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ORIGINAL ARTICLE

Impact of ascending aortic wall thickness and atherosclerosis on the intermediate survival after coronary artery bypass surgery

Fausto Biancari*, Jarmo Lahtinen and Jouni Heikkinen

Department of Surgery, Oulu University Hospital, Oulu, Finland

* Corresponding author. Department of Surgery, Oulu University Hospital, PL 21, 90029 Oulu, Finland. Tel: +358-40-7333973; fax: +358-8-3152486; e-mail: faustobiancari@yahoo.it (F. Biancari).

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Abstract

OBJECTIVES: We investigated the prognostic impact of atherosclerosis and wall thickness of the ascending aorta in patients undergoing coronary artery bypass grafting (CABG).

METHODS: A series of 781 patients who underwent CABG and in whom epiaortic ultrasound was performed to assess the status of the ascending aorta and to measure the thickness of its anterior and lateral walls were the subjects of the present analysis.

RESULTS: At multivariate analysis, thickness of the ascending aortic wall, but not atherosclerosis, was an independent predictor of all-cause intermediate mortality [relative risk (RR): 1.628; 95% confidence interval (CI): 1.219–2.176]. Five-year overall survival rates in patients with an aortic wall thickness ≥1.8 mm and less were 82.2 and 92.6%, respectively (log-rank test: $P < 0.0001$). Ascending aortic wall thickness (RR: 1.629; 95% CI: 1.135–2.339), but not atherosclerosis, was also an independent predictor of cardiovascular mortality. Aortic wall thickness ≥1.8 mm combined with the presence of atherosclerosis of the ascending aorta was associated with a rather dismal overall survival compared with patients with normal findings at epiaortic ultrasound (at 5 years, 77.0 vs. 93.2%; adjusted analysis: $P = 0.010$).

CONCLUSIONS: Ascending aortic wall thickness, but not the presence of atherosclerosis of any extent, is an independent predictor of intermediate all-cause and cardiovascular mortality. Thickened aortic wall is associated with significantly higher hazard of all cause and cardiovascular mortality and can be considered an important surrogate marker of aggressive atherosclerosis.

Keywords: Coronary artery bypass surgery • Ascending aorta • Atherosclerosis • Mortality • Survival

INTRODUCTION

Atherosclerosis of the ascending aorta is recognized to be associated with immediate postoperative stroke in patients undergoing cardiac surgery [1]. Epiaortic ultrasound scanning before coronary artery bypass grafting (CABG) permits us to accurately assess the status of the ascending aorta and to assist in the decision whether cross- or side-aortic clamping is safe or when avoidance of any aortic manipulation is indicated in the case of significant atherosclerotic changes [2, 3]. The risk of perioperative stroke is particularly high when atherosclerosis involves the anterior and lateral aortic walls [1]. Besides the increased risk of stroke, atherosclerosis of the ascending aorta may be an indicator of advanced atherosclerosis and therefore predictive of poor late outcomes. Indeed, two studies provided evidence of a strong association between ascending aorta atherosclerosis and development of stroke late after CABG [4–6]. However, whether atherosclerosis of the ascending aorta is associated also with higher risk of late mortality has not been extensively evaluated [6]. This issue has been investigated in the present study.

MATERIALS AND METHODS

This study includes a series of 781 patients out of 2001 patients who underwent isolated CABG at the Oulu University Hospital, Finland, between June 2006 and April 2011. These patients underwent intraoperative epiaortic ultrasound scanning and measurement of the ascending aortic wall thickness. Clinical characteristics and operative data are summarized in Table 1. The study protocol of this study was approved by the Ethics Committee of the Oulu University Hospital.

Baseline and operative data were provided by local institutional clinical registry which collects information in a computerized database. Intraoperative, anaesthesiological as well as nursing care data are prospectively collected in specific charts and databases. Furthermore, the full medical records of the eligible patients were reviewed in order to determine the preoperative comorbidities and the incidence of major operative complications. Operative risk was assessed by the original EuroSCORE risk scoring method [7].

Table 1: Baseline characteristics[a] and operative data on 781 patients who underwent isolated coronary artery bypass surgery

	No. (%)	All-cause mortality		Cardiovascular mortality	
		Univariate analysis *P*-value	Cox regression analysis RR (95% CI)	Univariate analysis *P*-value	Cox regression analysis RR (95% CI)
Age (years)	66.1 ± 9.2	<0.0001	1.070 (1.036–1.105)	<0.0001	1.073 (1.030–1.117)
Females	157 (20.1)	0.902		0.333	
Creatinine	88 ± 60	<0.0001	1.004 (1.002–1.006)	<0.0001	1.005 (1.003–1.007)
Renal failure	12 (1.5)	<0.0001		<0.0001	
Pulmonary disease	62 (7.9)	0.002		0.015	
Atrial fibrillation	75 (9.6)	0.002		0.001	
Hypertension	422 (54.0)	0.045		0.318	
Treatment with statin	611 (68.2)	0.112		0.652	
Diabetes	215 (27.5)	0.217		0.454	
Neurological dysfunction	19 (2.4)	0.054		0.057	
History of stroke	42 (5.4)	0.017		0.016	
Extracardiac arteriopathy	67 (8.6)	0.001		0.002	
Previous peripheral vascular intervention	43 (5.5)	0.004		0.073	
Previous percutaneous coronary intervention	87 (11.1)	0.596		0.598	
Previous cardiac surgery	4 (0.5)	0.287		0.628	
Unstable angina pectoris	109 (14.0)	<0.0001		<0.0001	
Recent myocardial infarction (<3 months)	357 (45.7)	0.087		0.014	
Left main coronary artery stenosis	241 (30.9)	0.068		0.432	
Left ventricular ejection fraction <50%	188 (24.1)	<0.0001	2.360 (1.426–3.907)	<0.0001	3.043 (1.637–5.658)
Emergency operation	37 (4.7)	<0.0001	3.349 (1.691–6.632)	<0.0001	4.642 (2.205–9.774)
Critical preoperative status	56/7.2)	0.010		0.004	
Recent ventricular arrhythmia	33 (4.2)	0.256		0.144	
Sys. pulmonary artery pressure > 60 mmHg	15 (1.9)	0.073		0.379	
Beating heart surgery	612 (78.4)	0.893		0.666	
Both mammary artery grafts	86 (11.0)	0.294		0.586	
At least one mammary artery graft	762 (97.6)	0.109		0.204	
Radial artery graft	166 (21.3)	0.011		0.003	
No. of distal anastomoses	4.0 ± 1.0	0.513		0.168	
Untouched aorta	36 (4.6)	0.335		0.892	
Atherosclerosis of the ascending aorta	115 (14.7)	0.045		0.029	
Ascending aortic wall thickness (mm)	1.6 ± 0.5	<0.0001	1.628 (1.219–2.176)	0.001	1.629 (1.135–2.339)
Additive EuroSCORE	4.2 ± 3.2	<0.0001		<0.0001	

Results of univariate and logistic regression in predicting intermediate all-cause and cardiovascular mortality are reported.
[a]Definition criteria for preoperative variables are according to EuroSCORE [7]; continuous variable are reported as mean ± standard deviation; values in parentheses are percentages. RR: relative risk; CI: confidence interval.

Inclusion and exclusion criteria

Patients who underwent CABG without any other major cardiac surgery procedures and in whom epiaortic ultrasound was performed to investigate the presence of any atherosclerosis change and to measure thickness of the anterior/lateral wall of the ascending aorta were considered for inclusion in the present study. Patients without complete ultrasound data or in whom epiaortic ultrasound was not performed at all were excluded from the present study. We excluded from this analysis also those patients with clear atherosclerotic changes of the ascending aorta as detected at palpation, but not assessed by ultrasound.

Epiaortic ultrasound

Intraoperative epiaortic ultrasound scanning was performed by an echocardiographic system (transducer 15-6L, Sonos 5500; Philips, Bothell, WA, USA), before planning the revascularization strategy. A film of gel was placed on the tip of the transducer, which was then placed inside a sterile plastic bag. The ultrasound findings were interpreted by both the surgeons and anaesthesiologists. The thickness of the anterior and lateral walls of the proximal and middle segment of the ascending aorta was measured and expressed in millimetres, whenever possible in an area free of atherosclerotic disease. Indeed, these segments of the ascending aorta are the ones less frequently affected by atherosclerotic changes [1]. This was done to measure the real thickness of the aortic wall unaffected by macroscopically evident atherosclerosis. In a few cases without any area free of atherosclerosis, aortic wall thickness was measured including these atherosclerotic changes. Although mapping of the atherosclerotic changes found at epiaortic ultrasound was planned and in most of cases performed, we found that the degree of atherosclerosis involving the ascending aorta was not easily and reliably quantifiable as the amount, thickness, type and extent of these macroscopic atherosclerosis changes could not be easily summarized in any plot because of their extreme heterogeneity. Therefore, we defined atherosclerosis of the ascending aorta as any irregularity or calcification of the intima and media of any aortic segment as detected at epiaortic ultrasound scanning.

Operative techniques

Epiaortic ultrasound was performed in all these patients. According to our previous results, which showed the benefits of planning the revascularization strategy based on the findings of meticulously performed epiaortic ultrasound [2], off-pump and on-pump were performed indifferently only in the absence of any atherosclerosis changes of the ascending aorta (Grade I) [3]. In the case of minimal atherosclerosis changes involving the posterior wall of the ascending aorta (Grade II), we performed off-pump surgery with aortic side clamping. Side clamping was applied also in a few cases with atherosclerosis involving the anterior wall of the ascending aorta, at the origin of the brachiocephalic trunk and enough far from the clamping site. Ascending aorta was left untouched in the cases of atherosclerosis changes involving the anterior and/or lateral walls of the ascending aorta (Grade III) [3]. In the latter condition, revascularization was performed employing one or both internal mammary arteries as inflow arteries with Y-grafts as needed. Despite this policy was endorsed by most surgeons, variability to adherence to this strategy has possibly occurred. In this series, only two patients, of whom one with diseased ascending aorta, had their saphenous vein grafts anastomosed to the ascending aorta using the Heartstring proximal anastomosis device (Guidant, Indianapolis, IN, USA).

Octopus stabilizer, and in a few cases also Starfish stabilizer, as well as intracoronary shunts (Medtronic, Minneapolis, MN, USA) were routinely used in patients who underwent off-pump coronary surgery. Intermittent antegrade and retrograde cold blood cardioplegia was used during conventional CABG. Proximal anastomoses were sutured to the ascending aorta during cross-clamping in patients undergoing on-pump surgery.

Outcome end-points

The main outcome end-points of interest were all-cause and cardiovascular intermediate mortality. Date and cause of death of all these patients were obtained from Statistics Finland on June 2011. We could not get any information about the cause of death in one patient and we categorized it as a cardiovascular event.

Statistical analysis

Statistical analysis was performed using a PASW v. 18 statistical software (IBM SPSS, Inc., Chicago, IL, USA). Continuous variables are reported as the mean ± standard deviation. Pearson's χ^2-test, Fisher's exact test, Mann–Whitney's test were used for univariable analysis. Logistic and linear regression with backward selection was used for multivariate analysis to identify independent predictors of aortic wall thickness and of immediate postoperative stroke. Survival analyses were performed by the Kaplan–Meier's test and Cox's regression method with backward selection. Hazard functions for each outcome end-point were plotted. Only variables having a $P < 0.050$ at univariate analysis have been included in the regression model. A P-value <0.050 was considered statistically significant.

RESULTS

Intermediate mortality

The mean follow-up of this study was 2.9 ± 1.4 years (median: 3 years; range: 0–5.2 years). During follow-up, 64 patients died and the overall 5-year survival was 89.1%. This figure was no significantly different from that of patients without epiaortic ultrasound data (87.0%, log-rank test: $P = 0.08$). Forty-three fatal cardiovascular events (67.2% of all causes of death: 36 coronary artery disease-related fatal events, 5 fatal cerebral events, 1 fatal acute mesenteric ischaemia and 1 fatal aortic dissection) occurred during follow-up, and 5-year freedom from fatal cardiovascular events was 92.6%.

Predictors of intermediate all-cause mortality at univariate analysis are summarized in Table 1. Despite its significant impact on intermediate all-cause mortality at univariate analysis (log-rank test: $P = 0.045$, Fig. 1), atherosclerosis of the ascending aorta was not predictive of intermediate all-cause mortality at multivariate analysis. Cox regression analysis showed that ascending aortic wall thickness was a significant predictor of all-cause mortality along with patient's age, serum creatinine, left ventricular ejection fraction ≤50% and emergency surgery (Table 1). These findings did not change when gender was included in the regression model. Similar findings were also observed when aortic wall thickness was included in the regression model as quintiles [$P < 0.0001$; relative risk (RR): 1.628; 95% confidence interval (CI): 1.219–1.2.176; Fig. 2]. Since Kaplan–Meier analysis showed that the mortality risk according to quintiles of aortic wall thickness (log-rank test: $P = 0.004$) was markedly increased when aortic wall thickness was ≥1.8 mm (5-year freedom from any fatal event: 82.2 vs. 92.6%, $P < 0.0001$), this cut-off value was considered for further analysis. Cox regression analysis showed that aortic wall thickness ≥1.8 mm was an independent risk factor for intermediate all-cause mortality ($P = 0.001$; RR: 2.356; 95% CI: 1.427–3.889; Fig. 3).

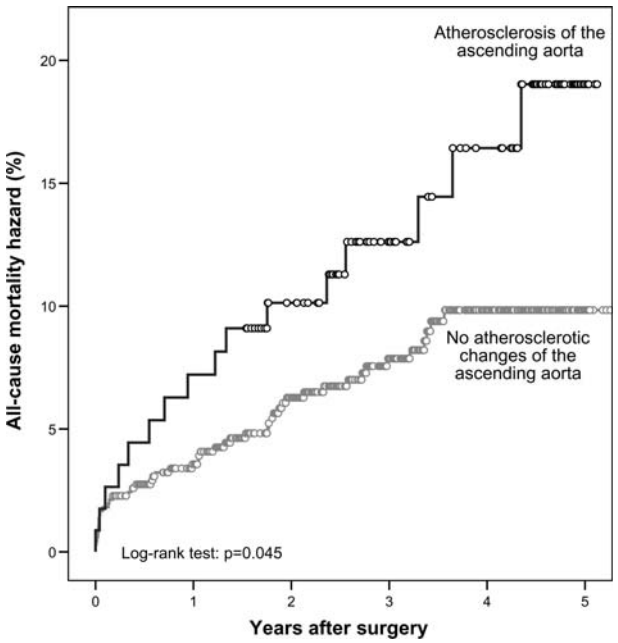

Figure 1: Kaplan–Meier estimate of all-cause mortality hazard after coronary artery bypass surgery in patients with and without atherosclerotic changes of the ascending aorta as identified at epiaortic ultrasound (log-rank: $P = 0.045$).

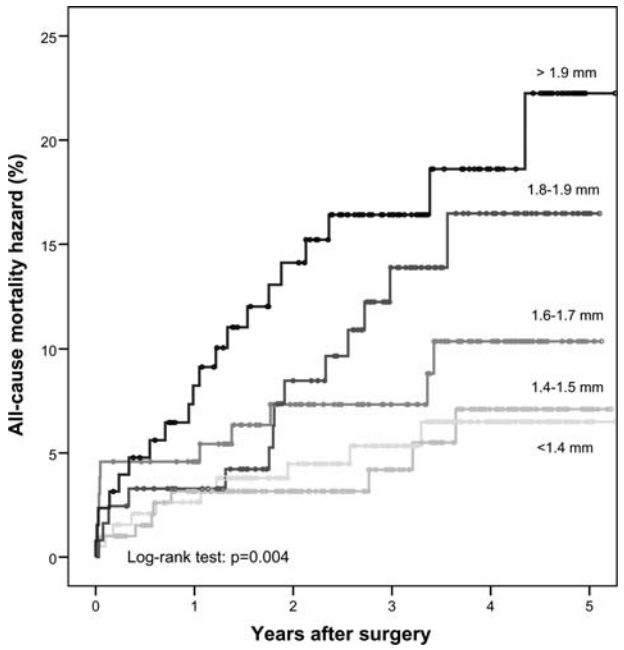

Figure 2: Kaplan–Meier estimate of all-cause mortality hazard after coronary artery bypass surgery according to quintiles of thickness of the ascending aorta as measured at epiaortic ultrasound (log-rank: $P = 0.004$).

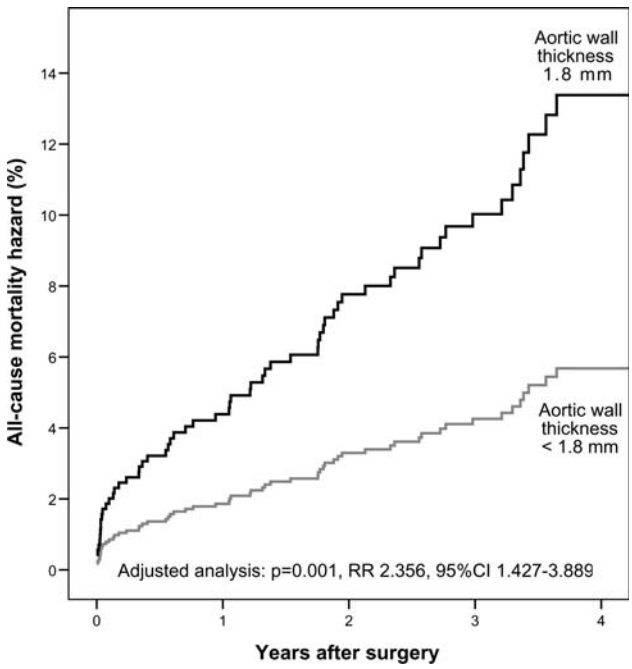

Figure 3: Cox-analysis estimate of all-cause mortality hazard after coronary artery bypass surgery in patients with an ascending aortic wall thickness ≥1.8 mm or less as measured at epiaortic ultrasound ($P = 0.001$; RR: 2.356; 95% CI: 1.427–3.889).

Similarly, patient's age, serum creatinine, left ventricular ejection fraction ≤50%, emergency surgery and aortic wall thickness ($P = 0.008$; RR: 1.629; 95% CI: 1.135–2.339), but not atherosclerosis of the ascending aorta, were independent predictors of intermediate cardiovascular mortality. When aortic wall thickness was included in the regression model as a dichotomous variable

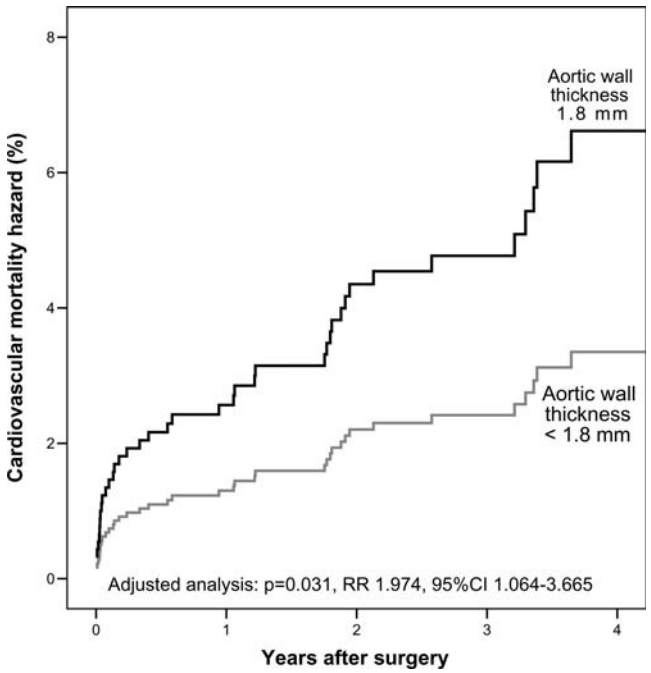

Figure 4: Cox-analysis estimate of cardiovascular mortality hazard after coronary artery bypass surgery in patients with an ascending aortic wall thickness ≥1.8 mm or less as measured at epiaortic ultrasound ($P = 0.001$; RR: 2.356; 95% CI: 1.427–3.889).

(cut-off 1.8 mm, 5-year freedom from any cardiovascular fatal event: 88.9 vs. 94.5%, log-rank test $P = 0.019$) instead as a continuous variable, also the former was predictive of intermediate cardiovascular mortality ($P = 0.031$; RR: 1.974; 95% CI: 1.064–3.665; Fig. 4).

We further investigated the combination of aortic wall thickness ≥1.8 mm and the presence of atherosclerotic changes in the ascending aorta. As shown in Fig. 5, aortic wall thickness ≥1.8 mm was associated with significantly increased risk of all-cause mortality, particularly when macroscopic atherosclerotic changes were also observed in the ascending aorta at epiaortic ultrasound. Such an increased risk was confirmed also at multivariate analysis when adjusted for patient's age, serum creatinine, left ventricular ejection fraction ≤50% and emergency surgery ($P = 0.010$). The combination of aortic wall thickness ≥1.8 mm and the presence of atherosclerotic changes in the ascending aorta was associated with a rather poor overall survival compared with patients with normal findings (at 5 years, 77.0 vs. 93.2%, log-rank: $P = 0.002$; Fig. 5). The same trend was observed also in terms of cardiovascular mortality, but the difference was not statistically significant at multivariate analysis (log-rank test: $P = 0.024$, adjusted analysis: $P = 0.148$).

Predictors of ascending aortic wall thickness

Univariate analysis identified male gender ($P < 0.0001$), recent myocardial infarction ($P = 0.031$), urgent or emergency procedure ($P = 0.022$), atrial fibrillation ($P = 0.047$) and non-diabetes ($P = 0.001$) as associated with thickened aortic wall. Linear regression identified male gender (1.7 ± 0.6 vs. 1.5 ± 0.3 mm, $P < 0.0001$; thickness ≥1.8 mm, 23.3 vs. 13.4%, $P = 0.001$), atrial fibrillation (1.8 ± 0.7 vs. 1.6 ± 0.5 mm, $P = 0.009$; thickness ≥1.8 mm,

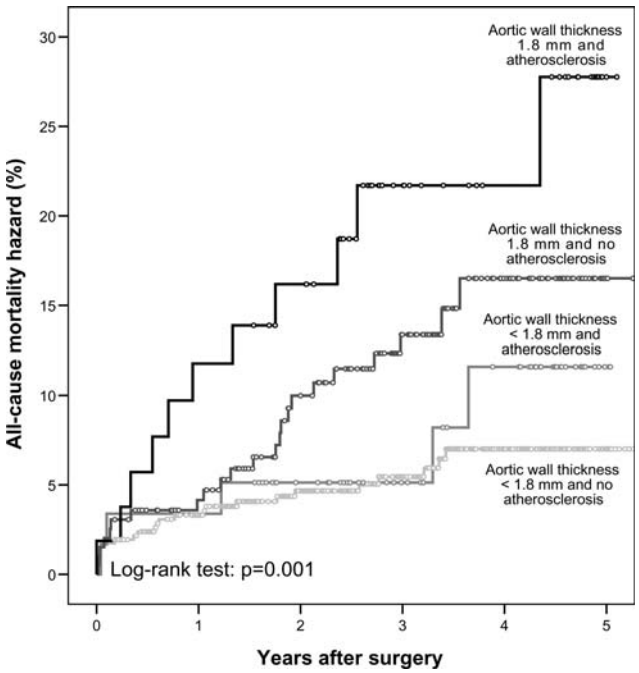

Figure 5: Kaplan–Meier estimate of all-cause mortality hazard after coronary artery bypass surgery according to thickness of the ascending aorta and presence of atherosclerotic changes as identified at epiaortic ultrasound (log-rank: $P = 0.001$).

12.3 vs 8.3%, $P = 0.08$) and non-diabetic (1.7 ± 0.5 vs. 1.6 ± 0.5 mm, $P = 0.009$; thickness ≥1.8 mm, 31.8 vs. 21.8%, $P = 0.006$) as independent predictors of increased thickness of the ascending aortic wall.

DISCUSSION

Atherosclerosis of the ascending aorta can be intuitively regarded as a marker of advanced and aggressive atherosclerosis with a significant impact on the early and late survival. However, the present study demonstrated that such an intraoperative finding should not discourage surgeons in carrying out a complete myocardial revascularization as, according to our study criteria, atherosclerotic changes of the ascending aorta were not predictive either of intermediate all-cause or cardiovascular mortality. Indeed, in the present series, the amount of distal anastomoses was similar in patients with or without diseased ascending aorta (4.0 ± 1.1 vs. 4.0 ± 1.0, $P = 0.95$). In fact, also in those cases, in whom manipulation is absolutely contraindicated, Y-grafts can be employed to achieve complete coronary revascularization without affecting late survival [8, 9]. Instead, aortic wall thickness was found an independent risk factor for all-cause and cardiovascular mortality. This is likely because aortic wall thickness, as herein measured in areas free of macroscopic atherosclerotic changes, may better depict the severity of a systemic disease. In fact, the ascending aorta is only a small segment of the entire aorta and may not be representative of the presence or not of atherosclerosis detected by ultrasound as intimal irregularities, frank atherosclerotic plaques or aortic wall calcifications. Indeed, daily experience often demonstrates that patients having extensive calcification of the aortic arch observed at chest X-ray have their ascending aorta completely free of any significant atherosclerotic changes. This suggests that an atherosclerotic plaque of the ascending aorta may not be such a powerful marker of aggressive atherosclerosis, at least in patients with coronary artery disease. On the contrary, ascending aortic wall thickness may be a significant marker of diffuse and aggressive atherosclerosis. Experimental studies showed that aortic wall thickening associated with aging and hypertension is the result of structural modification of the arterial wall with increased content in collagen, branching, breakage and disorganization of the elastic lamellae and hypertrophy with reduction in the number of medial smooth muscle cells [10]. Since aortic wall thickness correlates with carotid intima–media thickness, this suggests the systemic nature of this condition [11]. The present findings couple the higher cardiovascular mortality risk observed in patients with increased intima–media thickness of the carotid artery [12]. Indeed, there is a burden of evidence showing the value of carotid intima–media thickness as a surrogate marker of subclinical atherosclerosis [13]. Interestingly, carotid intima–media thickness was shown to correlated significantly with the severity of coronary artery disease as graded by the Syntax score [14]. A recent study showed that, in patients younger than 50 years, abdominal aortic wall thickness correlated with predicted cardiovascular risk [15]. Similarly, we may expect that measuring ascending aortic wall thickness could improve our ability to stratify the risk of patients undergoing CABG.

An important issue to be take into account in this study is the fact that aortic wall thickness as herein measured at epiaortic ultrasound (1.6 ± 0.5 mm) is markedly lower than that commonly measured at magnetic resonance imaging in normal subjects at the level of the ascending (mean: 2.3 ± 0.5 mm) [16] or descending aorta (mean: 2.6 ± 0.5 mm) [17], but similar to the aortic wall thickness of the abdominal aorta as measured by magnetic resonance imaging in subjects younger than 50 years [15]. However, at gross pathologic measurement, in occidentals, the intima–media thickness of the ascending aorta, when adjusted for age, height and weight, has been estimated at being about 0.9 mm [18]. Regarding the accuracy of ultrasound scanning in measuring the aortic wall thickness, it has been shown that the normal abdominal aortic wall thickness was 1.7 ± 0.7 mm at gross pathologic examination and that this value did not markedly differ from measurement at B-mode ultrasound scanning (absolute error: 0.1 ± 0.1 mm) [19]. These latter observations suggest that our measurements performed at epiaortic ultrasound are likely more reliable than those obtained at magnetic resonance imaging.

Herein we observed that females had a significantly lower ascending aortic wall thickness than males as previously demonstrated in the abdominal aorta [15] and carotid arteries [20]. This study showed that preoperative atrial fibrillation was an independent predictor of thickened aortic wall. A recent study showed that increased carotid intima–media thickness was associated with significantly higher risk of atrial fibrillation [21]. It is possible that increased thickness of the arterial wall may be part of a process, leading also to structural changes observed also in the atria of patients with atrial fibrillation. Herein we observed that diabetics had lower aortic wall thickness. We cannot explain this finding, but we suspect that it is related to the specific structure of the ascending aortic wall in these patients.

Several important limitations may affect the present findings. First, this is a retrospective study, and epiaortic ultrasound was not performed with the purpose to answer the present issues. Second, we do not have data on the extension of the atherosclerotic changes because we believe that it cannot be reliably

quantified simply by plotting its presence on a map. In fact, the amount, size, type and extent of these macroscopic atherosclerosis changes could not be easily summarized in any plot because of their extreme heterogeneity. Therefore, we decided to define as atherosclerosis of the ascending aorta when any irregularity or calcification in any of its segments was detected at epiaortic ultrasound scanning. Indeed, this criterion is usually chosen to decide whether any manipulation of the aorta is safe or not. Third, we did not have any data regarding the maximum aortic wall thickness as we focused our measurements only to areas free of atherosclerosis. This is in contrast with previous studies which evaluated the maximum ascending aortic wall thickness, therefore taking into consideration the areas with most advanced atherosclerosis. Fourth, these findings are based on a single Institution's series with a rather small number of events occurring during a mean follow-up of 3 years. Therefore, further studies on non-Scandinavian patients with longer follow-up are needed to confirm these findings.

In conclusion, these findings suggest that the presence of macroscopic atherosclerotic changes of the ascending aorta is not an independent predictor of poor intermediate survival after CABG. On the contrary, thickened aortic wall is associated with significantly higher hazard of all-cause and cardiovascular mortality and may be considered an important marker of aggressive atherosclerosis.

Conflict of interest: none declared.

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