Infrarenal Aortic Diameter Predicts All-Cause Mortality

Paul Norman, Max Le, Carole Pearce, Konrad Jamrozik

Objective—To assess the relationship between infrarenal aortic diameter and subsequent all-cause mortality in men aged 65 years or older.

Methods and Results—Aortic diameter was measured using ultrasound in 12,203 men aged 65 to 83 years as part of a trial of screening for abdominal aortic aneurysms. A range of cardiovascular risk factors was also documented. Mortality over the next 3 to 7 years was assessed using record linkage. Initial aortic diameter was categorized into 10 intervals, and the relationship between increasing diameter and subsequent mortality was explored using Cox proportional hazard models. Median diameter increased from 21.4 mm in the youngest men to 22.1 mm in the oldest men. The cumulative all-cause mortality increased in a graded fashion with increasing aortic diameter. Using the diameter interval 19 to 22 mm as the reference, the adjusted hazard ratio for all-cause mortality increased from 1.26 (95% CI: 1.09, 1.44; \( P < 0.001 \)) for aortic diameters of 23 to 26 mm to 2.38 (95% CI: 1.22, 4.61; \( P = 0.011 \)) for aortic diameters of 47 to 50 mm. Analysis of causes of death indicated that cardiovascular disease was an important contributor to this increase.

Conclusion—Infrarenal aortic diameter is an independent marker of subsequent all-cause mortality. (Arterioscler Thromb Vasc Biol. 2004;24:1278-1282.)

Key Words: aortic diameter ■ ultrasound ■ mortality

The diameter of the infrarenal aorta only takes on clinical significance once it exceeds 30 mm, with this being the generally accepted threshold for an abdominal aortic aneurysm (AAA).\(^1\)\(^2\) There is reasonably good evidence to indicate that aortas that have reached 30 mm in diameter are indeed abnormal, with a propensity to continue to dilate and, if left untreated, eventually to rupture.\(^1\) A number of studies of patients with AAAs have shown that all-cause mortality also increases with aneurysmal diameter.\(^3\)\(^-\)\(^5\) In other words, not only is an AAA a potentially dangerous condition in its own right but also is it a marker for death from other causes. This appears to be primarily caused by an association with various manifestations of cardiovascular disease.\(^4\)\(^-\)\(^5\)

The distribution of infrarenal aortic diameter is continuous, albeit skewed to the right, and as such the choice of the 30 mm threshold is arbitrary.\(^6\)\(^-\)\(^7\) No attention has been given to the possibility that there may be a continuous relationship between infrarenal aortic diameter in the nonaneurysmal range (<30 mm in diameter) and all-cause mortality. We have used data collected as part of the Western Australian trial of screening for AAA\(^8\) to test the hypothesis that infrarenal aortic diameter predicts all-cause mortality in a cohort of 12,203 men aged 65 years and older.

Methods

Subject Recruitment and Screening

Details of the trial of screening are described elsewhere.\(^9\) Eligible men were identified and recruited from an electronic copy of the electoral roll, enrollment to vote being compulsory for Australian citizens, and invited to attend a screening clinic close to their home. Women were not invited for screening because their prevalence of AAA is one-sixth that in men.\(^9\) On arrival at the clinic, the study was explained to each participant and written consent was obtained. Each man completed a questionnaire about demographic factors, medical and occupational history, and aspects of diet and lifestyle relevant to cardiovascular disease. This was followed-up by a brief physical examination (height, weight, girth at hips and waist, blood pressure) by a nurse and then measurement of the maximum transverse and antero-posterior diameter of the infrarenal aorta using a Toshiba Capasee ultrasound machine with a 3.75 mol/L Hz probe (Toshiba Australia). The largest measurement was recorded as the aortic diameter, with images recorded on videotape for later verification by a radiologist if required. All 4 staff members performing ultrasound examinations participated in regular quality-control exercises in which interrater and intrarater agreement was examined by taking paired, blinded measurements of the maximum transverse and antero-posterior aortic diameters in a series of 10 men. This revealed that 95% of differences were <3 mm. On leaving the clinic, each man was given a letter setting out the results of his ultrasound examination and a copy of this letter for his general practitioner (GP). All follow-up management of men with AAAs (an aortic diameter of ≥30 mm) was arranged by the GP.
Procedures for Follow-Up

The majority of men with AAAs $\geq 50$ mm in diameter were referred to vascular surgeons. Men with aortic diameters of $\geq 30$ mm have been invited to join a separate and continuing study of rates of, and factors associated with, expansion of small AAAs.\(^{10}\) We used electronic record linkage to name-identified unit mortality records for Western Australia to identify all deaths in the original target population from the official death registry. The analysis was based on the most recent update of the coding data set: November 2002 for any death and December 2001 for specific cause of death. The main causes of death were identified using the combined ICD-9 Clinical Modification and ICD-10 diagnosis codes. Similar methods were used to identify all men admitted to any hospital in Western Australia with major manifestations of cardiovascular disease before and after screening. These methods have been previously validated.\(^{11}\)

Statistical Methods

Aortic diameter was initially measured in millimeters, rounded to 1 decimal place. It was logarithmically transformed because of positive skewness (3.64) and non-normality. Cox proportional hazards models were used to calculate the hazard ratio or relative risk of intervals of diameters. Logarithmic diameter was adjusted for baseline data including age, weight, height, medical history (angina, myocardial infarction, coronary angioplasty or bypass, stroke, diabetes, asthma, bronchitis), hospital admissions (for cardiovascular disease including myocardial infarction, stroke, peripheral vascular disease), smoking status (never, ex-smoker, current smoker <25 cigarettes/d or $\geq 25$ cigarettes/d), level of exercise (frequency of vigorous and nonvigorous exercise), dietary details (amounts of meat, fish, milk, and salt), systolic blood pressure.\(^{8}\) The assumption of proportional hazards was tested by plotting the weighted Schoenfeld residuals to check for nonzero slope. A distribution of residuals randomly oscillating at approximately zero suggested the validity of the assumption. Therefore, a separate test that included a time-dependent covariate in the same model further supported this assumption ($P=0.54$).

Although it would have been ideal to measure the relative risk of incremental differences in aortic diameter of 1 mm, ie, measuring hazard ratio of the pair (n, n+1) of diameters, this could not be performed because of the small numbers of subjects in the tails of the diameter distribution. We therefore categorized diameter into 10 intervals: 10 to 18 mm, 19 to 22 mm, 23 to 26 mm, 27 to 30 mm, 31 to 34 mm, 35 to 38 mm, 39 to 42 mm, 43 to 46 mm, 47 to 50 mm, and 51 to 95 mm. With the exception of the “tails,” these intervals span a range of aortic diameter of 4 mm each. This interval was chosen for 2 reasons. Firstly, 4 mm was well above 95% of all ultrasound measurement errors. Secondly, the continuous data indicated that a 1-SD increase in logarithmic diameter corresponded to a difference of $\approx 4$ mm in original data. Inspection of the continuous data revealed that the interval 19 to 22 mm contained the median and limits to the interquartile range of aortic diameters (n=6718). As a result, the interval 19 to 22 mm was used as the reference against which all other intervals were compared. Somers and Cochran-Armitage trend tests were used to assess associations and trends of specific causes of death and diameter. We used SAS V8.02, particularly PHREG and FREQ, procedures. For most causes of death, there were insufficient numbers for many diameter intervals to permit meaningful use of Cox proportional hazard modeling.

Results

Of 17,432 eligible men, 12,203 (70%) attended and underwent baseline scanning and assessment.\(^{8}\) The mean (SD; range) age at baseline was 72.6 (4.7; 65 to 83) years. The distribution of aortic diameter is shown in Figure 1, and the relationship of aortic diameter to age is in Figure 2. There were 875 men with AAAs: 699 were 30 to 44 mm in diameter, 115 were 45 to 54 mm in diameter, and 61 were $\geq 55$ mm in diameter. A total of 86 men underwent elective repair of their AAA during follow-up, and there were 7 deaths caused by AAA: 4 after elective surgery and 3 caused by rupture.

The median (range) length of follow-up was 5 years (3–7). The unadjusted cumulative all-cause mortality curves for each aortic diameter interval revealed that mortality tended to increase with increasing diameter above the 19 to 22 mm interval (Figure 3). Mortality in the 10 to 18 mm interval was also greater that that seen in the 19 to 22 mm interval. After adjustment for all variables described in Methods, the relative risk for each interval compared with the reference (19 to 22 mm) revealed a similar pattern (Table 1 and Figure 4). The hazard ratios for height, but not body mass index, within the same model had a weak relationship with mortality (data not shown).

Relative risk was stable within each interval with the exception of the interval 23 to 26 mm, which had a relative risk across the stratum of 13.34 (95% CI: 1.7, 106.4; $P=0.0145$). Further refinement of this interval into 23 to 24 mm and 25 to 26 mm removed any within-interval gradient in relative risk (data not shown). Analysis based on the 11 intervals reveals that, on average, a 9% or 1.9-mm increase (or decrease) in the aortic diameter from the reference (19 to 22 mm) yields a relative risk of $\approx 2.66$.

Data pertaining to the cause of death were only coded to the end of 2001, representing 1610 (93%) of the 1739 deaths. Tests of association and increasing trend (both unadjusted) between aortic diameter and mortality confirmed aortic diameter to be predictor of death from various manifestations of cardiovascular disease (Table 2).
Discussion

Our results confirm those of other studies that the mean diameter of the infrarenal aorta in men older than 65 years of age is \( \approx 22 \) mm (Figure 1).6,7 Aortic diameter increased slightly with age (Figure 2), again confirming other studies.6,7,12,13 The most important novel observation from this study is the independent graded relationship between aortic diameter and all-cause mortality for the whole range of diameter values, not just those in the aneurysmal range (\( \geq 30 \) mm in diameter).

The relationship between aortic diameter and subsequent all-cause mortality was initially explored using crude unadjusted cumulative mortality curves for each diameter interval (Figure 3). This revealed a general trend that mortality increased with increasing diameters above the 19 to 22 mm interval. The diameter interval 19 to 22 mm was initially chosen as the reference range as it includes the median and limits of the interquartile range of all measurements. In this sense, it could be considered to represent the normal range because the data come from a randomly selected population-based sample (Figure 1). In support of this proposition is the observation that all-cause mortality was lowest in men with aortas of increasing diameter would have increased levels of both cardiovascular risk and disease. We therefore further assessed the independence of the relationship between diameter and mortality using Cox proportional models (Table 1 and Figure 4). The model included all available risk factors and diagnoses relevant to cardiovascular mortality. Once again, mortality was increased for diameters less than the 19 to 22 mm interval and above it, in a graded fashion, with increasing aortic diameter up to \( \approx 50 \) mm. There was a trend of increasing hazard ratio, from 1.26 (95% CI: 1.09, 1.44; \( P = 0.001 \)) for aortic diameters of 23 to 26 mm to 2.38 (95% CI: 1.22, 4.61; \( P = 0.011 \)) for aortic diameters of 47 to 50 mm.

An association between aortic diameter and subsequent mortality has been previously reported for patients with aneurysmal aortas. An analysis of survival in 2305 patients with AAAs (all with aortic diameters \( \geq 30 \) mm) identified as part of the UK Small Aneurysm Trial found a hazard ratio for all-cause mortality per standard deviation (8 mm) of increasing aneurysm diameter of 1.31 (95% CI: 1.05 to 1.63).4 Similarly, in The Cardiovascular Health Study, the risk of cardiovascular mortality appeared to increase with aortic diameters \( \geq 30 \) mm or if the ratio of infrarenal to suprarenal aortic diameter exceeded 1.4.5 We have extended these earlier observations by demonstrating that infrarenal aortic diameter throughout its range predicts all-cause mortality, with the lowest mortality being seen in the interval 19 to 22 mm. This

<table>
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<th>Interval (mm)</th>
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<th>Action Between Intervals</th>
<th>HR</th>
<th>95% CI</th>
<th>( P )</th>
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Hazard ratios (HR) are adjusted as described in Methods and refer to diameter measured logarithmically.
is important because most older people (94% of men in our study) have aortas in the nonaneurysmal range (<30 mm in diameter), yet even in this range, diameters outside the interval (19 to 22 mm) are associated with increased mortality.

The reason for the association between baseline aortic diameter and subsequent mortality is unknown. Meaningful Cox modeling for risk of cardiovascular death could not be undertaken because of a lack of numbers in several diameter intervals. However, inspection of the causes of death and the unadjusted statistical measures of association and trend shown in Table 2 suggests that much of the increased mortality is caused by various manifestations of cardiovascular disease. This would be in keeping with the studies of patients with AAAs.

In addition to arterial wall thickening and stiffening, arterial dilatation is a recognized manifestation of aging, and some of the molecular events found in age-related dilatation are involved in the pathogenesis of cardiovascular disease. Although median aortic diameter only increases a small amount with age (Figure 2), it is possible that an individual’s aortic diameter may represent a morphometric measure of cumulative exposure to the host of genetic and environmental risk factors, including aging, that are implicated in atherosclerosis. It is only in the minority (≤1%) of individuals with normal infrarenal aortic diameters (≥50 mm) AAAs that the aortic dilatation is severe enough to be a clinical problem in its own right.

The higher mortality seen in men with aortic diameters <19 mm is interesting and also appears to be caused by a greater incidence of cardiovascular disease, particularly stroke (Table 2). Although anatomically small arteries are not a risk factor for atherosclerosis per se, it is likely the smaller an artery, the more trouble a given volume of plaque will cause. For example, anatomically small arteries have been implicated as one of the factors responsible for poor outcome after coronary stent placement and in women with significant atherosclerosis. Another possibility is that, for unknown reasons, these men are prone to constrictive rather than expansive remodeling and the small aorta is a manifestation of occlusive atherosclerosis.

The cumulative mortality curves indicate that men with significant AAAs (aortic diameters 51 to 95 mm) have the highest mortality rates. The decrease in the adjusted risk of mortality seen in this group may be because 86 (75%) of them underwent repair of an AAA during the study period. In other words, during the period of follow-up, there was an atypical level of intervention in the men in this interval. However, it is unlikely that the decrease in risk is simply caused by fewer deaths from AAAs. There were only 7 deaths from this cause in the whole cohort. A more likely explanation is that men with significant aneurysms had more effective management of cardiovascular risk factors and comorbidities as an indirect result of surgery of their aneurysm. An example of this was seen in the UK Small Aneurysm Trial in which a late survival advantage in the surgery arm may have been caused by greater rates of smoking cessation. Nevertheless, there is evidence from the literature that long-term cardiovascular mortality after surgery for AAA increases with original aneurysm diameter.

If the observation that baseline infrarenal aortic diameter is an independent predictor of subsequent mortality, particularly cardiovascular mortality, is confirmed in other populations, this simple noninvasive measurement may have a role in the stratification and management of patients at risk of cardiovascular disease. This is particularly relevant if population screening for AAAs in older men is introduced, because measurements of aortic diameter will be available at no additional cost or effort.

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