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The association between aortic valve calcification, cardiovascular risk factors, and cardiac size and function in a general population

Lida Khurrami[a*], Jacob Eifer Møller[a,b], Jordi Sanchez Dahl[a], Rasmus Carter-Storch[a], Nicolaj Lyhne Christensen[a], Manan Pareek[c], Jes Sandal Lindholt[d,e], Axel Cosmus Pyndt Diederichsen[a,e]

[a] Department of Cardiology, Odense University Hospital, Denmark

[b] Department of Cardiology, Copenhagen University Hospital Rigshospitalet, Denmark

[c] Department of Internal Medicine, Yale New Haven Hospital, Yale University School of Medicine, USA

[d] Department of Cardiothoracic and Vascular Surgery, Odense University Hospital, Denmark

[e] Elitary Research Centre of Individualised Medicine in Arterial Disease (CIMA), Denmark

*Corresponding author: Lida Khurrami, Department of Cardiology, Odense University Hospital, Sdr. Boulevard 29, 5500 Odense C, Denmark.

E-mail address: Lida.Khurrami2@rsyd.dk

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Abstract:

Purpose: To determine the presence and extent of aortic valve calcification (AVC) quantified by non-contrast cardiac computed tomography (NCCT), to determine the association between traditional cardiovascular risk factors and AVC score, and to evaluate the association between AVC and cardiac size and function assessed by echocardiography, in a general population aged 65-75 years.

Methods: A random sample of 2060 individuals were invited to undergo NCCT through which their AVC score was assessed. Individuals with an AVC score ≥300 arbitrary units (AU) were invited for a transthoracic echocardiography together with age-matched controls. Descriptive statistics and multiple regression analyses were performed to identify risk factors associated with AVC and to describe associations between AVC score and echocardiographic findings.

Results: Of 2060 individuals invited 664 males and 636 females participated. Among those, 455 (68.5%) of males and 358 (56.3%) of females had AVC scores >0 AU. The median AVC score was 6 AU (IQR 0-3064). Seventy-seven (11.6%) males and 20 (3.1%) females had an AVC score ≥300 AU. In a multiple regression, age, sex, prior cardiovascular disease, smoking, and hypertension were associated with AVC score, while diabetes, hypercholesterolemia and kidney function were not. Individuals with AVC ≥300 AU had higher peak and mean aortic valve gradient, smaller indexed aortic valve area, greater left ventricular mass, and larger left atrial (LA) volume.

Conclusion: In a random population sample of individuals aged 65-75 years, AVC was common and associated with most known cardiovascular risk factors. AVC ≥300 AU was associated with concentric remodeling and LA dilatation.

Keywords: Aortic Valve Calcification, Non-contrast Cardiac CT, Aortic Stenosis, cardiovascular risk factors, transthoracic echocardiography

Introduction

Calcific aortic stenosis (AS) is a chronic progressive disease starting as aortic sclerosis and eventually progressing to a condition with compromised valve-opening, causing left ventricular pressure overload. When severe, AS may lead to the development of heart failure symptoms and the need for aortic valve intervention, although despite corrective surgery patients with AS have increased mortality and morbidity (Carabello and Paulus 2009; Chin, et al. 2017; Malaisrie, et al. 2014; Otto, et al. 1999; Redfield, et al. 2003). Currently, trials have failed to identify therapies able to reduce the progression rate of AS, with a possible explanation being that the included patients were at an advanced stage of the disease (Capoulade, et al. 2017; Cowell, et al. 2005; Innasimuthu and Katz 2011; O'Brien, et al. 2005; Rossebo, et al. 2008; Teo, et al. 2011).

Echocardiography is considered the cornerstone of diagnosis and assessment of AS severity, despite discordant assessment in 40% of patients with reduced left ventricular (LV) function and low-flow low-gradient AS and inconclusive results among the obese or those with chronic obstructive pulmonary disease (Baumgartner, et al. 2017b). Furthermore, the calculation of gradients utilizing the simplified Bernoulli equation or valve area using the continuity equation may provide equivocal results when AS is mild or moderate (Malouf, et al. 2012). This probably makes echocardiography less useful in identifying and grading patients with mild aortic valve alterations and identifying patients suitable for trials, testing the potential reduction of AS progression.

Non-contrast cardiac computed tomography (NCCT) has recently emerged as a modality to quantify aortic valve calcification (AVC) and guidelines suggest to use AVC score for assessment of AS severity in an integrative approach, particularly

when echocardiography is inconclusive (Baumgartner, et al. 2017a; Cueff, et al. 2011). The degree of valve calcification at the time of diagnosis is the most consistent predictor of AS progression and is directly linked to cardiovascular mortality (Pawade, et al. 2019; Rosenhek, et al. 2000). AVC and its consequences are poorly explored in the general population.

This pilot study aims to describe the presence and extent of AVC quantified by NCCT in a random sample of Danish individuals, to determine the association between AVC score and traditional cardiovascular risk factors and to assess the association between the degree of AVC and possible abnormal echocardiographic findings.

Methods

Study Design

We performed a cross-sectional pilot study using baseline data from the DANish CArdioVAscular Screening (DANCAVAS) study (Diederichsen, et al. 2015). In brief, DANCAVAS aims to establish the effect and cost-effectiveness of an extensive cardiovascular screening and intervention program in a randomized, clinically controlled manner among individuals aged 65-75 from the general population. In 2014-15, 2060 participants were invited to a pilot study (Kvist, et al. 2017), and data from the men and women who accepted the examination were available for the present study. AVC scores were calculated based on the available NCCT scans using the Agatston method (Agatston, et al. 1990).

When designing the study in 2014 no well-defined cut off values of AVC for moderate AS existed. Therefore an arbitrary value of AVC score of 300 AU corresponding to the 90% percentile among the first 250 included was chosen as a cut- off value.

All participants with AVC ≥ 300 AU were subsequently invited to undergo transthoracic echocardiography. Age-matched participants with AVC <300 were also invited for echocardiography, to serve as controls. Participants with missing AVC scores (e.g., prior aortic valve surgery, artefacts on CT scan from implantable pacemaker leads, or missing CT scans) were excluded.

Baseline measures

All participants completed a health-questionnaire concerning medical conditions, current medication, smoking habits, and symptoms (exertional shortness of breath,

palpitations, chest pain, and syncope). Weight, height, body mass index (BMI), and body surface area (BSA, Du Bois equation) were measured and calculated. Hypertension was defined as self-reported, on-site diastolic blood pressure >100 mmHg, systolic blood pressure >160 mmHg, or treatment with antihypertensive medication. The cut-off value of moderate hypertension was chosen in order to detect hypertension of a grade which can induce organ damage and at the same time to accommodate for possible white coat hypertension during the stressful and rapidly changing setting of the screening procedure. Hypercholesterolemia was defined as self-reported hypercholesterolemia, total plasma cholesterol ≥5.0 mmol/L, low-density lipoprotein (LDL) cholesterol ≥3.0 mmol/L, or treatment with statins. Diabetes mellitus (DM) was defined as self-reported DM, HbA_{1c} >48 mmol/mol, or treatment with antidiabetic medications. Cardiovascular disease (CVD) was defined as self-reported prior stroke, myocardial infarction, coronary revascularization, valve surgery, or known peripheral artery disease (Diederichsen, et al. 2015).

Non-contrast cardiac computed tomography

A Siemens SOMATOM Definition Flash 128-slice Dual Source scanner was used with the following settings: Gantry rotation time 0.25 s, 3.0 mm collimation, slice acquisition 38 x 1.2 mm, 120 kV tube voltage, tube current per rotation 80 mAs, and a prospectively ECG-triggered scan (gating at 350 ms or 70% of the RR interval, depending on the heart rate, above or below 70 per minute, respectively). A temporal resolution of 75 ms made it possible to visualize high-quality images for participants with high or irregular heart rates. No any form of iterative reconstruction was used in our study **(Table S1).** The mean radiation dose during the DANCAVAS CT scan (heart and truncal) was 3.9 +/- 1.2 mSv, and the cardiac radiation dose is estimate to

be less than 2 mSv. For comparison, a typical dose of a mammogram is 0.2 mSv, the annual background radiation dose in Denmark is 3 mSv, and the average annual limit for radiation workers is 20 mSv (Diederichsen, et al. 2015; Einstein and Knuuti 2012).

Aortic valve calcification scoring

AVC scoring was performed off-line on a dedicated computer with the semiautomatic calcium scoring software (Syngo.via, Siemens Healthineer, Forchheim, Germany) using the Agatston method and expressed in AU. Precise AVC scoring is challenging on non-contrast CT scans. Using axial slices, AVC was defined as calcification within the valve leaflet, in the aortic sinus of Valsalva (starting 6 mm below the ostium of the coronaries), or in the aortic valve annulus (Paulsen, et al. 2016). Calcifications in the coronary arteries and mitral valve annulus were carefully excluded. The AVC score was calculated by adding up all spots of calcifications in the aortic valve areas and was arbitrarily classified as: none detectable (score 0 AU), detectable (score 1-149 AU), discrete (score 150-299 AU), moderate (score 300-799 AU), high (score 800-1199 AU), and severe (score >1200 AU).

Inter- and intra-observer variability of AVC score was assessed by repeating the measurements in 20 randomly selected participants by seven readers, and in 140 participants by a second reader with the same experience.

Transthoracic echocardiography

All transthoracic Doppler echocardiograms were performed by experienced echocardiographers using a Philips EPIQ 7 cardiovascular ultrasound system. Images were stored and analyzed blinded for patient data, including AVC. Echocardiography was conducted following the recommendations of the European Association of

Cardiovascular Imaging (Lang, et al. 2015) and the analyses included: LV dimensions measured in end-diastole, ejection fraction (LVEF) estimated using Simpson`s biplane method, LV mass calculated using LV dimensions and indexed by BSA (LVMi), peak mitral inflow velocity in early diastole (E) and medial/lateral mitral annular early diastolic velocities (é) derived from pulsed-wave Doppler and tissue Doppler imaging, E/é ratio, LA volume measured by tracings of the blood-tissue interface in the apical four- and two-chamber views and indexed by BSA (LAi), LV outflow tract velocity-time-integral measured with pulsed-wave Doppler by placing the sample volume just below the region of flow convergence approximately 5 mm apically from the aortic valve, peak flow velocity across the valve was determined in the window where the highest velocity was obtained with the cursor as parallel as possible to the flow across the valve, and aortic gradients calculated by modified Bernoulli. The absolute Aortic Valve Area (AVA) was calculated using the continuity equation and indexed for BSA (AVAi). For this paper, AS severity was graded using the AVAi and was considered as AS being unlikely when AVAi ≥ 0.85 cm^2/m^2, and likely if AVAi <0.85 cm^2/m^2 (Baumgartner, et al. 2017a).

Statistical analysis

Continuous variables are presented as mean (± standard deviation) or median with interquartile range (IQR) where appropriate, while categorical variables are presented as numbers and percentages. Comparisons for the difference between groups of continuous variables were made using two-sample t-tests for normally distributed data, and Mann-Whitney U tests for non-normally distributed data. Continuous variables were tested for normality by the Shapiro-Wilk test. For categorical data, comparisons were made using Chi-square test and Fisher's exact test as appropriate.

In order to avaid poor quality predictions due to excess of zeroes in the data set (>0.67%), a zero-inflated negative binomial multiple regression analysis was performed to find variables associated with AVC. Included in the model were cardiovascular risk factors as age, sex, smoking status, hypertension, DM, hypercholesterolemia, BMI, disposition to CVD, CVD and estimated glomerular filtration rate (eGFR). Data are presented by their incident rate ratio (IRR) and 95% Confidence interval (CI). Association between AS and AVC score was evaluated by receiver operating characteristic (ROC) analysis where sensitivity, specificity, positive and negative predictor values (PPV and NPV), and area under the curve (AUC) were calculated. Statistical analyses were performed using statistical analysis software Stata/IC V. 16.0 (Stata Corporation LP, College Station, Texas, USA).

Results

Characteristics of the participants

In the pilot study from which the current data were derived, a total of 1044 males and 1016 females were invited. There was no significant difference in the participation rate (677 (64.8%) males and 641 (63.1%) females, p=0.41). Exclusion criteria were met by 18 (1.4%) of the individuals, leaving a total of 1300 participants for further analysis: 664 males and 636 females (**Figure 1**).

Aortic Valve Calcification and cardiac risk factors

The AVC scores ranged from 0 to 3064 AU, with a median of 6 AU (IQR 0-67). Males had higher median AVC scores than females (16 AU (IQR 0-113) vs. 1.5 AU (IQR 0-32) p<0.001). An AVC >0 AU was detected in 455 (68.5%) of males (95% CI: 64.8% – 72.0%) and 358 (56.3%) of females (95% CI: 52.3% – 60.2%). We identified 77 (11.6%) males and 20 (3.1%) females with AVC values ≥300 AU. These individuals differed significantly from the 1203 individuals with AVC values <300 AU with respect to various traditional risk factors such as age, smoking status, prior CVD, hypertension, DM, lipid profile, BMI, and eGRF (**Table 1**). The baseline characteristics per sex are presented in the supplemental **Table S2.** Inter- and intra-observer agreements of AVC scores were assessed in 137 randomly selected CT scans. Both metrics had Pearson`s correlations of r=0.99 (p<0.001). Agreement by Bland-Altman plots are shown in supplemental **Figure S1**.

In the zero-inflated multiple regression analysis, age (IRR 1.10, 95% confidence interval (CI):1.05-1.15), male sex (IRR 2.04, 95% CI:1.55-2.67), current smoking status (IRR 1.50, 95% CI:1.02-2.21), former CVD (IRR 1.83, 95% CI:1.32-2.54), and hypertension (IRR 1.40, 95% CI:1.04-1.90) were all found to be associated with AVC

score (**Table 2**). While no significant associations were found between AVC score and DM, BMI, and eGFR in our population. We found no interactions between the two sexes and other cardiovascular risk factors in predicting AVC.

Aortic valve calcification and echocardiographic findings

Among the individuals with AVC ≥300 AU, 66 (86%) men and 16 (80%) women accepted the supplemental echocardiography, in addition to 123 (63%) of the 194 invited individuals with AVC <300 AU. In total, 205 participants were included (**Table 3**). Participants with AVC ≥300 AU had a significantly higher peak aortic jet velocity, mean aortic valve gradient, smaller AVAi, greater LVMi, and greater Lai. However, no significant differences were found for LVEF, relative wall thickness, and the diastolic measurements: E/e', E-wave deceleration time, and septal e' (**Table 4**). No significant interaction was found between AVC and hypertension in predicting LVMi or LAi. The association between AVC and AVAi is illustrated in **Figure 2**. Sex differences are displayed in **Table S3** and **Table S4**.

A total of 25 individuals ended up having a likely AS, while 180 did not. Among the individuals with AS, 21 participants had an undiagnosed AS, while four were previously diagnosed. The AS group had a significantly higher median AVC score than those without AS (median 808 AU (IQR 565 – 1357) vs. 170 AU (IQR 8 – 357), p<0.0001). In addition, the AS group had a lower mean HDL and a higher BMI (**Table 5**). No differences were found in other CVD risk factors such as age, smoking status, hypertension, and DM.

In the ROC analysis for the association between AVC score and likely AS, the AUC was 0.89 (95% CI: 0.03 - 0.95) (**Figure 3**). We found that the best threshold for AS

being likely was an AVC score of 415 AU (sensitivity 92%, specificity 83%, PPV of 43%, NPV of 99%).

In a multiple regression model including AVAi or AVC (</>300 AU) as risk factors associated with LVMi, AVC>300 AU was found to be significantly associated with LVMi (Coef. 10.35; p=0.001, R2=0.032) compared to AVAi (Coef. -3.76; p=0.421, R2=0.057). In a similar regression analysis for LAi, both predictor variables, i.e. AVAi and AVC (>/<300 AU) were significantly associated with LAi size; AVAi (Coef. -5.78; p=0.014, R2=0.029) and AVC (Coef. 3.733, p=0.015, R2=0.029).

Discussion

In this large cohort study, including a population of randomly selected elderly males and females, we demonstrate that AVC is common and associated with traditional cardiac risk factors, concentric LV remodeling, and LA dilatation. However, a large proportion of participants have a high AVC despite that they have no signs of AS by standard echocardiographic measures.

In the largest study of its time, based on echocardiographic findings of 5201 individuals of from the Cardiovascular Health Study it was found that traditional risk factors as age, gender, hypertension and smoking are independent predictors of aortic valve calcification and sclerosis (Stewart, et al. 1997), this was confirmed in another study(Cosmi, et al. 2002). These associations were found to be valid for later CT studies looking specifically at AVC and traditional risk factors including diabetes and dislypidemia in the Multi-Ethnic Study of Atherosclerosis (MESA) (Katz, et al. 2006) and later in the Framingham Offspring Study (Thanassoulis, et al. 2010) and the Heinz-Nixdorf Recall Study (Kalsch, et al. 2014). These associations have so far been explained by the evidence of 1) the association between hyperlipidaemia and leasons

of the aortic valve 2) the similarities between early lesions of aortic valve disease and atherosclerosis, including lipid deposition; (Olsson, et al. 1999) ; and 3) the location of the focal changes of sclerosis on the aortic side of the leaflets , suggesting endothelial injury from low shear stress and high tensile stress as possible initiating factors in the sclerotic disease process (Stewart, et al. 1997). Endothelial damage and disruption could lead to infiltration of inflammatory cells and along with lipid deposition starts a process similar to the early atherosclerotic process (Eckel, et al. 2005; Stewart, et al. 1997).

We found that AVC associated with older age, male sex, current smoking status, history of CVD, and hypertension. These findings corroborate the findings from the Heinz-Nixdorf Recall Study, a cohort study of ~ 4000 individuals (aged 59.3+/-7.7 years; 53 % female) currently the only study describing an association between AVC and traditional cardiac risk factors in a randomly selected group from a general population (Kalsch, et al. 2014). In the MESA and Heinz-Nixdorf Recall study, DM was also found to be associated with AVC, an association we were unable to confirm along with dyslipedemia, presumably due to the smaller sample size.

While echocardiography was not reported in Heinz-Nixdorf Recall Study, they did report AVC to be associated with cardiovascular events and death in a population without known AS.

The association between AVC and echocardiographic changes has been explored in several smaller studies, but only among patients with known AS (Clavel, et al. 2014; Messika-Zeitoun, et al. 2004; Yan, et al. 2017). In our study of random older individuals, a large proportion appears to have a high AVC without being aware of the condition. AVC was strongly correlated with AVAi, similar to the results obtained by Danielsen et al. in the AGES-Reykjavik study (Danielsen, et al. 2014). We extend

these data as we were able to demonstrate morphological changes of LV as a significantly higher LVMi and larger LAi in individuals with a high AVC, with the strongest association between AVC>300 and LVMi relative to LAi, which was more associated to AVAi. Thus, for some important risk factors but not for all, the association between risk factor and AVC was independent of AVAi.

The LVEF was preserved in all participants and not different between individuals with high and low AVC. Left ventricular hypertrophy and LA enlargement have been encountered in symptomatic and asymptomatic AS patients with increased LV filling pressure. These are indicators of increased hemodynamic burden and precede symptom onset in patients with AS (Christensen, et al. 2016; Dahl, et al. 2014; Pellikka, et al. 2005; Rusinaru, et al. 2017).

A large proportion of our participants demonstrate a high AVC despite no echocardiographic signs of valvular obstruction. This “mismatch” between calcium load and valvular hemodynamics lead to a small number of participants with AS in our study limiting our conclusions. Only 21 of the randomly selected individuals from the general population who were not previously known with AS were found to have AS.

However, our study does suggest that high AVC can be of importance long before the development of overt AS and well before patients become symptomatic. These findings may lead to the hypothesis that AVC might be a better tool to identify patients for future trials rather than echocardiography, as it identifies patients with atrioventricular disease irrespective of valvular hemodynamics.

The importance on focusing on the severity of valvular pathology rather than of valvular hemodynamics is further suggested by the finding by Clavel et al. who found an association between higher burden of absolute AVC and the survival of patients

with known AS under medical management, irrespective of valvular hemodynamics (Clavel, et al. 2014).

The AGES-Reykjavik Study looked at the prevalence of AS in various age groups from the general population in Iceland and prevalences of 0.9 to 7.3% were found in predefined age groups among 67 to 95 years old. An AVC ≥500 AU was indicative of severe AS (Danielsen, et al. 2014). In the current study, we investigated 65-75 years old citizens and found an almost similar threshold of AVC ≥415 AU to be the best predictor for AS being likely. A recent study by Pawade et al. found the optimal AVC thresholds for severe AS to be >1300 in women and >2000 AU in men (Pawade, et al. 2018). The latest European Society of Cardiology (ESC) guidelines consider severe AS to be likely if AVC scores are above 1200 for females and 2000 for males, and unlikely if AVC scores are below 800 and 1600, respectively. These cut-off values are based on studies on patients with known and severe AS, which probably led to higher AVC thresholds (Clavel, et al. 2013; Cueff, et al. 2011; Pawade, et al. 2018). We chose to explore likely AS – including mild, moderate and severe AS – in order to obtain a cut-off value that captures a potential window of opportunity for treatment and prevention of the disease before irreversible damage has occurred.

Strengths and limitations

A major limitation of our study may be the fact that participants were recruited from the ongoing DANCAVAS trial; thus, only individuals aged 65 to 75 years were included. In other words, the results may not apply to those younger or older. A major strength is the population-based set-up, but selection bias is inevitable as only about two-thirds of those invited accepted the screening. In addition, the subgroup that underwent echocardiography was arbitrarily selected with an AVC cut-off value of

300 AU, and a lower or higher cut-off point may have given a different result. From the group that underwent echocardiography, only 25 individuals turned out to have AS, of those 21 with previously undiagnosed AS, who could benefit of an early diagnose. Sex-specific differences are uncertain because of the small number of females and inequal distribution of AS. We acknowledge that our definition of hypertension was not according to the guidelines, but this was the best option in our study settings. If we instead used a cut-off value of 140/90 mmHg 87% of the participants had hypertension. When using the definition according to the guidelines in our analyses, hypertension remained without significant difference in Table 3 and 5.

In our population of individuals with AVC>300 the proportion of males was 3 times larger than female, an interesting point of discussion is whether the association of AVC>300 and AVAi could be solely explained with the male gender, as a bigger proportion of men have AVC, they have higher values of AVC and larger AVAi. These findings need to be explored further in larger studies before any solid conclusions can be made.

"Despite these shortcomings, our study population was adequate to clarify the importance of AVC score in the statistical analyses and at the same time to provide a great value as hypothesis generating research."

Perspectives

We observed echocardiographic changes well before the AVC scores reached the ESC guideline recommendation values for intervention. However, further studies with more participants need to be performed in order to confirm our findings and to determine whether NCCT can be used as a supplementary diagnostic tool to select

patients for assessment of likely AS. The purpose would be to detect significant AVC at an early stage and to assess the need and optimize the timing of intervention. Determining AVC score by NCCT is considered to be useful when echocardiography is inconclusive, but it can also be used "opportunisticly" in those individuals who already have undergone an NCCT for other diagnostic purposes. This can improve cost effectiveness in a healthcare system like the Danish system, where medical care is free of charge.

Conclusion

In a randomly selected asymptomatic group of individuals aged 65-75, calcification of the aortic valve was a common occurrence. The most common cardiovascular risk factors were associated with AVC score, and high AVC quantified by NCCT was associated with higher LVMi and LAi. However, a large proportion of patients with high AVC present with normal valvular hemodynamics.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Ethical approval:

The study was approved by the Regional Scientific Ethical Committees for Southern Denmark (Project ID: S-20140028).

Informed consent:

Written and oral informed consent was obtained from all individual participants included in the study.

Conflict of interest:

None

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Table 1. Baseline characteristics comparing participants with aortic valve calcification score ***below*** and ***above*** 300 AU.

545

546 Values are expressed as n (%) for categorical and mean (±SD) or median (IQR) for

Variables	**Total n= 1300**	**AVC < 300 AU N= 1203 (93%)**	**AVC ≥ 300 AU N=97 (7%)**	**p-Value**
Sex	664 (51) ♂ 636 (49) ♀	587 (88) ♂ 616 (97) ♀	77 (12) ♂ 20 (3) ♀	**<0.01**‡
Age, years	68.9 (±2.7)	68.8 (±2.7)	70.1 (±2.6)	**<0.001***
Smoking status				
Non-smokers	534 (41)	515 (43)	19 (20)	
Former smokers	577 (44)	517 (43)	60 (62)	**<0.001**‡/†
Active smokers	187 (14)	170 (14)	17 (18)	
Family history of CVD	222 (17)	206 (17)	16 (16)	0.82‡
Former CVD	197 (15)	170 (14)	27 (28)	**<0.001**‡
COPD	158 (12)	145 (12)	13 (13)	0.07‡
Hypertension	864 (66)	779 (65)	85 (88)	**0.0001**#
Systolic BP (mmHg)	154 (±20)	154 (±20)	155 (±21)	0.87*
Diastolic BP (mmHg)	84 (±10)	84 (±10)	84 (±12)	0.10*
Diabetes mellitus	145 (11)	121 (10)	24 (25)	**<0.001**‡
$HgbA_1c$ (mmol/mol)	39 (37-42)	38 (36-41)	40 (37-45)	**0.001**#
Statin treatment	482 (37)	427 (35)	55 (57)	**<0.001**‡
Total cholesterol (mmol/l)	5.3 (1.1)	5.3 (±1.1)	4.8 (±1.2)	**<0.001***
LDL (mmol/l)	3.0 (±1.0)	3. 0 (±1.0)	2.6 (±0.9)	**<0.001***
HDL (mmol/l)	1.5 (±0.4)	1.5 (±0.4)	1.3 (±0.4)	**<0.001***
Hypercholesterolemia	1168 (90)	1085 (90)	83 (86)	0.15‡
BMI (kg/m^2)	27 (±5)	27 (±5)	29 (±4)	**0.002***
BMI > 25 kg/m^2	877 (67)	798 (66)	79 (81)	**0.002**‡
Creatinine (µmol/L)	83 (±27)	82 (±19)	98 (±72)	**<0.001***
eGFR (mL/min)	75 (±14)	75 (±14)	71 (± 16)	**0.001***
eGFR <60 mL/min	178 (14)	161 (13)	17 (18)	**0.25**‡
Dyspnea				
NYHA 2	33 (8)	27 (8)	6 (13)	0.46†
NYHA 3	1 (0.3)	(0.3)	0 (0)	
Atypical angina	40 (3)	36 (4)	4 (4)	0.66†
Typical angina	51 (4)	46 (4)	5 (5)	
AVC score				
Median (IQR)	6 (0 – 67)	3 (0 – 40)	501 (358- 808)	
AVC=0	505 (39)	505(42)	0 (0)	
AVC >0-149.9	605 (46)	605 (50)	0 (0)	
AVC 150- 299.9	93 (7)	93(8)	0 (0)	
AVC 300- 799.9	71 (6)	0 (0)	71 (73)	
AVC 800-1199	14 (1)	0 (0)	14 (14)	
AVC >1200	12 (1)	0 (0)	12 (12)	

547 continuous variables. CVD, cardiovascular disease; COPD, chronic obstructive

548 pulmonary disease; BMI, body mass index (kg/m^2); AVC, aortic valve calcification.

549 * t-test, # Mann-Whitney test, ‡ Chi-square test, † Fisher`s exact test

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Table 2. Zero-inflated negative binomial regression. Associations between aortic valve calcification and traditional cardiovascular risk factors in men and women.

		All participants (n=1269)*	
	IRR	95% CI	p-value
Age, years	1.10	1.05-1.15	**<0.001**
Male	2.04	1.55-2.67	**<0.001**
Smoking status			
Former	1.15	0.87-1.52	0.32
Current	1.50	1.02-2.21	**0.04**
Family history of CVD	0.97	0.71-1.32	0.83
Former CVD	1.83	1.32-2.54	**<0.001**
Hypertension	1.40	1.04-1.90	**0.03**
Diabetes mellitus	1.25	0.87-1.80	0.23
Hypercholesterolemia	0.76	0.50-1.18	0.22
BMI, kg/m^2	1.02	1.00-1.05	0.21
eGFR, mL/min	1.00	1.00-1.00	0.44

AVC, aortic valve calcification; IRR, incidence rate ratio, CI, confidence interval; CVD, cardiovascular disease; BMI, body mass index; eGFR, estimated glomerular filtration rate. * number of patients with complete dataset.

Table 3. Baseline characteristics of participants with an echocardiography, divided in subjects with aortic valve calcification score ***below*** and ***above*** 300 AU

Variables	**Total** N=205	AVC score <300 AU N=123 (60%)	AVC score (≥300 AU) N= 82 (40 %)	**p-Value**
Sex	121 (59) ♂ / 84 (41) ♀	55 (45) ♂ / 68 (55) ♀	66 (80) ♂ / 16 (20) ♀	**<0.001**
Age, years	70 (±2.7)	69.8 (±2.8)	70.2 (±2.7)	0.32*
Smoking status				
Non-smokers	70 (34)	53 (43)	17 (21)	
Former smokers	99 (48)	49 (40)	50 (61)	**0.003** ‡
Active smokers	35 (17)	21 (17)	14 (17)	
Missing data	1 (0.5)	0	1 (1)	
Family history of CVD	41 (21)	26 (22)	15 (18)	0.74‡
Former CVD	61 (30)	35 (29)	26 (32)	0.62‡
COPD	30 (15)	18 (15)	12 (15)	1.00†
Hypertension	169 (82)	72 (79)	97 (88)	0.10‡
Systolic BP (mmHg)	155 (±22)	154 (±22)	155 (±22)	0.94*
Diastolic BP (mmHg)	84 (±11)	84 (±10)	84 (±10)	0.61*
Diabetes mellitus	32 (16)	16 (13)	16 (20)	0.21†
$HgbA_1c$ (mmol/mol)	39 (37-43)	39 (36-42)	40 (37-44)	0.10 #
Statin treatment	103 (50)	55 (45)	48 (59)	0.05‡
Total cholesterol (mmol/l)	5.0 (±1.1)	5.1 (±1.1)	4.8 (±1.1)	**0.03***
LDL (mmol/l)	2.8 (±1.0)	2.8 (±1.0)	2.6 (±0.9)	0.07*
HDL (mmol/l)	1.4 (0.44)	1.5 (±0.5)	1.3 (±0.40)	**0.003***
Hypercholesterolemia	179 (87)	109 (89)	70 (86)	0.50‡
BMI (kg/m^2)	28 (±4.8)	28 (±5)	29 (±4.5)	0.10*
eGFR (mL/min)	74 (±15)	75 (±15)	72 (±15)	0.26*
Dyspnea				
NYHA 2	21 (29)	13 (34)	8 (23)	0.55‡
NYHA 3	11 (15)	5 (13)	6 (17)	
Atypical angina	11 (5.5)	8 (7.0)	3 (4.0)	0.64†
Typical angina	9 (4.5)	4 (3.4)	5 (6.2)	
AVC score				
Median (IQR)	228 (17-420)	48 (0.9 – 174)	570 (361-869)	
AVC=0	27 (15)	27 (22)	0 (0.0)	
AVC 1-149	60 (30)	60 (49)	0 (0.0)	
AVC 150- 299	36 (18)	36 (30)	0 (0.0)	
AVC 300- 799	56 (27)	0 (0.0)	56 (7)	
AVC 800-1199	14 (7)	0 (0.0)	14 (17)	
AVC >1200	12 (6)	0 (0)	12 (15)	

Values are expressed as n (%) for categorical and mean (±SD) or median (IQR) for continuous variables. CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; BMI, body mass index (kg/m^2); AVC, aortic valve calcification; AS, aortic stenosis; No AS, no aortic stenosis. * t-test, # Mann-Whitney test, ‡ Chi-square test, † Fisher`s exact test.

Table 4: Echocardiographic data on participants with aortic valve calcification score ***below*** and ***above*** 300 AU

Variables	All n=205	AVC < 300 AU n=123	AVC ≥ 300 AU n=82	p-value
Peak aortic valve velocity (m/s)	1.7 (1.4-2.2)	1.4 (1.2-1.6)	1.8 (1.4-2.2)	**<0.001**[#]
Mean aortic valve gradient (mmHg)	5 (3-7)	4 (3 - 6)	7 (4 - 11)	**<0.001**[#]
AVA (cm^2)	2.3 (±0.6)	2.4 (±0.6)	2.1 (±0.7)	**0.010**[*]
AVAi (cm^2/m^2)	1.2 (± 0.3)	1.3 (±0.3)	1.1 (±0.3)	**<0.001**[*]
LV ejection fraction (%)	60 (55-65)	60 (55-62)	60 (55-64)	0.57[#]
LV IVSd (mm)	11 (±2)	11 (±2)	12 (±2)	**0.006**[*]
LV EDD (mm)	45 (±6.5)	44 (±6.3)	46 (±6.5)	**0.01**[*]
LV Pwd (mm)	10 (±2)	9 (±2)	10 (±2)	**0.001**[*]
LV mass index (g/m^2)	85 (±21)	81 (±20)	92 (±21)	**0.0006**[*]
Relative wall thickness (mm)	0.44 (±0.10)	0.44 (±0.11)	0.45 (±0.10)	0.60[*]
E/e' ratio	12 (±4)	12 (±4)	11 (±4)	0.21[*]
Deceleration time (ms)	220(±58)	215 (±55)	226 (±60)	0.20[*]
e'_{sep} (cm/s)	6.7 (±1.7)	6.6 (±1.6)	7.0 (±1.9)	0.07[*]
Left atrial volume index (ml/m^2)	27 (±11)	26 (±11)	30 (±10)	**0.002**[*]
Tricuspid regurgitation peak gradient (mmHg)	16 (±10)	15 (±10)	16 (±11)	0.75[*]

Values are expressed as mean (SD) or as median (IQR). AU, Arbitrary units; AVA, Aortic Valve Area; EDD, end-diastolic dimension; IVSd, Interventricular Septal Thickness at Diastole; LV, Left Ventricular; LVOT, Left Ventricular Outflow Tract; Pwd, Posterior wall thickness at diastole. * t-test, # Mann-Whitney test.

Table 5. Baseline characteristics of participants with an echocardiogram, divided based on presence of aortic valve stenosis

Variables	**Total** N=205	**AS** N=25	**No AS** N=180	**p-value**
Sex	121 (59) ♂ 84 (41) ♀	21 (84) ♂ 4 (16) ♀	100 (56) ♂ 80 (44) ♀	
Age, years	70 (±2.7)	70.4 (±2.7)	69.9 (±2.9)	0.41*
Smoking status				
Non-smokers	70 (34)	7 (28)	63 (35)	0.71‡
Former smokers	99 (48)	14 (56)	85 (47)	
Active smokers	35 (17)	4 (16)	31 (17)	
Missing data	1 (0.5)	0	1 (0.6)	
Family history of CVD	41 (21)	7 (28)	34 (19)	0.42‡
Former CVD	61 (30)	6 (24)	55 (31)	0.50‡
COPD	30 (15)	1 (4.0)	29 (16)	0.13†
Hypertension	169 (82)	22 (88)	147 (82)	0.43‡
Systolic BP (mmHg)	155 (±22)	155 (±20)	154 (±22)	0.88*
Diastolic BP (mmHg)	84 (±11)	86 (±11)	83 (±11)	0.30*
Diabetes mellitus	32 (16)	5 (20)	27 (15)	0.52#
$HgbA_1c$ (mmol/mol)	39 (37-43)	40 (39-44)	39 (36-42)	0.09#
Statin treatment	103 (50)	12 (48)	91 (51)	0.81‡
Total cholesterol (mmol/l)	5.0 (±1)	4.9 (±1)	5.0 (±1)	0.70*
LDL (mmol/l)	2.8 (±1)	2.8 (±1)	2.7 (±1)	0.10*
HDL (mmol/l)	1.4 (0.44)	1.2 (±0.42)	1.4 (±0.44)	**0.04***
Hypercholesterolemia	179 (87)	22 (88)	157 (87)	0.91‡
BMI (kg/m^2)	28 (±4.8)	30 (±4.3)	28 (±4.8)	**0.03***
Creatinine (µmol/L)	85 (±23)	91 (±18)	84 (±23)	0.13*
Dyspnea				
NYHA 2	21 (29)	2 (20)	19 (30)	0.20†
NYHA 3	11 (15)	0 (0)	11 (17)	
Atypical angina	11 (6)	2 (8)	9 (5)	0.56†
Typical angina	9 (5)	0 (0)	9 (5)	
AVC score				
Median (IQR)	228 (17-420)	808 (565-1357)	170 (8.1-357)	**<0.0001#**
AVC=0	27 (15)	0 (0)	27 (13)	
AVC 1-149	60 (30)	1 (4)	59 (33)	**<0.0001†**
AVC 150- 299	36 (18)	1 (4)	35 (19)	
AVC 300- 799	56 (27)	10 (40)	46 (26)	
AVC 800-1199	14 (7)	6 (24)	8 (4)	
AVC >1200	12 (6)	7 (28)	5 (3)	

Values are expressed as n (%) for categorical and mean (±SD) or median (IQR) for continuous variables. CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; BMI, body mass index (kg/m^2); AVC, aortic valve calcification; AS, Aortic stenosis; No AS, no Aortic stenosis. * t-test, # Mann-Whitney test, ‡ Chi-square test, † Fisher`s exact test.

Figure legends:

Figure 1 Flow chart of study participants

AS, Aortic stenosis; AVC, aortic valve calcification;

Figure 2 Association between AVC score and AVAi

Graph of AVC score in AU (on a logarithmic scale) versus AVAi score in cm^2/m^2 for 205 individuals. An AVAi ≤ 0.85 cm^2/m^2 indicates people with moderate or severe AS. Blue dots indicate males; red dots indicate females. The red line at the 300 AU level separates the participants with high and low AVC.

Figure 3 ROC curve with cut-off value for AVC score for AS being likely

AS was considered being likely at AVAi <0.85 cm^2/m^2

AVC and AVAi < 0.85 for the whole population in same graph (p= 0.0062)

Figure 1.

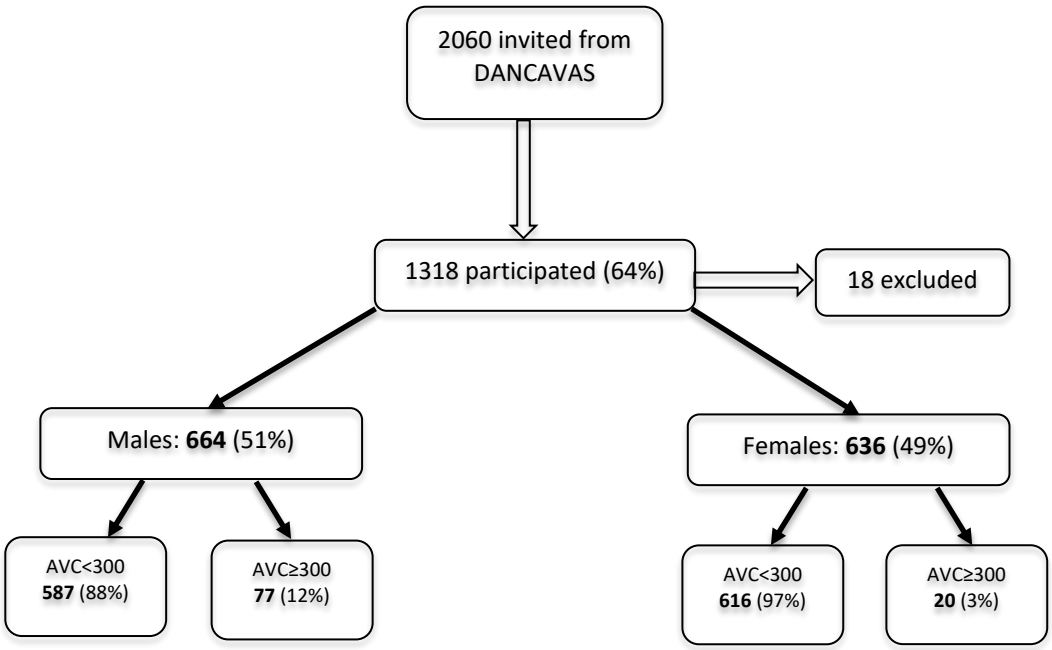

2060 invited from DANCAVAS
1318 participated (64%)
18 excluded
Males: **664** (51%)
Females: **636** (49%)
AVC<300 **587** (88%)
AVC≥300 **77** (12%)
AVC<300 **616** (97%)
AVC≥300 **20** (3%)

Figure 2.

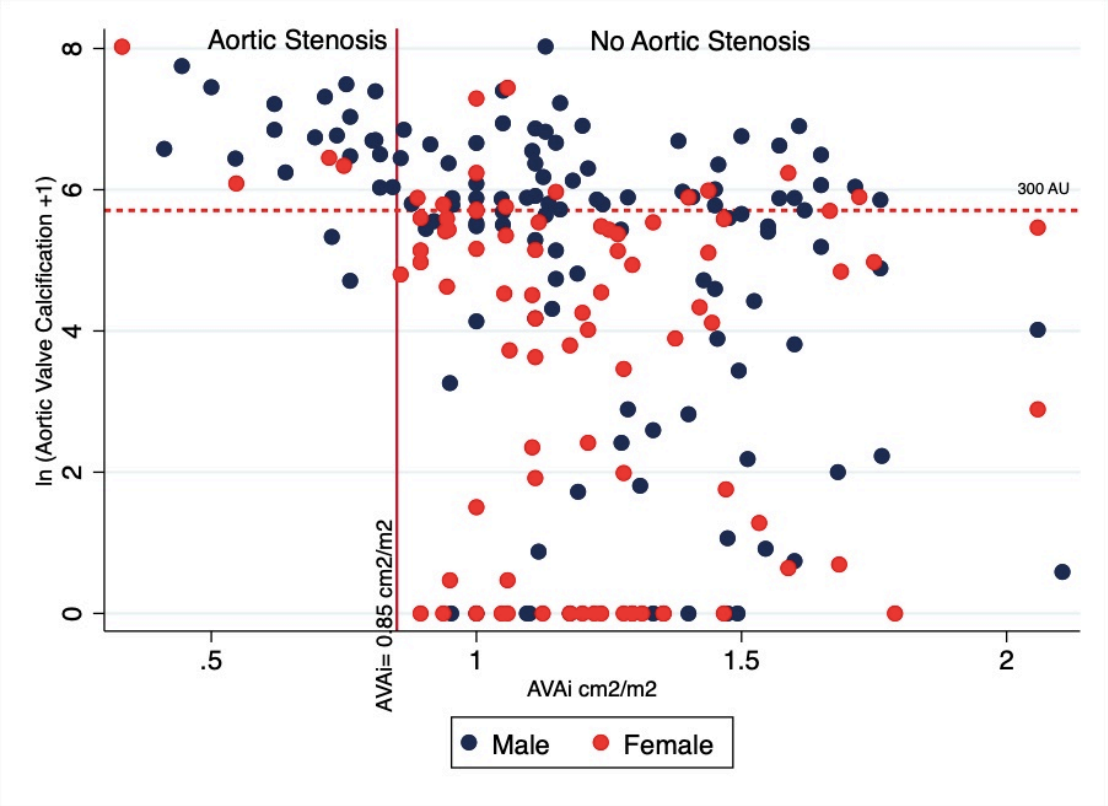
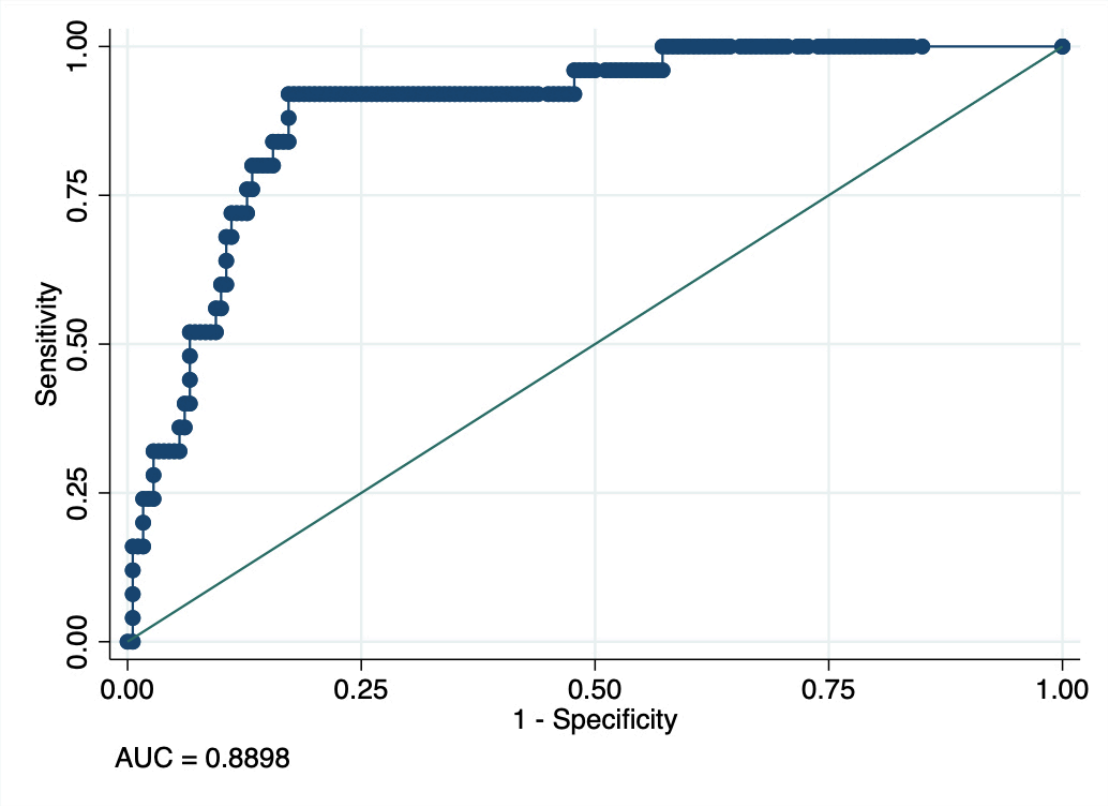

Aortic Stenosis
No Aortic Stenosis
300 AU
ln (Aortic Valve Calcification +1)
0
2
4
6
8
.5
1
1.5
2
AVAi= 0.85 cm2/m2
AVAi cm2/m2
Male
Female

Figure 3.


Sensitivity
0.00
0.25
0.50
0.75
1.00
1 - Specificity
0.00
0.25
0.50
0.75
1.00
AUC = 0.8898

Supplementary Materials

Table S1. Acquisition and reconstruction parameter used on cardiac CT of DANCAVAS study

Tube voltage (kV)	120
Reference tube current per rotation (mAs)	80
Slice acquisition (mm)	38 * 1.2
Rotation time (s)	0.25
Temporal resolution (ms)	75
Slice thickness (mm)	3.0 (no overlap)
Kernel	Qr36
Levels of Iterative reconstruction	0
$CTDI_{vol}$ (mGy)	2.4-7.3
Software	Syngo

Table S2. Baseline characteristics of the 1318 participants.

	All	Men	Women	P-value
N (participation rate %)	1318 (100.0)	677 (51.4)	641 (48.6)	0.41
Age, years	69.0 (±2.7)	68.9 (±2.5)	69.0 (±2.9)	0.50*
Smoking status				
Non-smokers	539 (41)	202 (30)	337 (53)	
Former smokers	589 (45)	365 (54)	224 (35)	**<0.001**‡
Active smokers	188 (14)	109 (16)	79 (12)	
Family history of CVD	225 (17)	113 (18)	112 (17)	0.13‡
Former CVD	211 (16)	134 (20)	77 (12)	**<0.001**‡
COPD	160 (12)	92 (14)	68 (11)	0.10‡
Hypertension	880 (67)	456 (67)	424 (66)	0.64‡
Systolic blood pressure (mmHg)	154 (±20)	153 (±20)	155 (±20)	0.06*
Diastolic blood pressure (mmHg)	84 (±10)	86 (±10)	83 (±9)	**<0.001***
Diabetes mellitus	149 (11)	95 (14)	54 (8.4)	**0.001**‡
$HgbA_1c$ (mmol/mol)	38 (36-41)	38 (36-42)	38 (36-41)	0.59#
Statin treatment	360 (27)	192 (28)	168 (26)	0.80‡
Total cholesterol (mmol/l)	5.3 (±1.1)	5.0 (±1.1)	5.6 (±1.1)	**<0.001***
LDL (mmol/l)	3 (±0.1)	2.9 (±0.1)	3.1 (±0.1)	**<0.001***
HDL (mmol/l)	1.5 (±0.35)	1.3 (±0.3)	1.7 (±0.4)	**<0.001***
Hypercholesterolemia	1184 (90)	587 (87)	597 (93)	**<0.001**‡
BMI (kg/m^2)	27 (±5)	28 (±4)	26 (±5)	**<0.001***
Creatinine (µmol/L)	83 (±27)	92 (±21)	74 (±30)	**<0.001***
eGFR (mL/min)	75 (±14)	75 (±14)	74 (±14)	0.14*
Dyspnoea				
NYHA 2	33 (8)	19 (6.6)	14 (11.4)	**<0.001**‡
NYHA 3	1 (0.2)	1 (0.4)	0 (0)	**<0.001**‡
Atypical angina	41 (3.1)	22 (3.3)	19 (3.0)	0.37†
Typical angina	53 (4.1)	33 (5.0)	20 (3.1)	
AVC score				
Median (IQR)	6 (0-67)	16 (0-113)	2 (0-32)	**<0.001**#
• AVC=0	505 (39)	222 (44)	283 (33)	
• AVC >0-149.9	605 (47)	299 (45)	306 (48)	
• AVC 150- 299.9	93 (7.2)	66 (10)	27 (4.2)	**<0.001**#
• AVC 300- 799.9	71 (5.5)	54 (8.1)	17 (2.7)	
• AVC 800-1199	14 (1.1)	14 (2.1)	0 (0)	
• AVC >1200	12 (0.9)	9 (1.4)	3 (0.5)	
Missing AVC scores	18 (1.4)	13 (1.9)	5 (0.8)	0.07‡
• Aortic valve replacement	13(0.1)	4(0.6)	9 (0.8)	
• Artefacts on CT	1(0.1)	1(0.1)	0(0)	
• Missing CT scan	5(0.7)	4(0.6)	1(0.2)	

Values are expressed as n (%) for categorical and mean (±SD) and median (IQR) for continuous variables. P-value signifies difference between sexes. * t-test, # Mann-Whitney test, ‡ Chi-square test, † Fisher`s exact test

Table S3. Baseline characteristics of the echo participants.

	All (n=205)	**Men (n=121)**	**Women (n=84)**	**P-value**
Age, years (SD)	70.0 (±2.7)	69.8 (±2.6)	70.1 (±2.9)	0.56*
Smoking status Non-smokers Former smokers Active smokers	 70 (34) 99 (48) 35 (17)	 26 (22) 70 (58) 24 (20)	 44 (52) 29 (34) 11 (13)	**<0.001**‡
Family history of CVD	41 (21)	22 (19)	19 (23)	0.35‡
Former CVD	61 (30)	39 (32)	22 (26)	0.35‡
COPD	30 (15)	20 (17)	10 (12)	0.42†
Hypertension	169 (82)	104 (86)	65 (77)	0.11‡
Systolic blood pressure (mmHg)	155 (±22)	154 (±21)	155 (±23)	0.84*
Diastolic blood pressure (mmHg)	84 (±11)	85 (±11)	82 (±11)	**0.02***
Diabetes mellitus	32 (16)	17 (14)	15 (18)	0.56†
$HgbA_1c$ (mmol/mol)	39 (37-43)	39 (37-43)	39 (37-43)	0.70#
Statin treatment	103 (50)	68 (56)	35 (42)	0.04‡
Total cholesterol (mmol/l)	5.0 (±1.1)	4.7 (±1.0)	5.5 (±1.1)	**<0.001***
LDL (mmol/l)	2.8 (±1.0)	2.6 (±0.9)	3.0(±1.0)	**0.0006***
HDL (mmol/l)	1.4 (±0.4)	1.2 (±0.3)	1.7 (±0.5)	**<0.001***
Hypercholesterolemia	179 (87)	102 (84)	77 (92)	0.12‡
BMI (kg/m^2)	28 (±4.8)	29 (±4.4)	27 (±5.2)	**0.003***
Creatinine (μmol/L)	85 (±23)	94 (±23)	73 (±16)	**<0.001***
eGFR (mL/min)	74 (±15)	73 (±15)	74 (±15)	0.60*
Dyspnoea NYHA 2 NYHA 3	 21 (29) 11 (17)	 11 (20) 9 (17)	 10 (53) 2 (11)	**0.04**†
Atypical angina Typical angina	11 (6) 9 (5)	6 (5) 8 (7)	5 (6) 1 (1)	0.30†
AVC score Median (IQR) • AVC=0 • AVC >0-149.9 • AVC 150- 299.9 • AVC 300- 799.9 • AVC 800-1199.9 • AVC >1200	 228 (17-419) 27 (13) 60 (29) 36 (18) 56 (27) 14 (7) 12 (6)	 330 (73-661) 9 (8) 29 (23) 17 (14) 43 (36) 14 (12) 9 (8)	 93 (0.95-259) 18 (21) 31 (37) 19 (23) 13 (15) 0 (0) 3 (4)	**<0.001**# **<0.001**‡

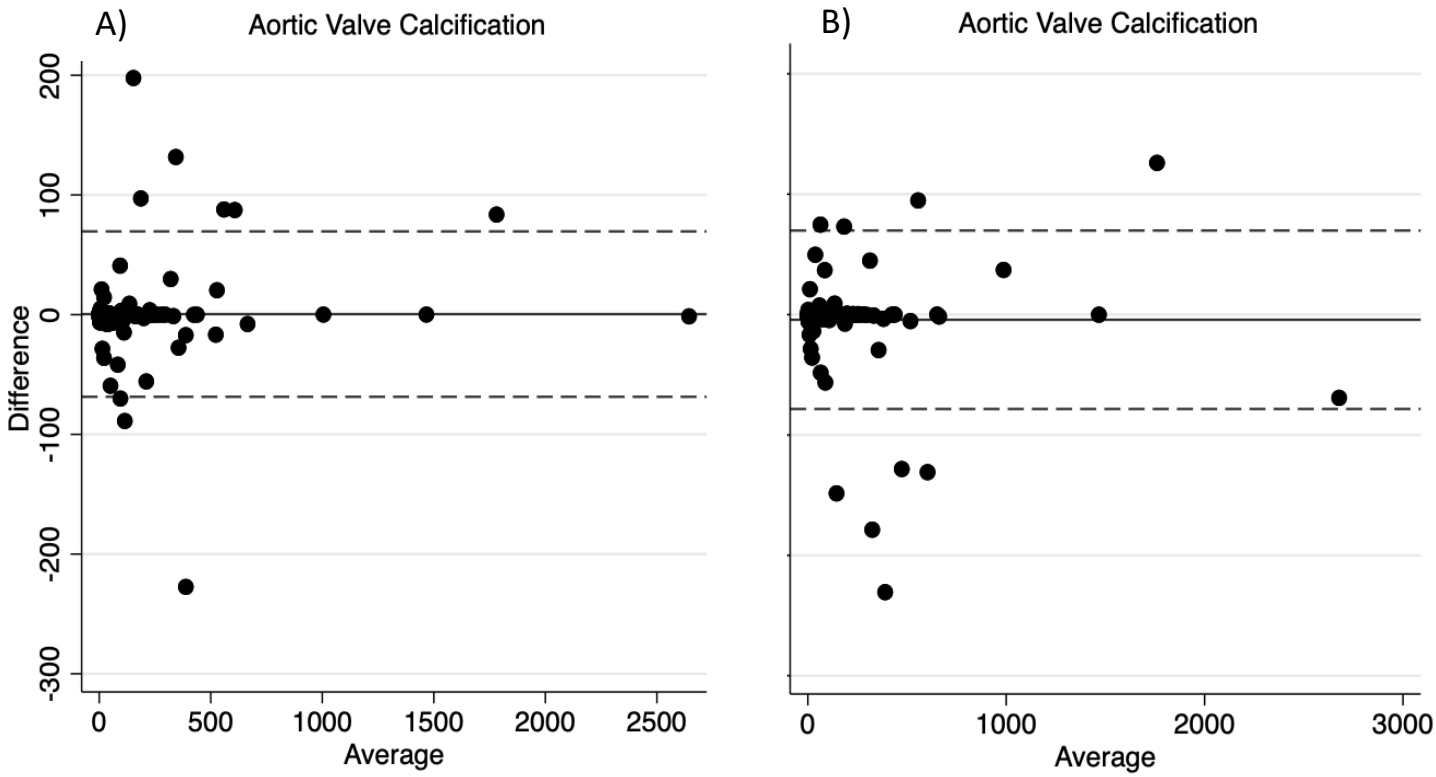
Values are expressed as n (%) for categorical and mean (±SD) and median (IQR) for continuous variables. P-value signifies difference between sexes. CVD= cardiovascular disease, COPD= chronic obstructive pulmonary disease, BMI=body mass index(kg/m^2), AVC= score aortic valve calcification score (AU), * t-test, # Mann-Whitney test, ‡ Chi-square test, † Fisher's exact test

Table S4: Echocardiographic data on women with AVC >300 and men with AVC >300 and controls.

Variables	Men n=121 (59)	Women n=84 (41)	N=205 p-value
Peak aortic valve gradient (mmHg)	9 (6-13)	9 (7-12)	0.86#
Mean aortic valve gradient (mmHg)	5 (3.4-7.2)	5 (3.5-6.8)	0.70#
Peak aortic valve velocity m/s)	1.6 (±0.5)	1.6 (±0.6)	0.95*
Mean aortic valve velocity m/s)	1.1 (±0.4)	1.1 (±0.5)	0.70*
AVA (cm^2)	2.4 (0.7)	2.1 (0.5)	**0.0003***
AVA (cm^2/m^2)	1.2 (0.3)	1.2 (0.3)	0.69*
LV ejection fraction (%)	60 (55-65)	60 (55-61)	**0.048#**
LV IVSd (mm)	12 (2.1)	11 (1.8)	**0.006***
LV EDD (mm)	46 (6.4)	42 (5.6)	**<0.001***
LV Pwd (mm)	10 (1.6)	9 (1.0)	**<0.001***
LV mass index (g/m^2)	91 (21)	77 (18)	**<0.001***
Relative wall thickness (mm)	0.5 (0.1)	0.4 (0.1)	**0.02***
E/e' ratio	11 (4)	13 (5.0)	**<0.001***
Deceleration time (ms)	220 (60)	220 (55)	0.10*
e'_{sep} (cm/s)	7 (2)	6 (1.5)	**0.01***
Left atrial volume index (ml/m^2)	32 (11)	21 (8)	**<0.001***
Tricuspid regurgitation peak gradient (mmHg)	13 (10)	18 (10)	**0.007***

Values are expressed as mean (SD) or as median (IQR). AU = Arbitrary units, AVA = Aortic Valve Area, EDD = end-diastolic dimension, IVSd = Interventricular Septal Thickness at Diastole, LV = Left Ventricular, LVOT = Left Ventricular Outflow Tract, Pwd = Posterior wall thickness at diastole, * t-test, # Mann-Whitney test.

Figure S1.



Dashed lines: 95% limit of agreement. Solid line: average agreement

Figure 1S. Bland-Altman scatter plots comparing intra- and inter-observer agreement of AVC (AU) measurements in NCCT (N=140).

A) Intraobserver variation agreement of AVC measurements.

B) Interobserver variation agreement of AVC measurements.