance for these patients is offered, as in the Swedish model at 5 years, this would represent a modest increase in the number of patients attending for rescreening (6300 patients per year), and 59.6% of these patients may then enter long term annual surveillance (3755 patients per year). Although an analysis of cost effectiveness is outside the remit of this study, as the Swedish Aneurysm Surveillance programme is known to be cost effective, and is the only programme to include sub-aneurysmal aortae at present, it is likely that including sub-aneurysmal aortae will be cost effective.

The outcomes from this study raise the question of rescanning patients with sub-aneurysmal aortae. Previous studies have advocated between 2 and 5 years [Hafez 2008, McCarthy 2003] and the proposal from several of the Swedish Counties surveillance programmes is also for a five year rescan of sub-aneurysma; aortae. If it is interpreted that the goal of screening is to prevent rupture then from the data in our possession, the rescreening interval required would need to be 5 years as it is at this time point which 10 of the 14 (the remaining 4 did not have a fifth year scans, 2 had died and 2 had a tenth year rescan) patients who suffered RAAA had reached a $>$30 mm aortic diameter and we propose should enter screening. However, recent data from the long term analysis of mortality in patients with sub-aneurysmal aortae has demonstrated a significant level of all-cause mortality (10.3% at a median of 7 years). This calls the rationale of surveillance of these patients in to question, although the data for this paper was collected in the early 21st century and improvement in the management of cardiovascular disorders and malignancies is likely to reduce this mortality. This makes the presence of a small aneurysm more significant clinically in the modern era.[7] In addition, entering these patients into the aneurysm screening programme will have a cost impact, the extent of which remains unknown. As such, the authors believe that a cost-effective analysis should be undertaken to determine the cost implications for screening sub-aneurysmal aortae prior to any implementation.

An additional limitation is that few patients from our original cohort completed 10 years of surveillance, roughly 25% of patients were still in follow up at this point and this must be taken in to account when evaluating the data.

The findings in this study are made more pertinent by recent evidence that AAA is an ageing disease.[19,20] The average age for presentation of clinically relevant aneurysm has increased[19] and in England, non-ruptured AAA presentation has shifted upwards by approximately 2 years.[2] This is thought to be due to a healthier lifestyle (reduction in smoking) which may serve to delay the onset of the disease in genetically predisposed individuals. Reduced rates of smoking, one third of previously observed rates, have been reported, with an etiological fraction over 70% for smokers.[3] This changing epidemiology of AAA indicates that a significant proportion of patients who would otherwise have been detected as true aneurysms by AAA screening programmes would now fall into the sub-aneurysmal aortic dilation group. A policy of surveillance for this group of patients to prevent aneurysm related mortality would seem even more important should the current trends in AAA epidemiology continue. In addition the general tendency for individuals to live longer will likely lead to an increased proportion of sub-aneurysmal aortae progressing to a diameter that would be clinically relevant. Additionally patients entered in to surveillance are likely to benefit from advice regarding cardiovascular health, as these patients are likely to possess several risk factors for heart disease.[21]

CONCLUSION

This study suggests that the majority of screening detected sub-aneurysmal aortae will progress to become fully aneurysmal. In the absence of sufficient natural history data, existing evidence based protocols for small AAA surveillance should be applied to these individuals. There is a need to define to role of ongoing screening in this group of patients and more studies are required, determining the effects of medical comorbidities on the rate of aortic expansion and rates of rupture.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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