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CLINICAL RESEARCH
Atrial fibrillation

Subclinical atherosclerosis is associated with incident atrial fibrillation: a systematic review and meta-analysis

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Aims Coronary artery disease is an established risk factor for incident atrial fibrillation (AF), but it is unclear whether subclinical atherosclerosis also increases the risk of incident AF. Therefore, the aim was to assess the association between subclinical atherosclerosis, defined by increased carotid intima-media thickness (cIMT) or coronary artery calcium score (CACS), and incident AF.

Methods and results A systematic review of MEDLINE, EMBASE, and Cochrane was done to find all cohort studies investigating the association between subclinical atherosclerosis, defined by increased cIMT or CACS, and incident AF. Eligible articles had to be available in an English full-text version; include adults over the age of 18 years; include ≥100 participants; and have a follow-up period ≥12 months. Data on cIMT were pooled using a fixed-effects model, while data on CACS (I^2 >25) were pooled using a random-effects model. Five studies on cIMT including 36 333 patients and two studies on CACS including 34 603 patients were identified. All studies investigating the association between increased cIMT and incident AF showed a significant association, with an overall hazard ratio (HR) of 1.43 [95% confidence interval (CI) 1.27–1.59]. The two studies investigating the association between increased CACS and AF also showed a significant association with an overall HR of 1.07 (95% CI 1.02–1.12).

Conclusion Data from seven observational studies suggest that subclinical atherosclerosis defined by increased cIMT or CACS is associated with an increased risk of incident AF. These findings emphasize the need for further research investigating whether treatment of subclinical atherosclerosis should be a part of the initiatives to prevent AF.

Keywords Atrial fibrillation • Subclinical atherosclerosis • Carotid intima-media thickness • Coronary artery calcium score • Meta-analysis

Introduction

Atrial fibrillation (AF) is the most frequent clinical arrhythmia. The prevalence and incidence increase with advancing age, affecting ∼4% of the population older than 60 years and more than 10% of the population older than 80 years. In western countries, the demographic dependency ratio is growing, and AF has become a major public health problem. Atrial fibrillation is associated with reduced quality of life, excess risk of stroke, dementia, heart failure, and death.[1]

Atrial fibrillation is commonly considered a progressive disease and perpetuated by ongoing electrical and structural remodelling of the atria.[2] In recent years, an increasing number of risk factors and

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What's new?

- This is the first systematic review and meta-analysis looking at the association between subclinical atherosclerosis and incident atrial fibrillation (AF).
- Our findings provide evidence that subclinical atherosclerosis identified through measuring carotid intima-media thickness by carotid ultrasound or coronary artery calcium score by non-contrast computed tomography of the heart is significantly associated with incident AF.

conditions have been identified that are associated with the development and progression of AF, including advancing age, coronary heart disease, hypertension, diabetes, heart failure, and obesity.[3] Many of them have also been found to contribute to atherosclerosis.[4] While previous myocardial infarction is a well-established risk factor for incident AF,[3] it is less well-established, whether subclinical atherosclerosis promotes structural atrial changes and, thus, creates a substrate for AF already during its long asymptomatic phase of progression. Interestingly, Weijs *et al.* found a high proportion of subclinical coronary artery disease (CAD) among patients undergoing catheter ablation for AF, which were originally diagnosed with lone AF.[5]

Subclinical atherosclerosis can be assessed using different measures.[4] Carotid intima-media thickness (cIMT), which is measured by carotid ultrasound and coronary artery calcium score (CACS), which is measured using non-contrast computed tomography of the coronary arteries, are non-invasive and widely accepted tools to detect subclinical atherosclerosis.[4,6,7]

We performed a systematic review and meta-analysis to evaluate, whether subclinical atherosclerosis, defined by increased cIMT and CACS, is associated with incident AF.

Methods

Study selection and data extraction

This systematic review was conducted according to PRISMA standards.[8] The review protocol is registered at PROSPERO—the international prospective register of systematic reviews (www.crd.york.ac.uk/PROSPERO; CRD42018114818). In October 2018, a systematic literature search was conducted with guidance from a medical librarian in the medical literature databases MEDLINE (OVID interface, 1990 onwards), EMBASE (OVID interface, 1990 onwards), and Cochrane Library (Wiley, 1999 onwards) using subject headings (MeSH and Emtree) and text words related to atherosclerosis, cIMT, CACS, and AF. We updated the literature search towards the end of the review in January 2019. The full literature search strategy is presented in Supplementary material online, *Tables S1* and *S2*.

Prospective and retrospective comparative cohort studies, investigating subclinical atherosclerosis as a predictor of AF, were eligible for inclusion. Furthermore, the articles had (i) to be available in an English full-text version; (ii) only to include adults over the age of 18 years; (iii) to include ≥100 participants; and (iv) to have a follow-up period ≥12 month. Authors were contacted if there were uncertainties concerning the articles.

Two reviewers (C.C.K. and L.H.N.) independently sorted the articles by screening titles and abstracts according to the predefined criteria. Hereafter, three reviewers (K.E.K., C.C.K., and L.H.N.) scrutinized the full text of the chosen articles for final selection of the primary literature. A chain search was conducted, in which eligible studies not found in previous searches were identified. Dispute was settled by mutual agreement between the three reviewers.

When multiple articles based on the same cohort and same data appeared in the search strategy, the study best fit was included.

Three reviewers independently extracted data from the seven articles regarding study design, population characteristics, baseline measurements (cIMT and CACS), and outcome measurements (AF). When additional study material was available, it was used to supplement the data extraction.

Validity and study quality assessment

The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses was used to evaluate the risk of bias for each study. It covers selection of study groups, comparability of groups, and ascertainment of exposure and outcomes (www.ohri.ca/programs/clinical_epidemiology/oxford). The Cochrane Collaboration recommends the NOS for observational studies (https://handbook-5-1.cochrane.org). Three reviewers (K.E.K., C.C.K., and L.H.N.) independently assessed the risk of bias for each study. Dispute was solved by mutual agreement.

Statistical analysis

Heterogeneity between studies was tested and visualized in forest plots. To quantify the heterogeneity, I^2 was calculated and the percentage evaluated according to the following percent ranges: might not be important (0–40%), may represent moderate heterogeneity (30–60%), may represent substantial heterogeneity (50–90%), and may represent considerable heterogeneity (75–100%). A statistical *P*-value <0.10 and/or I^2 >50% were considered representing significant heterogeneity.

Two meta-analyses were conducted on the most comprehensively adjusted hazard ratios (HRs) stated in each of the studies. Due to low heterogeneity, a fixed-effects model was used in the meta-analysis of the association between cIMT and AF. A random-effects model allowing for between-study variation was used in the meta-analysis of the association between CACS and AF, because of relatively high heterogeneity of the two included studies (I^2 = 76.8%), e.g., due to the marked difference in follow-up time and inclusion criteria (*Table 1*).[9,10] Hazard ratios were calculated using Cox proportional hazards model. All data analyses were performed using statistical software. STATA (version 15.0; StataCorp LLC, College Station, TX, USA), Covidence (Melbourne, Australia), and EndNote (version X9; Clarivate Analytics, Philadelphia, PA, USA) were used.

Results

Search outcome

The initial search conducted in October 2018 resulted in 466 articles. The full search and selection process is displayed in a PRISMA flow diagram (*Figure 1*). Of the 466 articles 97 were duplicates, which left 369 articles for screening at the title and abstract level. We excluded 348 articles because they did not meet the inclusion criteria. Three additional articles were identified through chain search, resulting in 24 articles for full-text screening. Data from the Rotterdam study were presented as a single cohort and in a pooled analysis, where we chose to include the single cohort study by Heeringa *et al.*[11,12] Two studies based on the Multi-Ethnic Study of Atherosclerosis (MESA) cohort were included, since one used cIMT and the other used CACS as measurement for subclinical atherosclerosis.[12,13] Authors of nine articles were contacted for further information. None of these correspondences led to further data material. The updated

Table 1 Study characteristics and baseline measurements of the studies investigating the association between carotid intima-media thickness or coronary artery calcium score and incident atrial fibrillation

	Chen *et al.*[12] (ARIC)	Chen *et al.*[12] (MESA)	Adamsson Eryd *et al.*[14]	Heeringa *et al.*[11]	Losi *et al.*[15]	O'Neal *et al.*[13]	Vinter *et al.*[16]
Trial size	13 595	6605	4846	4225	7062	6641	27 962
Follow-up (median in years)	17.8	8.5	15.3	7.5	3.0	8.5	2.9
Exclusion criteria	AF at baseline Race other than black or white	AF at baseline Physician diagnosed heart attack, angina or taking NTG, stroke or TIA Having undergone CABG, angioplasty, valve replacement, PM, or ICD implantation, any surgery on heart or arteries	History of hospitalization due to AF, HF, or MI	AF at baseline History of MI (typical, silent or non-Q-wave) Insufficient data to exclude previous MI Angina pectoris (Rose questionnaire) Not completed Rose questionnaire History of CABG or PTCA	History of AF History of CVD (MI, coronary revascularization, stroke, TIA, valvular heart disease) EF < 50% Chronic kidney disease Stage IV or V	AF at baseline CVD	History of AF History of valvular disease (mitral stenosis, mechanical prosthetic heart valve), AMI, PCI, heart surgeries (CABG), CAD Missing CACS
Recruitment	Residents of 4 communities in 4 American states, 45–64 years of age	Residents of 6 communities in 6 American states, 45–84 years of age	All men born 1923–1945 and women born 1923–1950 living in Malmö, Sweden, were invited	All residents of Ommoord district living in Rotterdam, the Netherlands, ≥55 years were invited	Hypertensive patients from 5 districts of the Campania Region, Italy	Residents of 6 communities in 6 American states 45–84 years of age	Patients, who underwent nCCT suspect CAD, identified through the WDHR, Denmark
Age (mean ± SD, years)	57.0 ± 5.7	62.0 ± 10.2	57.5 ± 6.0	M: 67.1 ± 7.8 W: 68.5 ±8.8	52 ± 12	62 ± 10	56.9 ± 11.1
Gender (%)	M: 44.5 W: 55.5	M: 47.2 W: 52.8	M: 40 W: 60	M: 37.9 W: 62.1	M: 57 W: 43	M: 47.1 W: 52.9	M: 44.6 W: 55.4
Baseline information obtained by	CIMT was measured bilateral by US on the posterior wall on CCA as the mean thickness in three segments: 1 cm proximal of the bulbus, the	CIMT was measured by US on the anterior and posterior wall on CCA and the ICA on right and left side and calculated as the mean of the maximum CIMT	CIMT was measured by US on the posterior wall of the right distal CCA as the mean thickness over a 1 cm segment proximal to the bifurcation	CIMT was measured by US on the anterior and posterior wall of the right and left CCA as the mean thickness over a 1 cm segment proximal to the bulbus	The maximum CIMT was measured by US in the right and the left, anterior and posterior wall of CCA over a 1 cm segment proximal ICA and bifurcation	CACS was measured by nCCT and determined by the Agatston score method. The total CACS was summed for LMCA, LAD, LCX, and RCA	CACS was measured by nCCT and determined by the Agatston score method. The total CACS was summed for LMCA, LAD, LCX, and RCA

Continued

Table 1 *Continued*

	Chen *et al.*[12] (ARIC)	Chen *et al.*[12] (MESA)	Adamsson Eryd *et al.*[14]	Heeringa *et al.*[11]	Losi *et al.*[15]	O'Neal *et al.*[13]	Vinter *et al.*[16]
	bifurcation, and the proximal ICA						
Carotid plaque definition	Two of the following: - cIMT >1.5 mm - Abnormal shape - Abnormal wall texture	Mean of maximum cIMT ≥25%	Focal thickening of IMT >1.2 mm	Focal broadening of intima-media relative to adjacent segments with protrusion into lumen	IMT >1.5 mm	NA	NA
Baseline measurement	Mean ± SD (mm): 0.75 ± 0.20	Mean ± SD (mm): 0.87 ± 0.19	Median (IQR) (mm): M: 0.77 (0.68–0.87) W: 0.73 (0.66–0.82)	Mean ± SD (mm): M: 0.84 ± 0.15 W: 0.80 ± 1.14	Mean ± SD (mm): No AF group: 1.6 ± 0.7 AF group: 1.9 ± 0.8	CACS 0: 50.4% CACS 1–100: 26.3% CACS 101–300: 10.7% CACS > 300: 12.2%	CACS 0: 52.2% CACS 1–99: 25.7% CACS 100–399: 12.6% CACS: 400–999: 5.9% CACS > 1000: 3.7%
Outcome AF information obtained by	-ECG at follow-up -Hospital diagnoses -Death certificates No differentiation between AF and atrial flutter	-ECG at follow-up -Hospital diagnoses -Death certificates -MICD -Interviews No differentiation between AF and atrial flutter	-Hospital diagnoses No differentiation between AF and atrial flutter	-ECG at follow-up -Medical files from GP -Hospital diagnoses No differentiation between AF and atrial flutter	-ECG at follow-up -Hospital diagnoses Differentiation between AF and atrial flutter is not specified	-ECG at follow-up -Hospital diagnoses -Death certificates -MICD -Interviews No differentiation between AF and atrial flutter	-Discharge diagnoses from administrative registries No differentiation between AF and atrial flutter

AF, atrial fibrillation; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CACS, coronary artery calcium score; CAD, coronary artery disease; CCA, Common carotid artery; cIMT, carotid intima-media thickness; CVD, cardiovascular disease; ECG, electrocardiogram; EF, ejection fraction; GP, general practitioner; HF, heart failure; ICA, internal carotid artery; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LMCA, left main coronary artery; M, men; MI, myocardial infarction; MICD, Medicare inpatient claims data; NA, not applicable; nCCT, non-contrast computed tomography; NTG, nitroglycerine; PCI, percutaneous coronary intervention; PM, pacemaker; PTCA, percutaneous transluminal coronary angioplasty; OP, operative procedures; RCA, right coronary artery; SD, standard deviation; TIA, transient ischaemic attack; US, ultrasound; W, women; WDHR, Western Denmark Heart Registry.

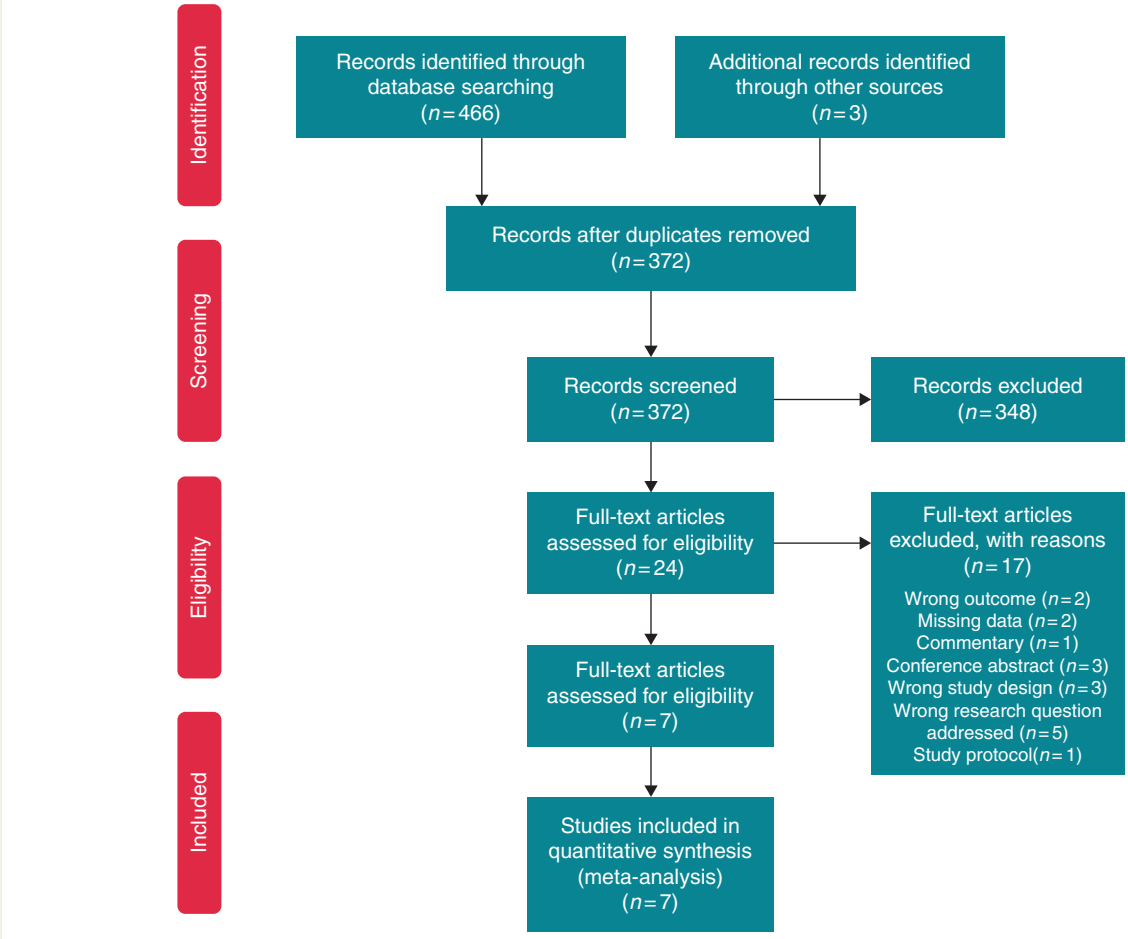

Figure 1 PRISMA flow diagram of the meta-analysis.

literature search conducted in January 2019 resulted in additional 21 articles, where none were eligible for inclusion.

After full-text assessment, seven cohort studies were included in the final analyses, of which five measured cIMT and two measured CACS.[11–16]

Study designs and patient characteristics

An overview of the study designs, individual characteristics, and baseline measurements is shown in *Table 1*. Overall, the included studies had relatively similar study designs and patient characteristics, but some differences should be noted.

Five of the seven studies were population-based prospective cohort studies.[11–14] Vinter *et al.* reported a retrospective registry-based cohort study in a population, which was notably different from the other studies. The population in this study consisted of individuals, which were suspected, but proven free of CAD.[16] The study based on the Campania-Salute Network by Losi *et al.* differed as well, as this was a retrospective cohort study in a hypertensive population.[15]

There were also differences in, how prevalent AF and clinically manifest atherosclerosis were determined in the studies to exclude these cases (*Table 1*). In the Atherosclerosis Risk in Communities (ARIC), MESA, and Rotterdam Studies, AF on the baseline electrocardiogram (ECG) was defined as prevalent AF.[11–13] In the three other studies, the definition of prevalent AF was based on registry-recorded diagnoses of AF before enrolment.[14–16] Clinically manifest atherosclerosis was determined from patient questionnaires and subsequent review of medical records in the ARIC, MESA, and Rotterdam Studies,[11–13] while the three other studies used registry-recorded diagnoses.[14–16] Interestingly, the ARIC study cohort included few patients with a history of myocardial infraction and heart failure.[12]

Moreover, the seven studies also differed in the data sources for their outcome incident AF. Five of them used a combination of ECG documentation and hospital diagnoses of AF,[11–13,15] of which four utilized additional data sources, e.g., death certificates and medical files from general practitioners.[11–13] The two other studies by Adamsson Eryd *et al.* and Vinter *et al.* only relied on hospital diagnoses from administrative registries.[14,16] Most studies did also not distinguish between AF and atrial flutter (*Table 1*).[11–14,16]

All studies included both men and women, while six of them also adjusted or stratified for sex in their analyses (*Tables 2* and *3*). The mean age was between 52.0 and 68.5 years, with a mean of all study participants of 58.3 years. The length of follow-up in the included studies was between a median of 2.9 years and 17.8 years (*Table 1*).

Table 2 Results from the five studies investigating the association between cIMT and incident atrial fibrillation

	Chen et al.[12] (ARIC)	Chen et al.[12] (MESA)	Adamsson Eryd et al.[14]	Heeringa et al.[11]	Losi et al.[15]
Incidence (incident AF/1000 person years):	7.3	6.0	4.8	Not specified	6.6
Hazard ratio (95% CI)	HR: 1.29 (1.08–1.54) 5th vs. 1st quintile M: HR: 1.25 (0.96–1.63) W: HR: 1.30 (1.01–1.66)	HR: 1.94 (1.15–3.28) 5th vs. 1st quintile	HR: 1.52 (1.08–2.16) 4th vs. 1st quartile M: HR: 2.00 (1.24–3.23) W: HR: 1.08 (0.65–1.81)	HR: 1.90 (1.20–3.00) 4th vs. 1st quartile M: HR: 1.61 (0.77–3.36) W: HR: 2.14 (1.19–3.86)	HR: 1.51 (1.27–1.79) >1.5 mm cIMT vs. ≤1.5 mm cIMT
Stratified or adjusted for:	-Age -Sex -Race -Weight -Height -Systolic BP -Diastolic BP -Antihypertensive medication -Smoking -Diabetes -HF -MI	-Age -Race -Weight -Height -Systolic BP -Diastolic BP -Antihypertensive medication -Smoking -Diabetes -HF -MI	-Age -Sex -Waist circumference -Systolic BP -Antihypertensive medication -Smoking -Diabetes -LDL -HDL -Education -Physical activity -CRP	-Age -Sex -BMI -Hypertension -Systolic BP -Smoking -Diabetes -Cholesterol -LV hypertrophy -Use of cardiac medication	-Age -Sex -Systolic BP -LV mass index -Duration of hypertension -Use of cardiac medication

AF, atrial fibrillation; BP, blood pressure; CI, confidence interval; cIMT, carotid intima-media thickness; CRP, C-reactive protein; HDL, high-density lipoprotein; HF, heart failure; HR, hazard ratio; LDL, low-density lipoprotein; LV, left ventricular; M, men; MI, myocardial infarction; W, women.

Carotid intima-media thickness and incident atrial fibrillation

The results of the studies investigating the association between cIMT and incident AF are shown in *Table 2*. The HRs and 95% confidence intervals (CI) are the most comprehensively adjusted. In four of the five studies, the cIMT groups were stratified in quartiles or quintiles, and the HRs for incident AF during the follow-up period were calculated comparing participants in the highest with the lowest quartile or quintile.[11,12,14]

All five studies showed a significant association between increased cIMT and incident AF. Hazard ratios (95% CI) were 1.29 (1.08–1.54), 1.94 (1.15–3.28), 1.52 (1.08–2.16), 1.90 (1.20–3.00), and 1.51 (1.27–1.79), respectively, with an overall HR of 1.43 (95% CI 1.27–1.59) (*Table 2* and *Figure 2*).

The HRs stratified for sex did not show consistent results. Chen *et al.* (ARIC study) and Heeringa *et al.* found a statistically significant association between cIMT and risk of AF in women, but not in men.[11,12] On the contrary, Adamsson Eryd *et al.*[14] only found a statistically significant HR in men.

It is important to note that the five studies used different measurement methods of cIMT and different definitions of carotid plaque. In the Rotterdam Study, Heeringa *et al.* only used qualitative criteria to define the presence of carotid plaques,[11] while Adamsson Eryd *et al.* and the ARIC Study used quantitative and qualitative criteria to define the presence of carotid plaques.[12,14] The two other studies only used (semi-)quantitative criteria, i.e., a cut-off value for IMT (*Table 1*).[12,15]

Coronary artery calcium score and incident atrial fibrillation

Table 3 displays the results of the two studies investigating the association between CACS and incident AF. The HRs and 95% CI shown are the most comprehensively adjusted. The results were stratified by CACS groups and the HRs were calculated for each group using CACS = 0 as reference.[13,16]

The two studies showed a significant association between increased CACS and incident AF in all groups except for the group CACS 1–99 in the study by Vinter *et al.*[16] Both studies showed an increase in HR with increasing CACS, except for a CACS >1000 in the study by Vinter *et al.*

The two studies analysed CACS as a continuous variable to examine the risk of AF when the CACS doubled. These analyses also showed a significant increase in the risk for incident AF with increased CACS with a Log2 (CACS + 1) HR of 1.1 (95% CI 1.05–1.13) and 1.05 (95% CI 1.03–1.08), respectively. The results remained unchanged in both studies when stratified or adjusted for sex. The overall HR was 1.07 (95% CI 1.02–1.12) (*Table 3* and *Figure 3*). The test for heterogeneity showed an I^2 of 76.8% ($P = 0.038$), which represent a substantial and considerable heterogeneity.

Table 3 Results from the two studies investigating the association between CACS and incident atrial fibrillation

	O'Neal *et al.*[13]	Vinter *et al.*[16]
Hazard ratio (95% CI):	HR: CACS 1–100: 1.4 (1.01–2.0) CACS 101–300: 1.6 (1.1–2.4) CACS > 300: 2.1 (1.4–2.9) (Reference CACS 0) CACS as a continuous variable: Log2(CACS+1) HR: 1.1 (1.05–1.13)	HR: CACS 1–99: (0.8–1.25) CACS 100–399: 1.36 (1.06–1.74) CACS 400–999: 1.76 (1.33–2.35) CACS > 1000: 1.67 (1.2–2.34) (Reference CACS 0) CACS as a continuous variable: Log2(CACS+1) HR: 1.05 (1.03–1.08)
Stratified or adjusted for	-Age -Sex -BMI -Race -Systolic BP -Smoking -Diabetes -Income -Lipid-lowering medications -Total cholesterol -HDL-cholesterol -Aspirin -Antihypertensive -CRP -LV hypertrophy -Education	-Age -Sex -BMI -Systolic BP -Diastolic BP -Smoking -Diabetes -HF -Lipid-lowering medication Reception -Antihypertensive medication reception -Prior stroke/TIA/systemic Embolism -CABG

BMI, body mass index; BP, blood pressure; CACS, coronary artery calcium score; CABG, coronary artery bypass grafting; CI, confidence interval; CRP, C-reactive protein; HDL, high-density lipoprotein; HF, heart failure; HR, hazard ratio; LV, left ventricular; M, men; TIA, transient ischaemic attack; W, women.

Both studies used the Agatston score method for the measurement of CACS.[17]

Validity and study quality assessment

The quality assessment of the seven studies according to the NOS is summarized in *Table 4*. All studies had sufficient exposure ascertainment. The studies by Adamsson Eryd *et al.*,[14] Losi *et al.*,[15] and Vinter *et al.*[16] did not explicitly evaluate, whether AF was present at baseline. However, Adamsson Eryd *et al.*[14] did not use AF, but hospitalization for AF as an outcome, and demonstrated in this way that their specific outcome of interest was not present at the beginning of the study.

Discussion

The findings in this systematic review and aggregate level meta-analysis provide evidence that subclinical atherosclerosis identified through measuring cIMT by carotid ultrasound or CACS by non-contrast computed tomography is significantly associated with the incidence of AF.

To our knowledge, this is the first systematic review on this topic. At present, there are only few studies available. In particular, there are very few studies describing the association between CACS and incident AF. The findings from this study are consistent with findings from previous cross-sectional studies and a previous meta-analysis, which all measured cIMT at baseline.[12,18,19] The meta-analysis by Chen *et al.* processed data from the ARIC, MESA, and Rotterdam studies and found an overall HR of 1.37 (95% CI 1.17–1.61), which is comparable to the overall HR in the present study.[12]

In contrast to our analysis, the population-based cohort Cardiovascular Health Study (CHS), found no significant association between cIMT and incident AF.[20] This study was not included in this systematic review and meta-analysis, because no data on cIMT measurements were reported. The differences between the findings from CHS compared to the other population-based cohort studies

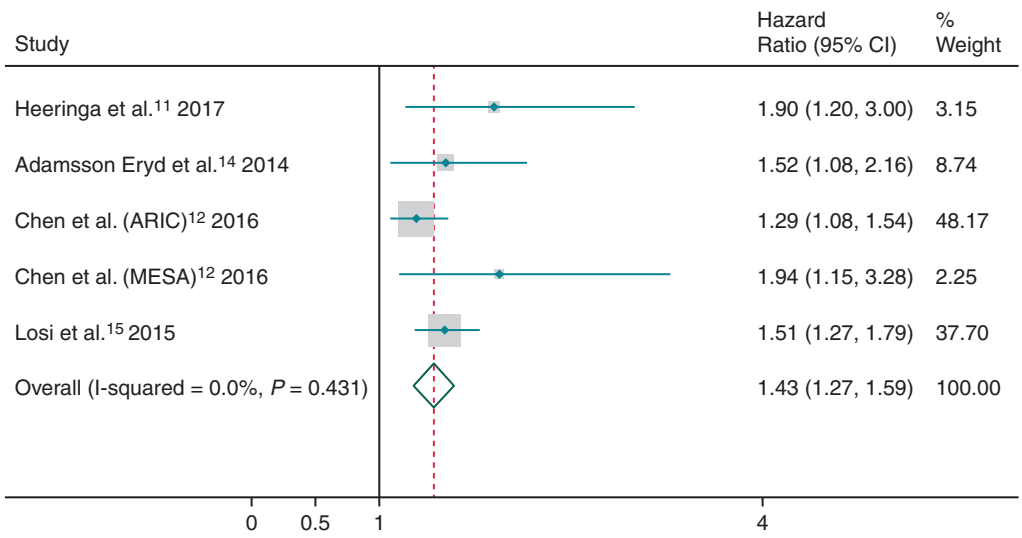

Figure 2 Association between subclinical atherosclerosis, defined by increased carotid intima-media thickness, and incident atrial fibrillation. Weights are from fixed-effects analysis. CI, confidence interval.

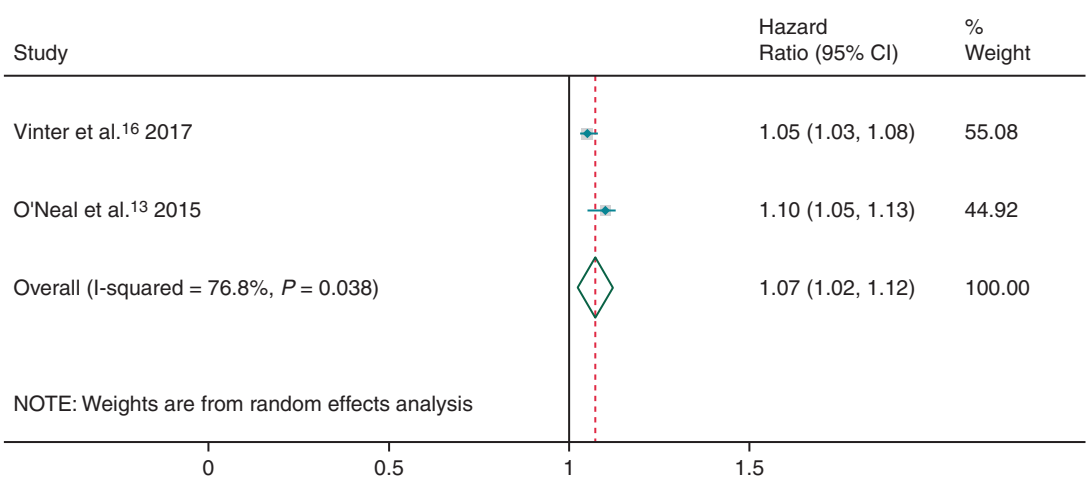

Figure 3 Association between subclinical atherosclerosis, defined by increased coronary artery calcium score, and incident atrial fibrillation. Weights are from random-effects analysis. CI, confidence interval.

included in this systematic review might be explained by the fact that the population in the CHS cohort was older and that self-reported cases of AF were included.

There are other parameters for identification of subclinical atherosclerosis beyond cIMT and CACS, e.g., the ankle-brachial index and maximum carotid plaque height. A low ankle-brachial index (<1.0) was an independent risk factor for AF.[21,22] Several cohort studies also found a significant association between maximum carotid plaque height and incident AF.[12] These findings also confirm the association of subclinical atherosclerosis with the development of incident AF.

The present analysis included two studies measuring CACS. The study by Vinter *et al.*[16] showed a weaker association between increased CACS and incident AF than the study by O'Neal *et al.*[13] The variation of these results might be explained by the differences between the two studies. Vinter *et al.* investigated a larger and younger population with a higher proportion of women, while O'Neal *et al.* had a longer follow-up period. In addition, the population in the study by Vinter *et al.* consisted of individuals, which were suspected of CAD and, thus, do not represent the general population. Although this is conflicting with our aim to investigate subclinical atherosclerosis, this study was nonetheless included, because all individuals were proven free of significant CAD. The above-mentioned differences between the two studies could possibly result in an unequal confounder distribution.

Table 4 The Newcastle-Ottawa Scale for quality assessment of cohort studies evaluating the association between subclinical atherosclerosis and incident atrial fibrillation

	Chen *et al.* (ARIC)[12]	Chen *et al.* (MESA)[12]	Adamsson Eryd *et al.*[14]	Heeringa *et al.*[11]	Losi *et al.*[15]	O'Neal *et al.*[13]	Vinter *et al.*[16]
Selection:							
(1) Representativeness of the exposed cohort	C	B*	B*	B*	B*	B*	A*
(2) Selection of the non-exposed cohort	A*	A*	A*	A*	A*	A*	A*
(3) Ascertainment of exposure	A*	A*	A*	A*	A*	A*	A*
(4) Demonstration that outcome of interest was not present at start of study	A*	A*	A*	A*	B	A*	B
Comparability							
(1) Comparability of cohorts on the basis of the design or analysis	A*	A*	A*	A* B*	A*	A*	A* B*
Outcome							
(1) Assessment of outcome	B*	B*	B*	A*	B*	B*	B*
(2) Was follow-up long enough for outcomes to occur	A*	A*	A*	A*	A*	A*	A*
(3) Adequacy of follow-up for cohorts	B*	B*	A*	B*	A*	A*	A*
Total score							
Selection:	S: 3	S: 4	S: 4	S: 4	S: 3	S: 4	S: 3
Comparability:	C: 1	C: 1	C: 1	C: 2	C: 1	C: 1	C: 2
Outcome:	O: 3	O: 3	O: 3	O: 3	O: 3	O: 3	O: 3

Selection:
(1) A*: truly representative of the average adult population in the community; B*: somewhat representative of the adult population in the community; C: selected group; D: no description of the derivation of the cohort.
(2) A*: Selection of the non-intervention cohort drawn from the same community as the intervention cohort; B: drawn from a different source; C: no description of the derivation of the non-intervention cohort.
(3) A*: secure record; B*: structured interview; C: written self-report; D: no description.
(4) A*: yes; B: no.
Comparability: (*A maximum of two stars can be given for Comparability*).
(1) A*: study controls for age, cardiovascular disease; B*: study controls for weight, smoking, sex, diabetes, heart surgery, blood pressure.
Outcome:
(1) A*: independent blind assessment; B*: record linkage; C: self-report; D: no description.
(2) A*: yes (≥2 years); B: no (<2 years).
(3) A*: complete follow-up; all subjects were accounted for; B*: Subjects lost to follow-up were unlikely to introduce bias because small numbers were lost; ≥80% had follow-up, or description was provided of those lost; C: follow-up rate <80%, and there was no description of those lost; D: no statement.

The overall HR for cIMT was based on the results from five studies.[11,12,14,15] Results from the MESA cohort study showed the strongest association between increased cIMT and incident AF, and the results from the ARIC cohort study showed the weakest association.[12] In both studies, the HR was calculated comparing the 1st and the 5th quintile, but there were some differences. The population of the ARIC study was younger, twice as large, and the follow-up period twice as long compared to the MESA study. This could possibly explain the different results.

The lowest incidence rate was found in the population investigated by Adamsson Eryd *et al.*[14] However, this was expected, since they only looked at the first hospitalization for AF as a measure of incident AF.

The population investigated by Losi *et al.* consisted of hypertensive patients.[15] Hypertension is a well-known risk factor for AF and atherosclerosis, why one would expect to find higher baseline measurements of cIMT and a higher incidence rate of AF in a hypertensive population.[19] The baseline measurements of cIMT were notably higher in the hypertensive population, compared to the other studies, but this could also be due to different measurement methods. The incidence rate in the study by Losi *et al.* was surprisingly not different from incidence rates in the ARIC study and the MESA study.[12,15] This might be explained by the fact that the hypertensive population was younger than the other populations. Moreover, the calculation of the HR was different between the studies. While Losi *et al.* calculated the HR comparing two groups categorized by cIMT values higher or lower than 1.5 mm, the other studies compared the highest with the lowest quartile or quintile of cIMT values, which expectedly would lead to a higher HR.[11,12,14,15] However, their HR was comparable to

the results of the other studies, which might be explained by the above-mentioned differences in measurement methods, population characteristics, and study design.

Strengths and limitations

The principal strength of this study is that the systematic literature search was conducted by three independent reviewers, who systematically searched three comprehensive medical literature databases. Other strengths are the consistency of the results across independent cohort studies and across the two measurement methods cIMT and CACS. Furthermore, all included studies have a relatively high quality assessed by the NOS.

However, this study also has some limitations. First, only few studies have been published on the topic, which is why the meta-analyses consist of results from only five studies on cIMT and two studies on CACS. The small number of studies resulted in two studies being weight more than 85% of the overall HR for cIMT. Second, a notable limitation is that all the included studies possibly miss cases of paroxysmal AF, because of the time-dependent nature of this condition. Third, there were some differences between the studies regarding ascertainment of baseline and outcome measurements, and the calculation of HRs, which resulted in decreased comparability. Fourth, the five studies investigating the association between cIMT and incident AF used different measurement methods and definitions of the presence of a carotid plaque, which may have had impact on their results. Fifth, as this is a systematic review and meta-analysis based on cohort studies bias may be present. Because of the low number of included studies, it is difficult to estimate the risk of publication bias, which could be relatively high, because the contradictory result found in the CHS study, was not included, due to lack of accessible data.

Implications

Current guidelines on AF management do not recommend specific treatment of subclinical atherosclerosis detected by cIMT or CACS measurement to reduce the risk of AF,[1] because this has yet to be demonstrated. Nevertheless, our findings could put additional focus on risk factor management in general. Further research is specifically needed to test the measurement of cIMT as screening tool in cardiovascular risk assessment. There is also an urgent need for standardization regarding the definition and measurement of cIMT as well as high quality data on its reliability, before it might be used as routine screening tool. More research is also needed to investigate the benefit of screening for AF in patients with subclinical atherosclerosis and vice versa.

Conclusion

In conclusion, increased values of both cIMT and CACS are associated with higher incidence of AF. This supports the growing evidence that subclinical atherosclerosis maybe a risk factor of AF and enhances the importance of clarifying whether treatment of subclinical atherosclerosis should be part of the initiatives to prevent AF.

Supplementary material

Supplementary material is available at *Europace* online.

Conflict of interest: none declared.

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