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CARDIOVASCULAR FINDINGS AND MANAGEMENT IN TURNER SYNDROME: INSIGHTS FROM A FRENCH COHORT

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ABSTRACT

Objective: Congenital cardiovascular malformations and aortic dilatation (AD) are frequent in patients with Turner syndrome (TS). The objective of this study was to investigate cardiovascular findings and management in a large cohort of patients, including children and adults.

Design/Methods: We recruited 336 patients with TS from a network of tertiary centers. We reviewed their files, checking for cardiovascular events, cardiac valve abnormalities, and aortic diameters indexed to body surface area (BSA) from magnetic resonance imaging (MRI) (n=110) or echocardiography (n=300).

Results: Informative cardiovascular data were available for only 233 patients. Vascular surgery was reported in 7.4% of the cohort. The first cause of surgery was aortic coarctation, detected in 6.9% at a median age of 9.5 years (range: 0-60). Aortic bicuspid valve (BAV) was detected in 21% at a median age of 20 years [25th-75th percentiles: 15-30]. At least one aortic diameter exceeded 32 mm in 12% of the cohort. This was detected at a median age of 19 years [7-30]. When indexed to BSA, at least one aortic diameter exceeded 20 mm/m^2 in 39% of the cohort.

Conclusion: Our study shows that cardiovascular monitoring for Turner syndrome patients is currently insufficient in France. BAV is present at birth, but often remains undiagnosed until later in life. Therefore improved management in cardiovascular monitoring is required and a more systematic approach should be taken.

INTRODUCTION

Turner syndrome, affecting 1/2500 liveborn girls, results from the total or partial absence of the X chromosome. Mortality rates are three times higher in women with Turner syndrome than in the general female population (SMR = 3.0; 95% CI 2.7–3.4)(1). These higher mortality rates are largely due to cardiovascular complications, such as aortic dilatation and dissection. The estimated incidence of dissection is 36 per 100,000 Turner syndrome-years, versus only 6 per 100,000 in the general population (2).

In the last few years, several recommendations for the medical follow-up of patients with Turner syndrome have been published (3). Monitoring is mostly based on expert consensus. Cardiovascular screening includes blood pressure measurement, echocardiography and cardiovascular MRI. It has been recommended that, in the absence of cardiac vascular disease, echocardiography or MRI should be carried out every five to 10 years. Annual imaging is recommended in cases of an aortic diameter greater than 32 mm or 20 mm/m^2 (3, 4). However, several studies have suspected suboptimal diagnosis in those patients with high cardiovascular mortality (1, 5, 6) The aim of this study was to investigate cardiovascular findings and management in a large cohort of French patients with Turner syndrome, including infants, children, adolescents and adults. For this purpose, we reviewed the medical charts of patients. We investigated the occurrence and timing of cardiovascular abnormalities, to facilitate the standardization of cardiovascular follow-up in patients with Turner syndrome.

SUBJECTS AND METHODS

The French Ministry of Health set up the Reference Center for Rare Growth Disorders (CRMERC) in Paris, in 2006. This network of specialized tertiary centers was established to improve and harmonize the care of patients with these rare diseases during the transition from adolescence to adulthood. It brings together the endocrine units of the Saint-Antoine, Robert-Debré, Pitié-Salpétrière, Armand Trousseau, Necker and Bicêtre Hospitals. Patients' files are recorded in a web database called CEMARA. This database has been declared to the French data protection agency (CNIL). We studied the cohort of patients followed up at this center between January 1999 and April 2009. This cohort includes patients with Turner syndrome diagnosed between 1954 and 2008. The study was approved by the institutional review board of our faculty.

The patients with a standard peripheral leukocyte karyotype, with more than 10% of cells displaying a total or partial loss of the X-chromosome, were eligible. We considered the following data for each patient: age at diagnosis of Turner syndrome, timing of cardiac and aortic surgery, timing and results of the most recent echocardiogram and/or magnetic resonance imaging (MRI).

Two-dimensional echocardiography of the aortic root was performed at end-diastole in the parasternal long-axis views, at four levels: the aortic annulus, the aortic sinuses, the supra-aortic ridge and the proximal ascending aorta, as described by Roman *et al*. (7). We also collected data concerning valve morphology, according to the European Association of echocardiography (8).

Patients underwent imaging on a 1.5 Tesla MRI scanner. Aortic diameters were measured at the level of the aortic cusp, the aortic sinuses, the supra-aortic ridge, the proximal ascending aorta, the aortic arch and the descending aorta. Standardized imaging included morphologic ECG-gated sequences in the axial, coronal and leftanterior-oblique axes and cine-MR sequences in a coronal view of the ascending aorta and through the aortic valve, to check for aortic regurgitation or stenosis and to determine valve morphology (9-11).

For each patient, we recorded the largest aortic diameter (mm) at the most recent cardiovascular examination, together with the height, weight and body mass index (BMI) of the patient at the time of that examination. Body surface area (BSA) was calculated according to the formula of Dubois and Dubois (12). According to previous recommendations (3, 4), aortic dilatation (AD) was defined as an aortic diameter exceeding 32 mm or 20 mm/m². In cases of "normal" cardiac evaluations with no documentation of aortic diameter, the patient's file was excluded from the analysis.

We first focused on the most recent cardiological screening results and then searched the file to determine the time at which any abnormalities was first noted. The original cardiovascular reports were looked for in each patient's file. We excluded patients (n=13) whose most recent cardiovascular examination had taken place before 1998 (Fig. 1).

Statistical analysis

The characteristics of the patients are expressed as frequencies and percentages for categorical variables, and as mean ± standard deviation (SD) or median [25th-75th percentiles] and range for continuous variables. Relationships between categorical variables were assessed with Chi-squared tests.

We used the Kaplan–Meier method to generate survival curves from birth and to determine survival rates and their 95% confidence intervals (Greenwood variance). The events studied were BAV, aortic coarctation and aortic dilatation. Analysis was carried out with the SAS V9.2 System (SAS Institute, Cary, NC, USA) and R software version 2.7.2 (R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org) for analyses of agreement and survival.

RESULTS

Our cohort included a total of 336 women with Turner syndrome seen at our center between 1999 and 2009. No detailed cardiovascular monitoring was carried out in 20 of the 336 cases (5.9%)(Fig. 1). Cardiovascular tests were presumably carried out but no cardiovascular data were available for 10 cases (3.0%) and data available before 1998 in 13 cases were excluded. In 60 cases (17.8%), cardiovascular imaging results were reported as "normal" with no written record of the aortic diameter measured. Informative cardiovascular data were therefore available for 233 patients .

The clinical characteristics of these patients are reported in Table 1. In summary, 73 children (31.3%) and 160 adults were analyzed. A monosomy was present in 108 of the 233 patients (46%). The other karyotypes observed were 46,Xi(Xq) (21%), 45,X mosaicism (16.3%), 45,X/46,XrX (9%), 45,X/Y+ mosaicism (4%), 46,XdelX and others (4%). The mean age at diagnosis of Turner syndrome was 8.0 ± 7.9 years (range: 0 to 50 years). Mean age at diagnosis was 4.9 ± 5.1 years for pediatric units and 9.4 ± 8.5 years for adult units (p=0.003). Mean age at most recent cardiac evaluation was 21.6 ± 11.8 years (range: 0 to 67 years).

Mean delays from the age at general diagnosis of the syndrome to the age at diagnosis of aortic coarctation and BAV were 3.94 years (range: 0 to 30 years) and 13 years (range: 0 to 30 years), respectively.

Cardiovascular surgery had been carried out on 17 of our 233 patients (7.4%). No dissection was reported. Median age at surgery was 1 year (range: 0 to 48 years). Most (70%) of the surgical procedures were carried out to correct aortic coarctation (n=12), at a median age of 0.5 years. In the cohort, 59% of these operations occurred before the age of five years; ranging from 0 to 16 years. The second most frequent surgical procedure was valve surgery (n=5): three aortic commissurotomies, one aortic valve replacement and one transcutaneous pulmonary valvuloplasty. Combined surgery was carried out in seven patients. In three cases, atrial or interventricular septal defects were corrected together with aortic coarctation. In three other patients, bicuspid aortic valves were corrected together with aortic coarctation. The remaining patient underwent coronary artery bypass during aortic surgery for ischemic coronary disease at the age of 48 years. Three surgical procedures — pulmonary valve surgery or correction of aortic dilatation — were performed in patients, aged 19, 32 and 48 years. One patient underwent surgery for aortic stenosis at the age of nine years. In one case, surgery for a dilated subclavian artery was performed at the age of 16 years.

Echocardiography and MRI data were available for 222 and 101 cases, respectively. In total, 90 patients (38.6% of the cohort) underwent both echocardiography and MRI. Cardiological evaluation revealed no abnormality in 131 cases (56.2%).

BAV were detected in 49 patients (21.0%), with an age at diagnosis ranging from 0 to 66 years. BAV was detected before the age of five years in only 10 cases. For the remaining patients, the median age of detection of BAV evaluation was 20 years [25th-75th percentiles: 15-30]. Survival without the detection of BAV after 20 years of follow-up was 83.2% [IC95%: 77.6 - 88.9] (Fig. 2a).

Aortic coarctation was detected in 16 cases (6.9%), at a mean age of 9.5 ± 16 years (range: 0-60) and abnormalities were detected before the age of five years in 60% of cases. Other malformations were minor, and included pulmonary (n=17) and tricuspid (n=45) insufficiencies, trivial mitral insufficiency (n=32), aortic insufficiency (grade I-II)(n=29), persistent left superior vena cava (n=6), dysmorphic pulmonary veins (n=2) and transverse aortic arch elongation (n=1).

At least one aortic diameter exceeded 32 mm in 28 cases (12%) and 35 mm in 10 cases (4.3%). The median age at detection of aortic dilatation/BSA in our cohort was 19 [25th-75th percentiles: 7-30] (range: 0-67). Survival without the detection of AD after 20 years of follow-up was 77.8% [IC95%: 72.6 – 83.5] (Fig. 2b). When aortic diameter was indexed to BSA, 91 (39%) patients from the cohort had at least one aortic diameter greater than 20 mm/m^2 (Fig. 3).

In total, 27 of the 49 cases of BAV presented an aortic diameter greater than 20 mm/m^2. AD was therefore more frequent in patients with BAV than in patients without BAV (62.5% versus 31.3%, $p<0.001$). A 45,X karyotype was present in 63% of the patients with BAV and only 37% of those without BAV ($p=0.007$). Furthermore, a 45,X karyotype was present in 57.9% of patients with AD and 42% of patients without AD ($p < 9.10^{-3}$).

DISCUSSION

Our observational study included 336 patients with Turner syndrome. It constitutes a large population, including infants, children, adolescents and adult patients, followed over a long period of time. Most studies on cardiovascular status in patients with Turner syndrome have included less patients (13-15). The largest study by Mazzanti et al. included 594 patients with Turner syndrome, aged 1 month to 24 years. In our study, we included patients up to the age of 60 (16). In our population, the mean age at diagnosis of Turner syndrome was 8.0 ± 7.9 years. The statistically significant difference between ages of diagnosis in pediatric and adults units ($p=0.003$) suggests that the age at diagnosis is improving over time, in France. In other cohorts from US or Sweden, the age at diagnosis reached 14.5 (1) or 15.1 years (95% CI, 14.5-15.8)(17).

A weakness of our study is the fact that it could be considered as an audit rather than research. However, we considered that it was very important to evaluate current care of patients with Turner syndrome. So far, few prospective studies on cardiac outcomes have been reported in patients with Turner syndrome. Among 17 patients, MRI detected aortic anomalies in seven patients, and the time to lesion detection was between two and six years in adults with TS (18). In an Italian cohort of 80 adults, aortic diameter increased with growth rates of 0.1-0.4 mm/year (19). Informative cardiovascular data were available for only 233 of our cases. Despite the follow-up of these patients at a reference center, cardiovascular evaluation was not carried out in 5.9% of cases. Furthermore, reports of evaluations summarized the findings as “normal” rather than giving precise aortic diameters in millimeters, for 18% of the patients. Our study highlights the need for improvement, with cardiovascular monitoring being made systematic in patients with Turner syndrome. Interestingly, a recent study showed that only 3.5% of patients with Turner syndrome are being followed in accordance with NIH recommendations (20). The authors of this previous study highlighted the contribution of the loss of patients during the transition from pediatric to adult care. However, missing cardiovascular data rates in our cohort did not differ between children and adults. Freriks et al. have recently reported in 150 patients that standardized multidisciplinary evaluation yields significant previously undiagnosed morbidity in adult women with Turner syndrome (6). Since the results of our study, we have set up cardiovascular forms to be filled by physicians. We are planning to evaluate in 2 years from now the efficacy of this procedure on improving cardiovascular follow-up. As our study is only an assessment of referred patients, our findings cannot be extrapolated to the entire population of patients with Turner syndrome.

Among our informative patients, no cardiovascular abnormalities were observed in 56.2% of the cohort. This percentage is not very different from previous studies (9, 14, 21).

Bicuspid aortic valves were detected in 21% of cases. The prevalence of this abnormality was identical in children and adults. Bondy *et al.* previously reported a prevalence of BAV, as assessed by highly focused echography and MRI, of 30% (13). Interestingly, although BAV are present at birth, we found that they were frequently detected much later in life, at a mean age of 19.1 ± 14.8 years (range: 0-66). Echocardiography was carried out by trained physicians at our reference center, but this examination can be difficult to carry out in infants and children and may fail to detect bicuspid valves due to pectus excavatum or limited acoustic windows.

In our cohort, aortic coarctation was detected much sooner than BAV, at a mean age of 9.1 years, with 10 cases identified before the age of five years.

Our present findings could be influenced by the well known general delay in diagnostic of Turner syndrome (17). Indeed, delayed cardio-vascular screening may be due to late diagnostic of Turner syndrome. This seems to be true for BAV, as the mean delay between Turner syndrome diagnosis and BAV diagnosis, in our cohort is 13 years, ranging from 0 to 30. However, it does not seem do be the case for aortic coarctation, as the mean delay is rather short (3.94 years). Data on BAV could justify that specifically cardiac diagnostic is poor, even in presence of a timely cardiac assessment for all patients in a reference center.

In our population, we found that 39% of the patients with BSA indexation had a dilated aorta (Fig. 3). This percentage is high, even though our observational study might have underestimated the amount of dilated aorta. The relationship between AD and BAV was significant ($p<0.001$), as suggested in previous studies (13, 22). All of our patients with an aortic diameter greater than 32 mm are alive and none underwent cardiac surgery between 2009 and 2011.

We confirmed statistically significant relationships between the 45,X karyotype and BAV and between 45,X and AD. We therefore conclude that patients with X monosomy should have more frequent cardiovascular follow-up. The natural history of AD remains unknown in patients with Turner syndrome. An intrinsic abnormality of elasticity in the ascending aorta has been suggested (23), involving disruption of the transforming growth factor beta pathway (24, 25).

In summary, our study sheds further light on the cardiovascular features in Turner syndrome. It emphasizes the fact that cardiovascular monitoring for Turner syndrome patients is currently insufficient in France. Furthermore, although BAV is present at birth, it often remains undiagnosed until later in life. Therefore, careful cardiovascular monitoring is thus required, and a more systematic approach should be taken.

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TABLE & FIGURES LEGENDS

Table 1: Population studied

Values are expressed as means ± SD. All patients under the age of 18 years were considered to be children. BSA: Body surface area (10) - BMI: Body mass index.

Figure 1: Flow chart of the cohort

Figure 2: Disease-free survival from birth without BAV or aortic dilatation

We used the Kaplan–Meier method to generate survival curves from birth and to determine survival rates without detection of an event and their 95% confidence intervals (Greenwood variance). The events studied were detection of BAV and aortic dilatation. *Fig 2a*: Disease-free survival without bicuspid aortic valves (BAV). *Fig 2b*: Disease-free survival without aortic dilatation.

Figure 3: Aortic diameters at the level of Valsalva sinus, according to age at most recent examination

The dotted line represents the limit of 32 mm (left) and 20 mm/m² (right). Figure 3a shows crude diameters, figure 3b shows indexed levels (mm/m^2).

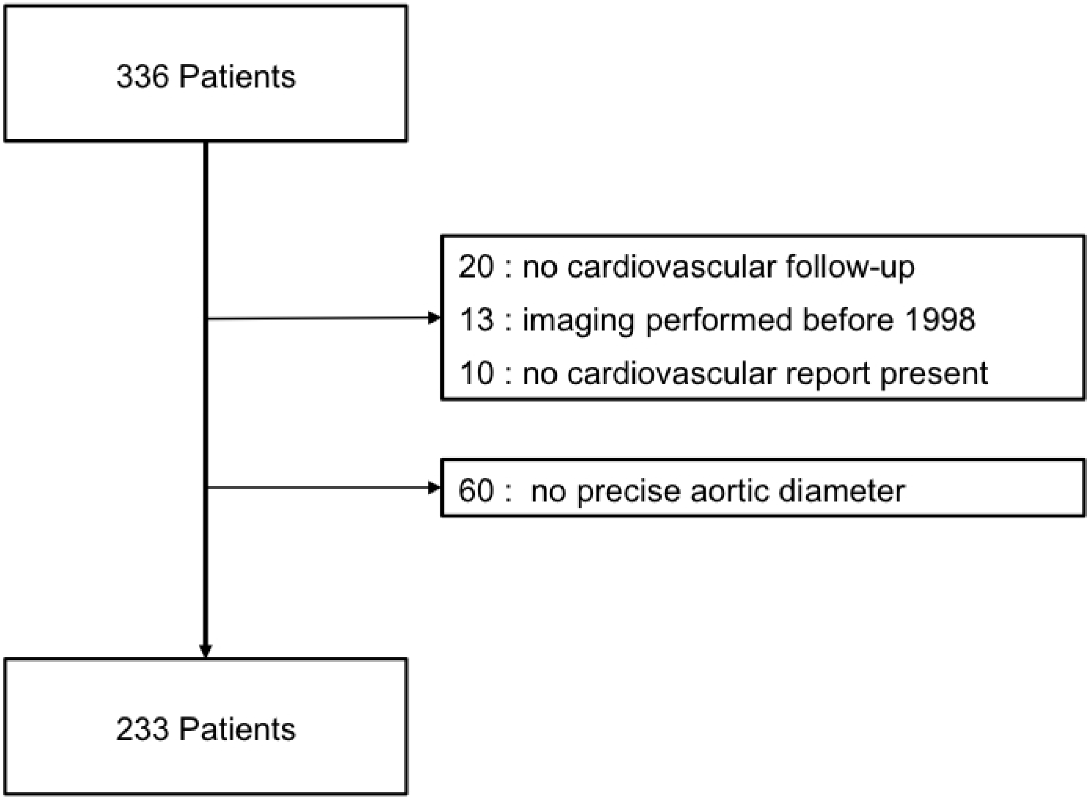
336 Patients
20 : no cardiovascular follow-up
13 : imaging performed before 1998
10 : no cardiovascular report present
60 : no precise aortic diameter
233 Patients

FIGURE 1

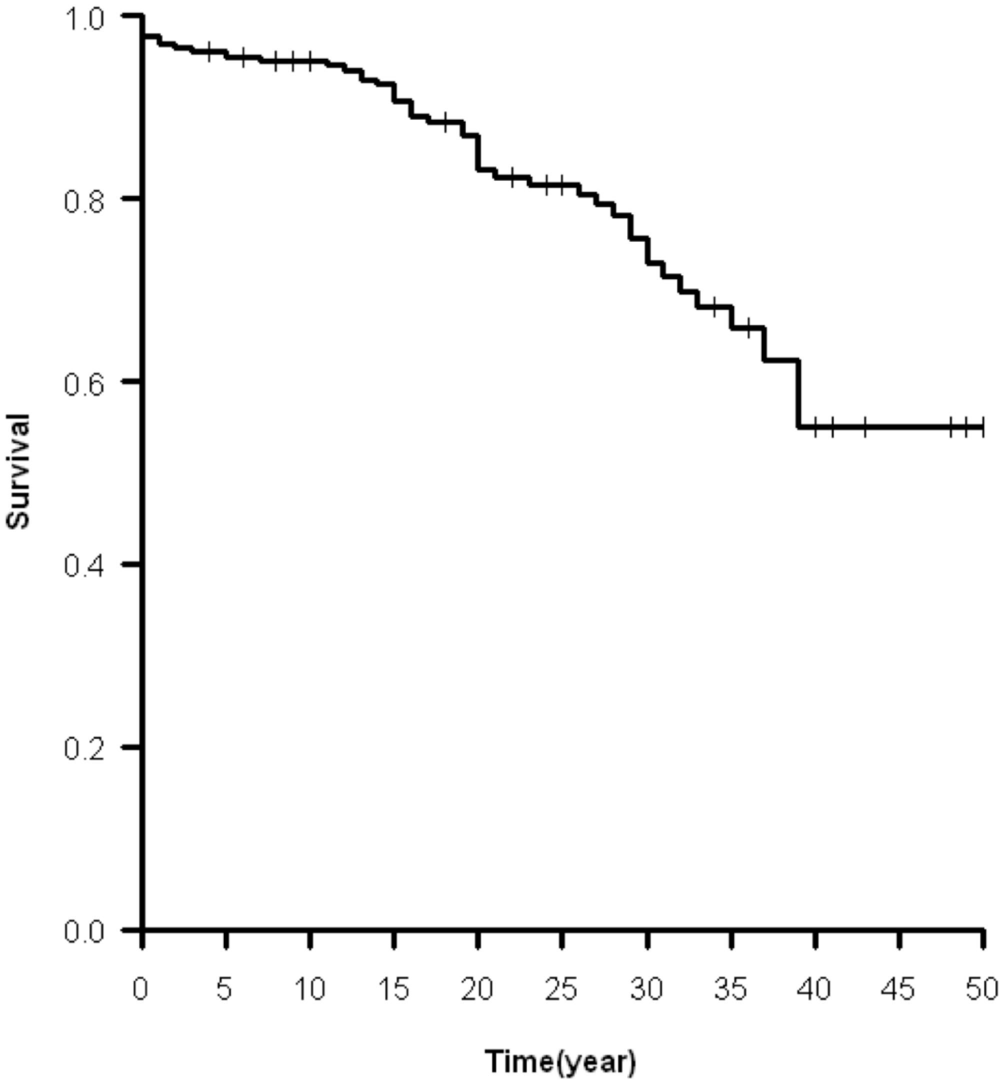

FIGURE 2a

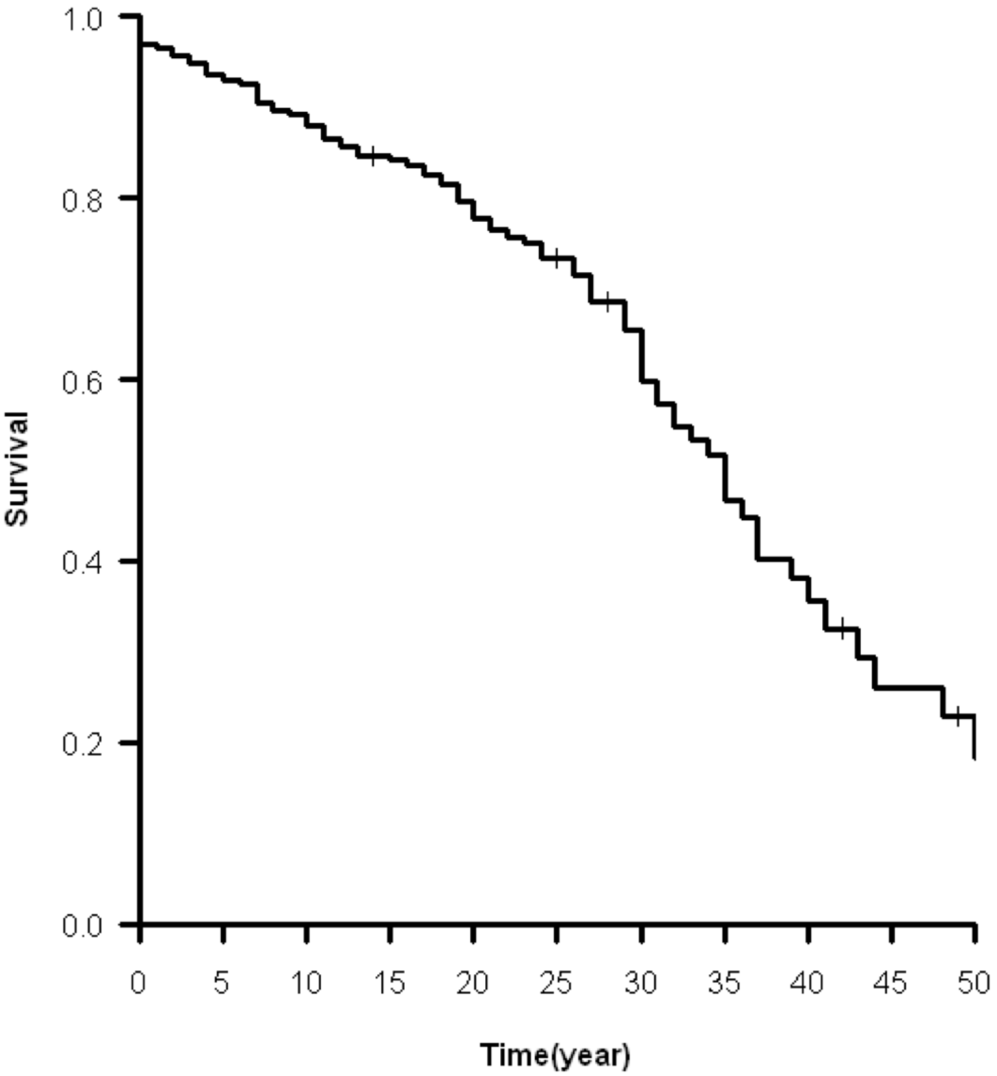

FIGURE 2b

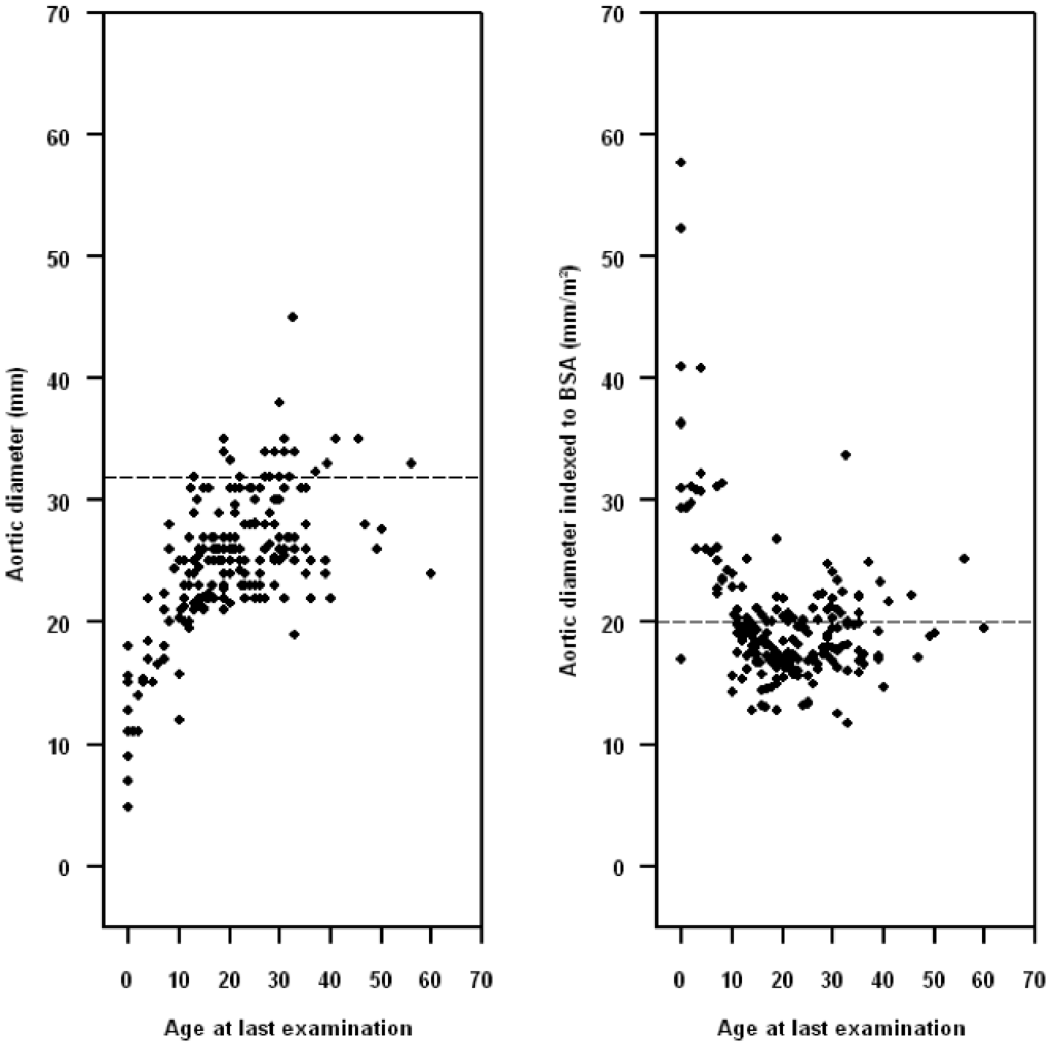
Aortic diameter (mm)
Aortic diameter indexed to BSA (mm/m²)
Age at last examination
Age at last examination
0
10
20
30
40
50
60
70

FIGURE 3