

Original Article



Mitral Annulus Calcification and Cardiac Conduction Disturbances: A DANCAVAS Sub-study

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ABSTRACT

BACKGROUND: Due to its location very close to the bundle of His, mitral annulus calcification (MAC) might be associated with the development of atrioventricular (AV) conduction disturbances. This study assessed the association between MAC and AV conduction disturbances identified by cardiac implantable electronic device (CIED) use and electrocardiographic parameters. The association between MAC and traditional cardiovascular risk factors was also assessed.

METHODS: This cross-sectional study analyzed 14,771 participants, predominantly men aged 60–75 years, from the population-based Danish Cardiovascular Screening trial. Traditional cardiovascular risk factors were obtained. Using cardiac non-contrast computed tomography imaging, MAC scores were measured using the Agatston method and divided into absent versus present and score categories. CIED implantation data were obtained from the Danish Pacemaker and Implantable Cardioverter Defibrillator Register. A 12-lead electrocardiogram was available for 2,107 participants. Associations between MAC scores and AV conduction disturbances were assessed using multivariate regression analyses.

RESULTS: MAC was present in 22.4% of the study subjects. Participants with pacemakers for an AV conduction disturbance had significantly higher MAC scores (odds ratio [OR], 1.11; 95% confidence interval [CI], 1.01–1.23) than participants without a CIED, whereas participants with a CIED for other reasons did not. Prolonged QRS-interval was significantly associated with the presence of MAC (OR, 1.45; 95% CI, 1.04–2.04), whereas prolonged PQ-interval was not. Female sex and most traditional cardiovascular risk factors were significantly associated with high MAC scores.

CONCLUSIONS: MAC was associated with AV conduction disturbances, which could improve our understanding of the development of AV conduction disturbances.

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Conflict of Interest

The authors have no financial conflicts of interest.

Data Sharing Statement

Data from the Danish Cardiovascular

Keywords: Mitral annulus calcification; Cardiac non-contrast computed tomography; Heart block; Cardiac pacing, artificial; Electrocardiography

INTRODUCTION

Mitral annulus calcification (MAC) is defined as calcium deposition at the base of the mitral valve, typically in the posterior aspect.¹ MAC is a common finding, with a prevalence of 5–42% depending on the age and sex of the examined population and the modality used to identify MAC.¹ Due to the anatomical location of MAC, very close to the AV-node and bundle of His (**Figure 1**), it has been hypothesized that MAC could be associated with atrioventricular (AV) conduction disturbances.² In that case, MAC might be a predictor of AV conduction disturbances that require the use of a cardiac implantable electronic device (CIED) but not of CIED implantation in general. In some publications, MAC has been associated with AV conduction disturbances and pacemaker (PM) implantation,³⁻⁶ but not all studies agree.⁷ Overall, this potential association remains poorly investigated, and the association between MAC and the need for other types of CIED has not been studied. The development of acquired AV conduction disturbances is poorly understood, with idiopathic degeneration of the cardiac conduction system being the most common cause.⁸ Therefore, studying MAC might help explain why AV conduction disturbances develop and could have potential clinical implications in the future.

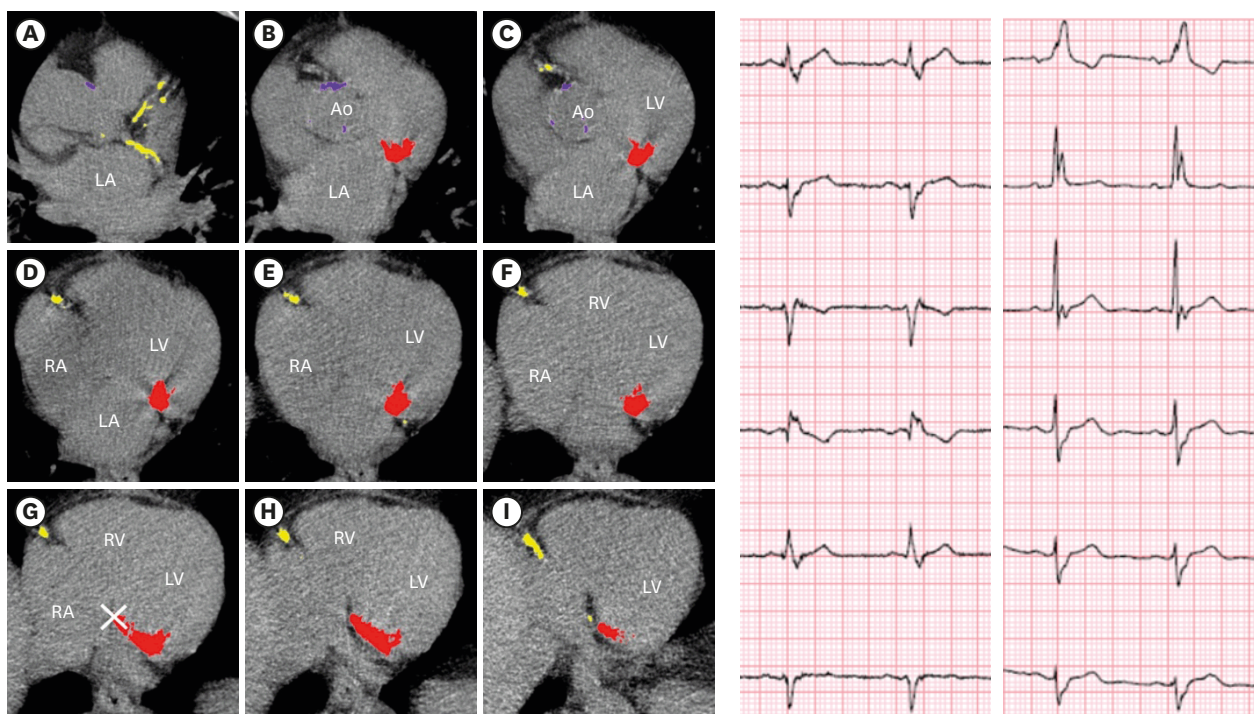


Figure 1. Cardiac non-contrast computed tomography images and 12-lead electrocardiography from a patient with MAC (MAC score = 7,154 Agatston unit) and a prolonged QRS-interval (146 ms). The bundle of His is located close to the posterior aspect of the mitral annulus and is marked with a white cross (G). Red, MAC; Yellow, coronary artery calcification; Purple, Ao calcification.
 Ao: aortic valve, LA: left atrium, LV: left ventricle, MAC: mitral annulus calcification, RA: right atrium, RV: right ventricle.

Screening (DANCAVAS) trial cannot be shared publicly due to participant privacy. Data from the DANCAVAS trial will be shared upon reasonable request to the corresponding author. Data provided by the Danish Pacemaker and ICD Register (DPIR) will be shared upon reasonable request to the corresponding author with permission from DPIR.

Author Contributions

Conceptualization: Diederichsen ACP; Data curation: Rasmussen JH, Fredgart MH, Diederichsen ACP; Formal analysis: Rasmussen JH, Fredgart MH, Diederichsen ACP; Investigation: Rasmussen JH, Fredgart MH, Lindholt JS, Hasific S, Sønderkov P, Steffensen FH, Frost L, Lambrechtsen J, Karon M, Busk M, Urbonaviciene G, Egstrup K, Diederichsen ACP; Methodology: Rasmussen JH, Fredgart MH, Diederichsen ACP; Project administration: Rasmussen JH, Fredgart MH, Lindholt JS, Diederichsen ACP; Supervision: Fredgart MH, Johansen JB, Sandgaard N, Diederichsen ACP; Writing - original draft: Rasmussen JH; Writing - review & editing: Rasmussen JH, Fredgart MH, Lindholt JS, Johansen JB, Sandgaard N, Yousef AH, Hasific S, Sønderkov P, Steffensen FH, Frost L, Lambrechtsen J, Karon M, Busk M, Urbonaviciene G, Egstrup K, Diederichsen ACP.

Cardiac non-contrast computed tomography (NCCT) imaging is currently the best modality allowing precise and reproducible quantification of MAC using the Agatston method.^{2,9)} Risk factors for MAC have previously been reported to include age, female sex, diabetes, obesity, smoking, hypertension, dyslipidemia, and renal dysfunction,^{2,10,13)} but most studies have used echocardiography, which is less sensitive than cardiac NCCT imaging to identify MAC.²⁾

In this large, population-based, cross-sectional study, we assessed the association between MAC scores identified using cardiac NCCT imaging and AV conduction disturbances identified by CIED implantation and electrocardiographic (ECG) parameters. In addition, we assessed the association between MAC scores and traditional cardiovascular risk factors.

METHODS

Study population

All participants from the population-based, multicenter Danish Cardiovascular Screening (DANCAVAS) trial were included.¹⁴⁾ Predominantly men aged 60–75 years were enrolled between September 2014 and February 2019. See the DANCAVAS trial protocol for further information.¹⁴⁾

The DANCAVAS trial was approved by the Regional Scientific Ethical Committee for Southern Denmark (S-20140028 and S-20160105) and the Danish Data Protection Agency. Data were collected and managed using REDCap® data management and hosted at the Odense Patient Data Explorative Network (OPEN).

Cardiac NCCT

All participants received a cardiac NCCT scan during their screening examination. The computed tomography (CT) specifications are provided in the supplementary material (**Supplementary Data 1**) and have previously been described in detail.¹⁵⁾ Using a SyngoVia (Siemens Healthcare Solutions) workstation, 7 trained radiographers, blinded to clinical data, measured heart valve calcification scores using the Agatston method.⁹⁾ MAC was defined as calcium deposition at the junction between the left atrium and left ventricle at the level of the mitral annulus, excluding calcium in the mitral leaflets; aortic valve; left main, circumflex, and right coronary artery; and leads (**Figure 1**). Due to a non-normal distribution, MAC scores were divided into absent (0 Agatston unit [AU]) versus present (≥ 1 AU) and 8 MAC score categories (0, 1–9, 10–99, 100–199, 200–299, 300–599, 600–1,199 and $\geq 1,200$ AU) for different parts of our analysis. Inter- and intra-observer variability in MAC score measurements were assessed by all 7 radiographers and a second reader (M.H.F.) in 140 randomly selected participants.

Cardiovascular risk factors

Diabetes was defined as the use of antidiabetic medication (oral antidiabetics or insulin), hemoglobin A1c > 48 mmol/mol, or self-reported diabetes. Hypertension was defined as the use of antihypertensive medication, systolic or diastolic blood pressure ≥ 160 or 100 mmHg, respectively, or self-reported hypertension.¹⁴⁾ The estimated glomerular filtration rate (eGFR) was calculated and divided into decreased kidney function (< 60 mL/min/1.73 m²) and normal kidney function (≥ 60 mL/min/1.73 m²).¹⁶⁾ High- and low-density lipoproteins (HDL and LDL, respectively) and total cholesterol were measured using standardized methods. Hypercholesterolemia was defined as total cholesterol ≥ 5 mmol/L, LDL ≥ 3 mmol/L, or the use of lipid lowering medication.

CIEDs

Data regarding CIED implantation were obtained from the Danish PM and Implantable Cardioverter Defibrillator (ICD) Register (DPIR) from January 2000 to December 2018.¹⁷⁾ The data included indication, date of implantation, and CIED type. DPIR contains data for all CIED implantations in Denmark. Data from DPIR were linked to the DANCAVAS trial data using the Civil Personal Registration (CPR) number that is assigned permanently to all Danish citizens at birth or upon immigration. All Danish citizens have unrestricted, tax-provided access to health care. At each contact with the Danish healthcare system, the CPR number is registered. That unique identifier enabled coordination of data between the Danish national registries and the DANCAVAS trial.

In this study, PMs were either a single chamber atrial PM, dual chamber PM, single chamber ventricular PM or cardiac resynchronization therapy PM. ICDs were either a single chamber ventricular ICD or dual chamber ICD. Cardiac resynchronization therapy defibrillator (CRT-D) was reported separately.

In the data, CIED implantation was reported as having an implanted CIED at the screening examination or first receiving a CIED after the screening examination. Although CIED implantations after the screening date were prospective data, we reported those participants as having a CIED in this cross-sectional study to boost the number of participants with a CIED and enhance the power of our results.

Participants were divided into 5 CIED groups: 1) no CIED, 2) a PM implanted due to an AV conduction disturbance, 3) a PM implanted due to an indication other than an AV conduction disturbance, 4) a CRT-D, and 5) an ICD. Implantation due to an AV conduction disturbance was defined as one of the following indications: 1° AV block, 2:1 AV block, 2° AV block advanced type, 2° AV block type I or II, 3° AV block, unspecified sinus node dysfunction with impaired AV conduction, chronic atrial fibrillation with 3° AV block or bradycardia, right bundle branch block, left bundle branch block, or unspecified bundle branch block.

Electrocardiography

In the DANCAVAS trial, a standard resting 12-lead ECG was performed just after the screening examination in 1,357 consecutive participants. Subsequently, all participants with heart valve calcification above the 90th percentile were invited to receive a supplementary 12-lead ECG within a month after the screening examination, and 750 of those 1,712 participants accepted.

The available ECG parameters were PQ-interval and QRS-interval. The PQ-interval was defined as the beginning of the P-wave to the beginning of the QRS-segment, with a normal range of 120–219 milliseconds (ms). The QRS-interval was defined as the beginning of the Q-wave to the ending of the S-wave (J-point), with a normal range of up to 119 ms.¹⁸⁾ Participants with a ventricular pace rhythm were excluded from the PQ- and QRS-interval analyses, and participants with an atrial pace rhythm were excluded from the PQ-interval analysis.

Statistical analysis

Continuous variables are presented as the means \pm standard deviations, and categorical data are given as numbers (percentage). Non-normally distributed continuous variables are presented as medians and 25th–75th percentiles. Normality was assessed visually using quantile-quantile plots. Comparisons between groups were performed using non-paired Student's t-testing and Wilcoxon signed-rank testing.

To investigate the associations between CIED implantation and the presence of MAC (≥ 1 AU) or MAC score categories, multivariate logistic regression analyses were performed. Each CIED group was individually compared to participants without a CIED as the dependent variable (binary variables: one analysis for each CIED group), and the presence of MAC, the MAC score category, and traditional cardiovascular risk factors were the independent variables. To investigate the association between a prolonged PQ-interval or prolonged QRS-interval and the presence of MAC or MAC score category, multivariate logistic regression analyses were performed. A prolonged PQ-interval or prolonged QRS-interval was the dependent variable, and presence of MAC, MAC score category, and traditional cardiovascular risk factors were the independent variables. All those analyses were repeated as sensitivity analyses after excluding patients treated with beta-blockers or calcium antagonists as potential confounding factors for AV conduction disturbances (**Supplementary Tables 1 and 2**). The association between the MAC score (as a continuous variable) and traditional cardiovascular risk factors was analyzed using a zero-inflated negative binomial regression due to the non-normal distribution of the MAC scores, with overdispersion and an excess of zeros. In that analysis, the MAC score was the dependent variable, and the traditional cardiovascular risk factors were the independent variables. The effect estimate is reported as the ratio of expected count (REC) rather than the incidence rate due to the cross-sectional design.

The inter- and intra-observer variability in MAC score measurements were assessed using Pearson's correlation coefficients and Bland-Altman limits of agreement.

A p-value of < 0.05 was considered statistically significant for all analyses, and STATA version 16.1 (Statacorp LP, College Station, TX, USA) was used for all statistical analyses.

RESULTS

Overall, 14,987 participants were enrolled in the DANCAVAS trial (**Figure 2**). Participants without a MAC measurement ($n = 115$), with prior heart valve surgery ($n = 100$), or with the implantation of an unspecified CIED type ($n = 1$) were excluded, leaving 14,771 participants eligible for our study. Of those subjects, MAC was present in 3,302 (22.4%) participants. Overall, 14,414 participants had no CIED, and 357 participants had a CIED. Among participants who did not have a CIED prior to the screening date who received a CIED afterward ($n = 100$), the median time to CIED implantation was 1.25 years (25th–75th percentile: 0.65–2.05). Among participants with a CIED in our study, 134 subjects had a PM implanted due to an AV conduction disturbance; 106 participants had a PM implanted due to an indication other than an AV conduction disturbance; 31 participants had a CRT-D; and 86 participants had an ICD.

Participant characteristics are shown in **Table 1**. Participants with a CIED were significantly older (except for participants with a CRT-D), had a higher body mass index (BMI) (some CIED groups), had a higher proportion of hypertension and diabetes, were more often taking a lipid lowering medication, and had a lower eGFR than participants without a CIED. Participants with a PM or CRT-D had a significantly higher presence of MAC and higher MAC score category than participants without a CIED. The distribution of CIED types is shown in **Table 2**.

CIEDs and MAC scores

In the multivariate logistic regression analysis, participants with a PM implanted due to an AV conduction disturbance had a significantly higher MAC score category (odds ratio

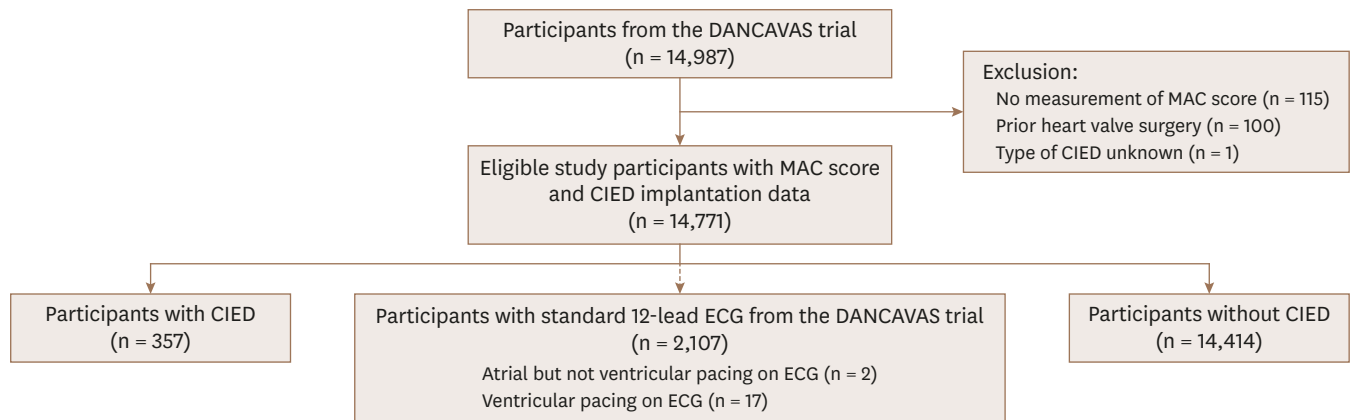


Figure 2. Inclusion and exclusion flowchart.

CIED: cardiac implantable electronic device, DANCAVAS: Danish Cardiovascular Screening, ECG: electrocardiographic, MAC: mitral annulus calcification.

Table 1. Participant characteristics

Variable	Total	No CIED	PM due to AV conduction disturbance	PM not due to AV conduction disturbance	CRT-D	ICD
Number	14,771	14,414	134	106	31	86
Age (years)	67.3 ± 3.8	67.3 ± 3.8	69.4 ± 3.1*	69.2 ± 3.7*	67.8 ± 4.2	68.5 ± 3.5*
Sex (male)	14,032 (95.0)	13,688 (95.0)	130 (97.0)	99 (93.4)	31 (100.0)	84 (97.7)
BMI (kg/m ²)	28.0 ± 4.4	28.0 ± 4.4	28.9 ± 4.6*	28.4 ± 5.2	31.8 ± 5.5*	28.6 ± 4.5
Hypertension	9,143 (61.9)	8,851 (61.4)	104 (77.6)*	77 (72.6)*	30 (96.8)*	81 (94.2)*
SBP (mmHg)	149.4 ± 18.7	149.5 ± 18.7	147.5 ± 20.9	148.1 ± 18.3	138.6 ± 19.4*	139.8 ± 18.4*
DBP (mmHg)	82.5 ± 9.8	82.6 ± 9.8	80.0 ± 9.8*	80.4 ± 10.3*	78.6 ± 11.9*	77.7 ± 9.4*
Hypertensive medication						
Thiazide	1,780 (12.1)	1,733 (12.0)	20 (14.9)	15 (14.2)	3 (9.7)	9 (10.5)
Beta-blocker	2,203 (14.9)	2,022 (14.0)	46 (34.3)*	39 (36.8)*	26 (83.9)*	70 (81.4)*
ACE inhibitor/ARB	4,862 (32.9)	4,660 (32.3)	70 (52.2)*	46 (43.4)*	28 (90.3)*	58 (67.4)*
Calcium antagonist	2,800 (19.0)	2,705 (18.8)	40 (29.9)*	28 (26.4)*	5 (16.1)	22 (25.6)
Diabetes mellitus	1,822 (12.3)	1,746 (12.1)	26 (19.4)*	22 (20.8)*	9 (29.0)*	19 (22.1)*
HbA1c (mmol/mol)	39.2 ± 7.7	39.1 ± 7.6	40.3 ± 8.2	40.4 ± 7.2	47.3 ± 14.9*	43.2 ± 10.6*
Hypercholesterolemia	12,271 (83.1)	11,964 (83.0)	117 (87.31)	87 (82.1)	29 (93.55)	74 (86.05)
Total cholesterol (mmol/L)	5.0 ± 1.1	5.0 ± 1.1	4.6 ± 1.0*	4.7 ± 1.3*	4.2 ± 1.1*	4.2 ± 1.0*
HDL (mmol/L)	1.4 ± 0.4	1.4 ± 0.4	1.3 ± 0.4*	1.4 ± 0.4	1.1 ± 0.4*	1.3 ± 0.4*
LDL (mmol/L)	2.9 ± 1.0	2.9 ± 1.0	2.5 ± 0.9*	2.7 ± 1.1*	2.3 ± 0.9*	2.2 ± 0.8*
Lipid lowering medication	4,846 (32.8)	4,638 (32.2)	71 (53.0)*	50 (47.2)*	24 (77.4)*	63 (73.3)*
eGFR (mL/min/1.73 m ²)	78.3 ± 13.6	78.4 ± 13.5	71.9 ± 15.8*	71.9 ± 15.8*	66.5 ± 18.0*	73.2 ± 15.7*
Smoking						
Active	2,359 (16.0)	2,316 (16.1)	18 (13.4)	13 (12.3)	3 (10.0)	9 (10.6)
Former	7,363 (50.1)	7,161 (49.9)	67 (50.0)	61 (57.5)	15 (50.0)	59 (69.4)
Never	4,990 (33.9)	4,880 (34.0)	49 (36.6)	32 (30.2)	12 (40.0)	17 (20.0)
MAC score						
Absent (0 AU)	11,469 (77.6)	11,214 (77.8)	97 (72.4)*	73 (68.9)*	20 (64.6)*	65 (75.6)
Present (≥ 1 AU)	3,302 (22.4)	3,200 (22.2)	37 (27.6)*	33 (31.1)*	11 (35.4)*	21 (24.4)
1–9 AU	1,199 (8.1)	1,172 (8.1)	8 (6.0)	11 (10.4)	3 (9.7)	5 (5.8)
10–99 AU	1,130 (7.7)	1,091 (7.6)	11 (8.2)	13 (12.3)	3 (9.7)	12 (13.9)
100–199 AU	310 (2.1)	302 (2.1)	5 (3.7)	1 (0.9)	1 (3.2)	1 (1.2)
200–299 AU	167 (1.1)	163 (1.1)	0 (0.0)	3 (2.8)	1 (3.2)	0 (0.0)
300–599 AU	213 (1.4)	209 (1.5)	1 (0.7)	1 (0.9)	1 (3.2)	1 (1.2)
600–1,199 AU	143 (1.0)	136 (0.9)	4 (3.0)	0 (0.0)	1 (3.2)	2 (2.3)
≥ 1,200 AU	140 (1.0)	127 (0.9)	8 (6.0)	4 (3.8)	1 (3.2)	0 (0.0)

Data are expressed as mean ± standard deviation and number (%).

ACE: angiotensin converting enzyme, AU: Agatston unit, ARB: angiotensin II receptor blocker, AV: atrioventricular, BMI: body mass index, CIED: cardiac implantable electronic device, CRT-D: cardiac resynchronization therapy defibrillator, DBP: diastolic blood pressure, eGFR: estimated glomerular filtration rate, HbA1c: hemoglobin A1c, HDL: high density lipoprotein, ICD: implantable cardioverter defibrillator, LDL: low density lipoprotein, MAC: mitral annulus calcification, PM: pacemaker, SBP: systolic blood pressure.

*p-value < 0.05 when comparing the CIED group with participants with no CIED using non-paired Student's t-testing and Wilcoxon signed-rank testing.

Table 2. Distribution of CIEDs

Type of CIED	PM due to AV conduction disturbance	PM not due to AV conduction disturbance	CRT-D	ICD
AAI-PM	0 (0.0)	8 (7.5)		
DDD-PM	94 (70.2)	89 (84.0)		
VVI-PM	26 (19.4)	7 (6.6)		
CRT-P	14 (10.4)	2 (1.9)		
CRT-D			31 (100.0)	
DDD-ICD				11 (12.8)
VVI-ICD				75 (87.2)
Total	134	106	31	86

Data are expressed as number (%).

AAI: single chamber atrial, AV: atrioventricular, CIED: cardiac implantable electronic device, CRT-D: cardiac resynchronization therapy defibrillator, CRT-P: cardiac resynchronization therapy pacemaker, DDD: dual chamber, ICD: implantable cardioverter defibrillator, PM: pacemaker, VVI: single chamber ventricular.

[OR], 1.11; 95% confidence interval [CI], 1.01–1.23, $p = 0.04$), were older (OR, 1.16; 95% CI, 1.10–1.23; $p < 0.001$), had a higher proportion of hypertension (OR, 1.58; 95% CI, 1.03–2.41; $p = 0.04$), and decreased kidney function (OR, 1.77; 95% CI, 1.14–2.75; $p = 0.01$) compared with participants without a CIED, but no association was found with sex, BMI, diabetes, hypercholesterolemia, or smoking (**Figure 3**). The multivariate logistic regression analyses between the other CIED groups, individually, and participants without a CIED, showed no significant association with the MAC score categories (**Table 3**). However, participants with a CRT-D had borderline-significantly ($p = 0.06$) higher MAC score categories than participants without a CIED. The sensitivity analyses excluding patients treated with beta-blockers and calcium antagonists produced similar findings (**Supplementary Tables 1 and 2**). Multivariate logistic regression analyses between individual CIED groups and participants without a CIED found no significant association with the presence of MAC.

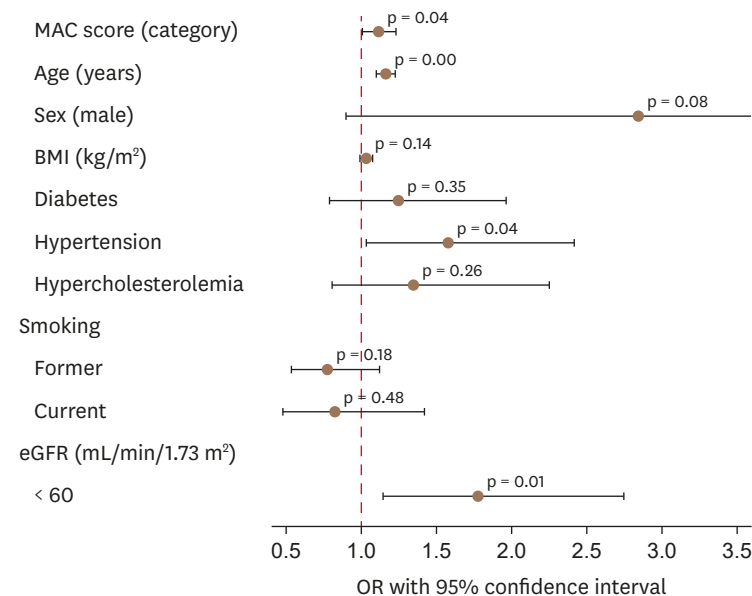


Figure 3. Multivariate logistic regression analysis showing associations between pacemaker implantation due to an atrioventricular conduction disturbance, MAC scores, and traditional cardiovascular risk factors. BMI: body mass index, eGFR: estimated glomerular filtration rate, MAC: mitral annulus calcification, OR: odds ratio.

Table 3. Multivariate logistic regression analyses between each CIED group and the MAC score categories

CIED group	Association with MAC score categories
PM due to AV conduction disturbance*	1.11 (1.01-1.23)
PM not due to AV conduction disturbance*	1.05 (0.93-1.19)
CRT-D*	1.18 (0.98-1.43)
ICD*	0.94 (0.79-1.11)

Data are expressed as odds ratios (95% confidence intervals) adjusted for age, sex, body-mass index, diabetes, hypertension, hypercholesterolemia, kidney function, and smoking.
 AV: atrioventricular, CIED: cardiac implantable electronic device, CRT-D: cardiac resynchronization therapy defibrillator, ICD: implantable cardioverter defibrillator, MAC: mitral annulus calcification, PM: pacemaker.
 *Each CIED group was compared with participants with no CIED.

Electrocardiography and MAC scores

The DANCAVAS trial data contained an ECG for 2,107 participants (Figure 2), and MAC was present in 579 (27.5%) of them. Participants with an atrial pace rhythm (n = 2) or ventricular pace rhythm (n = 17) were excluded from the PQ-interval analysis, resulting in 2,088 participants. Participants with a ventricular pace rhythm (n = 17) were excluded from the QRS-interval analysis, resulting in 2,090 participants.

When adjusting for traditional cardiovascular risk factors in a multivariate logistic regression, a prolonged QRS-interval was significantly associated with the presence of MAC (OR, 1.45; 95% CI, 1.04–2.04; p = 0.03), but a prolonged PQ-interval was not (OR, 1.06; 95% CI, 0.72–1.56; p = 0.77). In addition, neither a prolonged QRS-interval nor prolonged PQ-interval was significantly associated with the MAC score categories (OR, 1.08; 95% CI, 0.99–1.16; p = 0.05 and OR, 0.95; 95% CI, 0.87–1.04; p = 0.29, respectively). The sensitivity analyses excluding patients treated with beta-blockers and calcium antagonists produced similar findings (Supplementary Tables 1 and 2). Figure 1 shows a representative patient with severe MAC and cardiac conduction disturbance (prolonged QRS-interval).

MAC scores and cardiovascular risk factors

A zero-inflated negative binomial regression (Figure 4) was performed in all participants eligible for analysis (n = 14,771), and it showed that the MAC score increased significantly

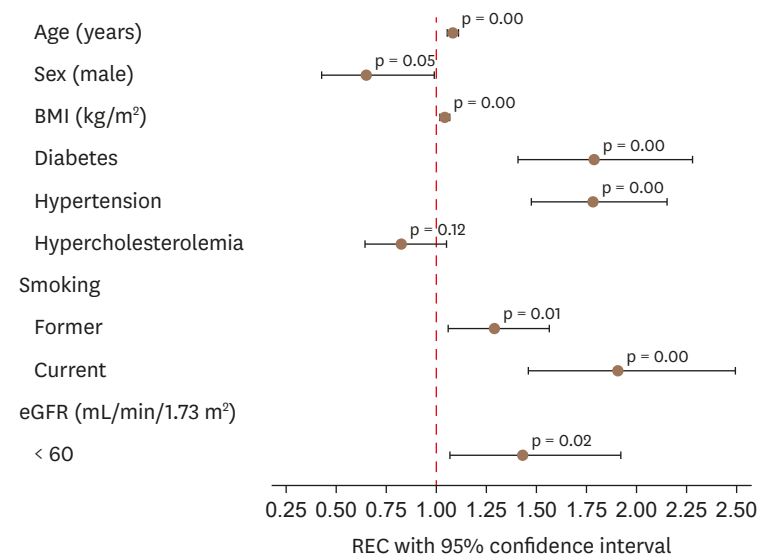


Figure 4. Zero-inflated negative binomial regression analysis including all study participants (n = 14,771) showing associations between mitral annulus calcification scores and traditional cardiovascular risk factors. BMI: body mass index, eGFR: estimated glomerular filtration rate, REC: ratio of expected count.

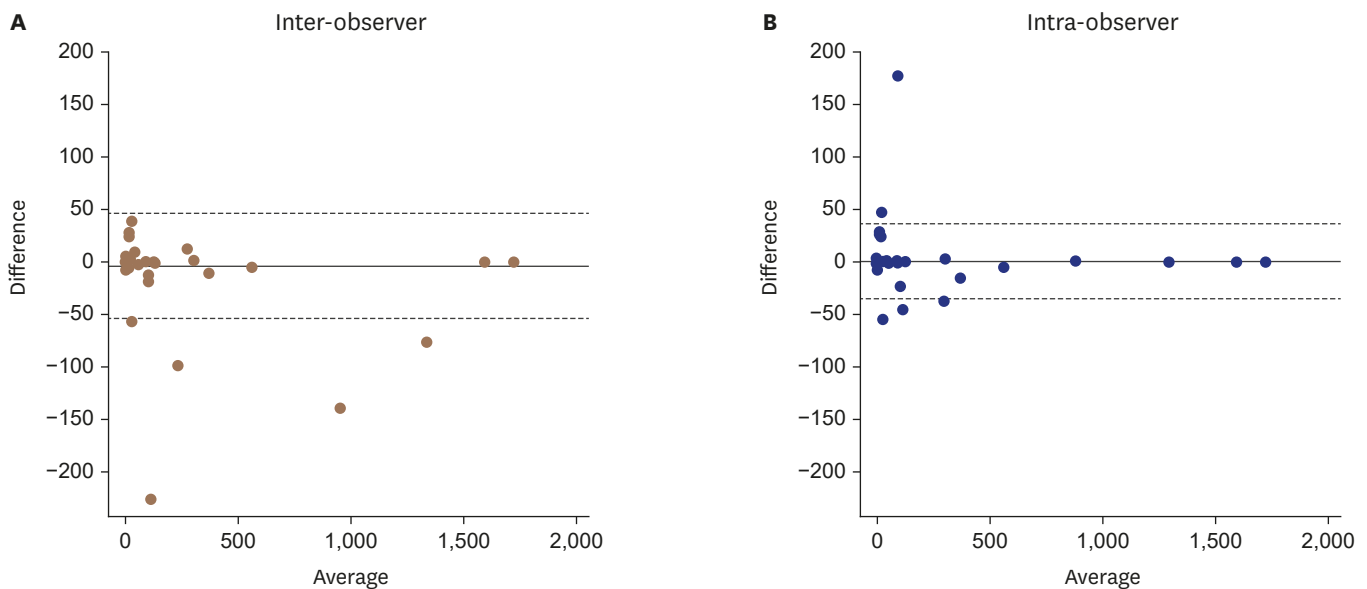


Figure 5. Bland-Altman plots comparing inter- and intra-observer agreement in the mitral annulus calcification score measurements from non-contrast computed tomography imaging ($n = 140$). Solid line: average difference (bias estimate). Dashed lines: 95% Bland-Altman limits of agreement.

with increasing age (REC, 1.08; 95% CI, 1.06–1.11), BMI (REC, 1.04; 95% CI, 1.02–1.06), diabetes (REC, 1.79; 95% CI, 1.41–2.28), hypertension (REC, 1.78; 95% CI, 1.48–2.16), current smoking (REC, 1.91; 95% CI, 1.46–2.50), former smoking (REC, 1.29; 95% CI, 1.07–1.57) and decreased kidney function (REC, 1.43; 95% CI, 1.07–1.92). Male sex (REC, 0.65; 95% CI, 0.43–0.99) was associated with a decrease in MAC scores, and thus female sex was associated with an increase in MAC scores. No association was found between hypercholesterolemia and MAC scores.

Variability of MAC score measurements

The Pearson's correlations for inter- and intra-observer variability in MAC score measurements were $r = 0.995$ and $r = 0.997$, respectively ($p < 0.001$ for both). The Bland-Altman plots showed a mean difference in inter-observer variability of -3.9 AU (limits of agreement: -54.1 to 46.4 AU) and intra-observer variability of 0.3 AU (limits of agreement: -35.4 to 36.0 AU) (Figure 5).

DISCUSSION

In this large, population-based, cross-sectional study, we explored the importance of MAC in relation to cardiac conduction disturbances. We found that participants with a PM implanted due to an AV conduction disturbance had higher MAC scores (by category) than participants without a CIED. In addition, we found that a prolonged QRS-interval was significantly associated with the presence of MAC, whereas a prolonged PQ-interval was not. Finally, we found that most traditional cardiovascular risk factors and female sex were significantly associated with higher MAC scores.

The association between MAC and a PM implanted due to an AV conduction disturbance is remarkable in our study, and the implantation of a CIED other than a PM or PM implantation for an indication other than an AV conduction disturbance were not associated with MAC. We

found a borderline-significant association between CRT-D implantation and MAC. A CRT-D is usually implanted in patients with severe heart failure and a risk of tachyarrhythmia and cardiac conduction disturbances. Hence, the borderline-significant association between MAC and CRT-D implantation supports our primary finding that MAC is associated with CIED implantation due to an AV conduction disturbance, though the small number of participants with CRT-D ($n = 31$) carries a risk of type-2 error. In short, MAC was found to be associated with symptomatic AV conduction disturbances requiring CIED implantation, but it was not associated with CIED implantation in general.

In the ECG analyses, which included more than 2000 individuals, we found no association between AV conduction disturbances, in terms of a prolonged PQ-interval or QRS-interval, and the MAC score categories, though we did find an association between a prolonged QRS-interval and the presence of MAC. Thus, the presence of MAC was associated with AV conduction disturbances in the ECG parameters, but the extent of MAC was not. Furthermore, the ECG analyses indicate that the AV conduction disturbances are primarily located along the bundle of His and its major branches (prolonged QRS-interval), not along the AV-node (prolonged PQ-interval).

In this study, we used highly sensitive cardiac NCCT imaging to identify MAC, whereas prior studies have used less-sensitive echocardiography. The association between MAC and PM has been reported in 3 previous studies,^{5,7} whereas the association with other types of CIED has remained unexplored. Participants with PM implantation due to symptomatic bradyarrhythmias (complete AV block, sinoatrial disease, or atrial fibrillation with bradycardia) had a significantly higher presence of MAC in a case-control study, regardless of implantation indication,⁶ and MAC was associated with incident PM implantation in a prospective cohort study.⁵ However, those findings were not confirmed in a third study.⁷ Several studies have scrutinized the association between MAC and ECG parameters. Cross-sectional studies have shown that severe MAC (≥ 5 mm) was associated with AV conduction disturbances and atrial fibrillation³ and that MAC was associated with a 3° AV block, left bundle branch block, and sinoatrial disease,⁴ but not all studies have confirmed those findings.⁷ Interestingly, one study that subdivided MAC by location found that AV conduction disturbances were associated with moderate to severe MAC (≥ 3 mm) but only when it was localized medial-posterior in the mitral annulus, which is very close to the AV-node and bundle of His.¹⁹

Our results are in line with those prior studies: MAC seems to be associated with AV conduction disturbances. Importantly, the time delay from the development of MAC to the subsequent development of AV conduction disturbances is not detected in a cross-sectional design, which might have affected our results. The association between MAC and symptomatic AV conduction disturbances that required PM implantation is notable in our study. Our findings could improve our understanding of the development of symptomatic AV conduction disturbances and strengthen the hypothesis that MAC plays a role in the pathogenesis of AV conduction disturbances. Extension of calcification from the mitral annulus to the adjacent AV-node and bundle of His could be possible, but whether MAC is just associated with AV conduction disturbances or provokes calcification or fibrosis of the cardiac conduction system is unclear. In addition, MAC was not associated with the implantation of other CIED types in our study, indicating that MAC is not associated with cardiac conduction disturbances in general. Finally, traditional cardiovascular risk factors were not strongly associated with symptomatic AV conduction disturbances requiring CIED implantation in our study, which further clarifies the need for novel predictors of

symptomatic AV conduction disturbances requiring CIED implantation. Moreover, the lack of association between traditional cardiovascular risk factors and AV conduction disturbances indicates that MAC might be an independent predictor and not just an interaction or product of the traditional cardiovascular risk factors. Whether MAC is a predictor of AV conduction disturbances remains uncertain because long-term prospective studies are needed, but MAC scoring could have potential clinical implications. For instance, preprocedural MAC scoring has been reported to be independently associated with the risk of AV conduction disturbances and permanent PM implantation after transcatheter aortic valve implantation.^{20,21} Moreover, it is possible that MAC scoring could be used as an adjudication factor for permanent PM implantation in individuals at significant risk for AV conduction disturbances.

In this large population-based study in which MAC was identified by highly sensitive cardiac NCCT imaging, most traditional cardiovascular risk factors and female sex were found to be associated with MAC. Previous studies identified MAC using less-sensitive echocardiography, with the exception of the Multi-Ethnic Study of Atherosclerosis (MESA),¹¹ which reported results similar to ours except for hypertension. Previous studies have reported similar results regarding age,^{4,7,10,13,22} female sex,^{7,10,22} diabetes,^{4,10,13,22} and hypertension.^{4,7,10,13,22} Obesity has been associated with MAC,^{7,10,11} but not all studies confirm that.¹³ Several studies report that smoking is not associated with MAC,^{7,10,13} but our study and the MESA study disagree. Renal dysfunction was associated with MAC in a previous cross-sectional study.¹³ The association between hypercholesterolemia and MAC has been poorly examined, though studies reported that individuals with MAC had higher LDL and total cholesterol levels^{10,13,22} and tended to be on lipid lowering medication more often than individuals without MAC.¹¹ In conclusion, minor discrepancies have been reported, but MAC seems to be associated with most traditional cardiovascular risk factors, with the exception of sex.

The strengths of our study include the use of cardiac NCCT imaging to identify MAC. Cardiac NCCT imaging is currently the best modality for identifying MAC,² and our intra- and inter-observer agreements for the MAC score measurements indicate reliability (**Figure 5**). Lower agreements were found primarily in participants with low MAC scores as expected, because it is difficult to distinguish small calcifications from CT imaging artefacts. Another strength is our large population, which was selected randomly without any exclusion criteria and thus allows our findings to be extrapolated to a general population, though generalizing should always be done with caution. Finally, detailed information about CIED implantation was acquired from a national registry, which provides high-accuracy data.

Some important limitations should be taken into account when reading our study. First, we used a cross-sectional design and therefore cannot draw any conclusions about causal relationships within the observed associations. Second, there is a risk of residual confounding in our analyses, though we included many factors. Third and highly notably, the study population consisted of Danish people, predominantly middle-aged and elderly men, which should be considered when examining external validity. Females constituted only about 5% of the study population, though that is still a considerable number (739) of participants. Given the higher prevalence of MAC in women, this is a very important limitation of our study. It will be important for future studies to include a more sex-balanced population. Fourth, we did not have ECG data for all participants, and participants with significant heart calcification were invited to receive a supplementary 12-lead ECG after the screening examination, which introduces a selection bias. Fifth, only 357 of the 14,771 (2.42%) participants had a CIED, which lowers the power of our study and could produce type-2 errors in some of our findings about MAC scores

and CIED implantation (especially CRT-D). Consequently, those results should be interpreted with caution. Participants who received their first CIED implantation after the screening date were reported here as having a CIED so that we could obtain a sufficient number of participants with a CIED and thereby enhance the power of our study. Although those implantations were prospective data, the median time to implantation was rather low, and thus we assume that our demotion of prospective data into a cross-sectional design affected our results only slightly. Lastly, the MAC scores were measured as a total score and not subdivided by location, although that would be highly relevant because the location of MAC and not just the extent could be important regarding the development of AV conduction disturbances.¹⁹⁾²⁰⁾ Therefore, we emphasize that future studies should include and focus on the MAC location.

In conclusion, individuals with a PM due to an AV conduction disturbance had higher MAC scores than individuals without a CIED, whereas individuals with a CIED other than a PM or a PM due to an indication other than an AV conduction disturbance did not have higher MAC scores than individuals without a CIED. Moreover, AV conduction disturbances shown by a prolonged QRS-interval, but not by a prolonged PQ-interval, were associated with the presence of MAC. The association between MAC and AV conduction disturbances could improve our understanding of the development of AV conduction disturbances and might have clinical implications. However, long-term prospective studies are needed to examine whether MAC is a predictor of symptomatic AV conduction disturbances that require CIED implantation.

SUPPLEMENTARY MATERIALS

Supplementary Data 1

Protocol for non-contrast cardiac computed tomography (CT)

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Supplementary Table 1

Multivariate logistic regression analyses between each CIED group and mitral annulus calcification score category

[Click here to view](#)

Supplementary Table 2

Multivariate logistic regression analyses of ECG parameters (prolonged PQ-interval or prolonged QRS-interval) and MAC score (as category or present)

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