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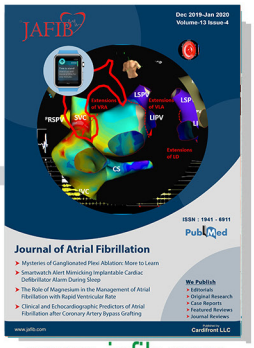


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# Concealed Coronary Atherosclerosis in Idiopathic Paroxysmal Atrial Fibrillation is Associated with Imminent Cardiovascular Diseases

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## Abstract

**Background: Previous research showed a significant difference in the presence of subclinical coronary artery disease (CAD) on cardiac CT angiography (CTA) between patients with idiopathic paroxysmal atrial fibrillation (iAF) versus a matched sinus rhythm population (iSR). Here we present 5-year follow-up data and the consequences of subclinical CAD on baseline CTA on the development of cardiovascular disease in iAF.**

**Methods: In 99 iAF patients (who underwent CTA as part of work-up for pulmonary vein isolation) and 221 matched iSR controls (who underwent CTA for CAD assessment), the incidence of hypertension, diabetes and major cardiovascular events (MACCE) during follow-up was obtained. Multivariable Cox regression analysis was used to reveal predictors of incident cardiovascular disease in the iAF group.**

**Results: During a follow-up of 68±11 months, over one third of patients developed cardiovascular disease, with no difference between iAF and iSR (log-rank p=0.56), and comparable low rates of MACCE (4.0% vs 5.0%,p=0.71). Within the iAF group, age (HR1.12(1.03–1.20);p=0.006), left atrial diameter (HR1.16(1.03–1.31);p=0.01), Segment Involvement Score (total number of coronary segments with atherosclerotic plaque; HR1.43(1.09–1.89);p=0.01) and the number of calcified plaques on CTA (HR0.53(0.30–0.92);p=0.01) were independent predictors of incident cardiovascular disease.**

**Conclusion: Subclinical coronary disease on CTA may be useful to identify the subset of patients with iAF that harbour concealed cardiovascular risk factors and need intensive clinical follow-up to ensure timely initiation of appropriate therapy once CV disease develops, including anticoagulation and vascular prophylactic therapy.**

## Introduction

Idiopathic atrial fibrillation (iAF) is defined as the presence of this arrhythmia in which none of the predisposing factors are present, such as hypertension, diabetes mellitus, heart failure, structural abnormalities on echocardiography, pulmonary disease, thyroid disease, and renal disease. A number of underlying pathophysiologic mechanisms have been proposed for iAF, including increased atrial stretch, autonomic imbalance, systemic inflammation, oxidative stress, and structural and electrophysiological alterations. These mechanisms may reflect a shared underlying pathophysiology between iAF, atherosclerosis and other forms of cardiovascular disease (CVD)[1], and it may thus be hypothesized that iAF is the first overt expression of the underlying pathophysiological processes that lead to various forms of CVD[2,3]

In a previous study, Weijs et al.[4] showed that patients originally diagnosed with paroxysmal iAF more often show subclinical atherosclerosis on cardiac computed tomographic angiography (CTA) than a matched sinus rhythm (iSR) control group. Here we present 5-year follow-up data on both the iAF group and the iSR group to assess the development of CVD in this previously presumed healthy population. Furthermore, we studied the role of CTA in distinguishing between patients that will or will not develop CVD after the initial diagnosis of i AF.

## Key Words

Atrial Fibrillation, Coronary Artery Disease, Computed Tomography Angiography, Hypertension

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## Material and methods

### Study population

The patients in this cohort were described previously[4]. In short, 390 consecutive patients (mean age 55±10 years, 67.7% male), who underwent CTA at the Maastricht University Medical Centre between January 2008 and March 2011 were included: 115 patients with paroxysmal iAF as part of work-up for pulmonary vein isolation (PVI) or for exclusion of coronary artery disease (CAD) before initiation of anti-arrhythmic drugs, and 275 healthy patients in sinus rhythm (SR) who were referred by their treating physician for CTA to assess the presence of CAD. iAF and iSR were defined as the absence of any form of CVD, including hypertension (defined as antihypertensive drug use, systolic blood pressure ≥140mmHg, or diastolic blood pressure ≥90mmHg on CTA visit, or left ventricular hypertrophy (LVH)), diabetes, or hypercholesterolemia. All patients had no history of CAD, renal dysfunction, stroke, malignancy, obstructive sleep apnea, thyroid or pulmonary disease, and no evidence of structural CVD on echocardiogram, including valvular heart disease. Angina or abnormal stress test were never an indication for CTA. iAF and iSR patients were matched on sex, age at time of CTA (±1 year), and PROCAM risk score[5]. All patients underwent transthoracic echocardiography. This study was approved by the Institutional Review Board and complies with the ethical principles of the Declaration of Helsinki. All patients gave written informed consent.

### CTA data acquisition and analysis

At baseline, a prospective unenhanced coronary scan was performed in all patients as described previously[4]. The Agatston score was calculated using a 3-mm CT slice thickness and detection threshold ≥130 Hounsfield units involving ≥1mm2 area/lesion (3 pixels). Coronary arteries were evaluated according to the 16-segment classification scheme. Coronary plaques were defined as structures >1 mm2 within and/or adjacent to the coronary artery lumen, which could be clearly distinguished from the vessel lumen and the surrounding pericardial tissue. Plaques were categorized as soft, mixed or calcified plaques, based on visual judgment of plaque composition. The Segment Involvement Score (SIS), the sum of segments in which a plaque was found, was calculated as a measure of the extent of CAD[6].

## Follow-up

Development of hypertension, diabetes and major cardiovascular and cerebrovascular events (MACCE) during follow-up (between the date of CTA and July 2016) were obtained and cross-checked by two independent observers. Data were derived from the patient records as kept by the (referring) hospital and general practitioner. MACCE was defined as cardiovascular death, acute coronary syndrome, percutaneous coronary intervention, coronary bypass grafting, congestive heart failure, transient ischemic attack or stroke. Development of CVD was defined as the occurrence of MACCE, the development of hypertension (blood pressure repeatedly ≥140mmHg systolic and/or ≥90mmHg diastolic, prescription of anti-hypertensive drugs or development of LVH on echocardiography) and diabetes mellitus.

## Statistical analysis

Statistical analysis was performed using SPSS statistical software (SPSS statistics 23.0, IBM Corporation, Armonk, NY). Categorical variables are reported as number (percentage) of patients and compared using Chi-square testing. Continuous variables are presented as mean±SD or as median[interquartile range], depending on distribution, and were compared with an independent T-test and Mann–Whitney test respectively. All demographic, echocardiographic and CT parameters showing a significant univariable relation with the development of CVD during follow-up - using Cox regression - were included as covariates in a multivariable Cox regression model. Proportional hazards were checked. Manual backwards elimination was used to construct the final models (retention level set at 0.10), yielding hazard ratios and 95% confidence intervals. Results were checked for collinearity and interaction among covariates. P<0.05 was considered statistically significant.

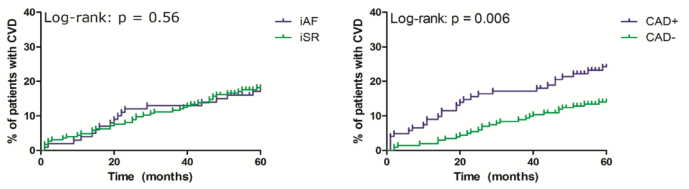


**Figure 1: Kaplan-Meier curves for the cumulative incidence of cardiovascular risk factors.**

There is no difference in the cumulative incidence in the idiopathic atrial fibrillation (iAF) versus the sinus rhythm control group (iSR; Log-rank p=0.56; Panel 1). However, there is a highly significant difference in development of risk factors in iAF patients with coronary artery disease on CT (CAD+) when compared to those without (CAD-; Log-rank p=0.006; Panel 2). All iAF patients developing cardiovascular risk factors receive one (hypertension, diabetes, vascular disease, heart failure) or two (TIA/stroke) extra points on the CHA2DS2-VASc-score, leading to an indication for the use of anti-coagulant therapy

## Results

### Incidence of cardiovascular disease during follow-up

Follow-up was complete in 99 iAF (13.9% lost to follow-up; median AF history 29 months) and 221 iSR patients (19.6% lost to follow-up). Patients in whom follow-up was not complete did not differ significantly from the study patients at baseline characteristics and number and type of plaques on CT. During a follow-up duration of 68±11 months, one third of patients developed CVD, with no

**Table 1: Incidence of MACCE and cardiovascular diseases during 5 years of follow-up for patients with idiopathic atrial fibrillation (iAF) compared to sinus rhythm controls (iSR).**

| | iAF (N=99) | iSR (N=221) | p |
|---|---|---|---|
| Death | 0 | 0 | - |
| ACS | 0 (0) | 3 (1.4) | 0.40 |
| PCI | 0 (0) | 4 (1.8) | 0.18 |
| CABG | 1 (1) | 0 (0) | 0.14 |
| CHF | 0 (0) | 1 (0.5) | 0.50 |
| TIA | 4 (4.0) | 5 (2.3) | 0.37 |
| Stroke | 0 (0) | 2 (0.9) | 0.34 |
| Any MACCE | 4 (4.0) | 11 (5.0) | 0.71 |
| Hypertension | 24 (24.2) | 67 (30.3) | 0.27 |
| DM2 | 4 (4.0) | 9 (4.1) | 0.99 |
| Any cardiovascular disease | 32 (32.3) | 82 (37.1) | 0.41 |

Shown is n (%). ACS=Acute Coronary Syndrome; CABG=Coronary Artery Bypass Grafting; CHF=Congestive Heart Failure; DM2=Type 2 Diabetes Mellitus; iAF = idiopathic AF; iSR=idiopathic Sinus Rhythm control group; MACCE=Major Adverse Cardiac and Cerebrovascular Events; PCI=Percutaneous Coronary Intervention; TIA=Transient Ischemic Attack

**Table 2: Baseline characteristics of idiopathic AF (iAF) patients who do and do not develop cardiovascular disease during follow-up.**

| | | No CVD (n=67) | CVD development (n=32) | p |
|---|---|---|---|---|
| Sex (female) | | 22(32.8) | 7(21.9) | 0.26 |
| Age (years) | | 52.9±10.4 | 59.2±8.7 | 0.004 |
| BMI | | 25.9±3.3 | 26.9±3.0 | 0.20 |
| BSA | | 2.01±0.26 | 2.03±0.16 | 0.70 |
| Family history of CAD | | 8(11.9) | 5(15.6) | 0.61 |
| Smoking | | 8(11.9) | 6(18.8) | 0.36 |
| $CHA_2DS_2$-VASc score | 0 | 37(55.2) | 20(62.5) | 0.02 |
| | 1 | 28(41.8) | 7(21.9) | |
| | 2 | 2(3.0) | 5(15.6) | |
| Systolic blood pressure (mmHg) | | 125±13 | 128±14 | 0.21 |
| Fasting glucose (mM) | | 5.4±0.6 | 5.5±0.6 | 0.23 |
| LDL (mM) | | 3.7±0.8 | 3.3±0.9 | 0.09 |
| HDL (mM) | | 1.3±0.4 | 1.2±0.3 | 0.25 |
| Total cholesterol (mM) | | 5.6±0.9 | 5.2±1.0 | 0.07 |
| Triglycerides (mM) | | 1.7±1.1 | 1.5±0.6 | 0.35 |
| eGFR (MDRD; ml/min/1.73m²) | | 81±13 | 82±17 | 0.73 |
| VKA | | 22(32.8) | 11(34.4) | 0.88 |
| Aspirin | | 33(49.3) | 19(63.3) | 0.19 |
| Beta blocker | | 22(32.8) | 15(50.0) | 0.11 |
| Non-dihydropyridine CCB | | 6(9.0) | 4(13.3) | 0.51 |
| ACE inhibitor | | 0(0.0) | 0(0.0) | - |
| ARB | | 0(0.0) | 0(0.0) | - |
| Dihydropyridine CCB | | 0(0.0) | 0(0.0) | - |
| Statin | | 4(6.0) | 6(18.8) | 0.048 |
| Echocardiography | | | | |
| Aorta diameter (mm) | | 34.2±3.1 | 34.3±3.2 | 0.89 |
| LA diameter (mm) | | 39.3±4.8 | 41.5±5.2 | 0.04 |
| LVEF (%) | | 61.4±5.8 | 60.1±5.2 | 0.28 |
| IVSd (mm) | | 8.4±0.8 | 8.7±0.9 | 0.16 |
| LVPWd (mm) | | 8.3±0.6 | 8.6±0.8 | 0.04 |
| CT angiography | | | | |
| Agatston score >0 | | 22(32.8) | 18(56.3) | 0.03 |
| Agatston score | | 0.0[22] | 11.1[140] | 0.017 |
| Any soft plaque | | 7(10.4) | 14(43.8) | < 0.001 |
| Number of soft plaques | | 0[0] | 0[1] | < 0.001 |
| Any mixed plaque | | 18(26.9) | 9(28.1) | 0.90 |
| Number of mixed plaques | | 0[1] | 0[1] | 0.66 |
| Any calcified plaque | | 16(23.9) | 14(43.8) | 0.04 |
| Number of calcified plaques | | 0[0.75] | 0[3] | 0.03 |
| Any plaque | | 28(41.8) | 22(68.8) | 0.01 |
| Segment Involvement Score | | 0[2] | 1[8] | < 0.01 |

Shown is n(%) or mean±SD. ACE=angiotensin-converting-enzyme; ARB=Angiotensin II receptor blocker; BMI=Body Mass Index; BSA=Body Surface Area; CAD=Coronary Artery Disease; CCB=Calcium Channel Blocker; CT=Computed Tomography; CVD=Cardiovascular Disease; eGFR=estimated Glomerular Filtration Rate; HDL=High Density Lipoprotein; IVSd=Interventricular Septum thickness at end diastole; LA=left atrium; LDL=Low Density Lipoprotein; LVEF=Left Ventricular Ejection Fraction; LVPWd=left ventricular posterior wall thickness at end diastole; VKA=Vitamin K Antagonist.

significant differences between the iAF and iSR group (32.3% vs 37.1%, p=0.41; Table 1). The occurrence of MACCE did not differ between groups (4.0% vs 5.0%, p=0.71). Patients developed hypertension most frequently (24.2% and 30.3% respectively). The Kaplan–Meier curve for the cumulative incidence of CVD is not different for both groups (Log-rank p=0.56; Fig 1, Panel 1).

## Characteristics of iAF patients who develop cardiovascular disease

As the development of risk factors has effects on the necessity to initiate anti-coagulation therapy, we studied factors associated with CVD development in the iAF patients. Patients who developed CVD during follow-up were on average older than patients who did not (59.2±8.7 vs 52.9±10.4, p=0.004), and more often used a statin at baseline (18.8% vs 6.0%; p=0.048; Table 2). The percentage of smokers and patients with a family history of CAD did not differ significantly between patients that developed CVD and those who did not. Echocardiography showed a larger left atrial diameter (41.5±5.2 vs 39.3±4.8 mm, p=0.04) and higher left ventricular posterior wall thicknessat end diastole (LVPWd; 8.6±0.8 vs 8.3±0.6 mm, p=0.04) in patients who developed CVD. At the end of follow-up, in patients who did not develop CVD, 14.9% used VKA and 4.5% NOAC, while in those who developed CVD, 46.9% used VKA and 16.2% used NOAC.

On the coronary calcium scan, patients who developed CVD more often had an Agatston score greater than zero (56.3% vs 32.8%, p=0.03) and a higher median coronary Agatston score (11.1[140] vs 0.0[22], p=0.02). CTA showed a higher median SIS (iAF 1[8] vs 0[2], p<0.01), with a higher number of soft plaques (43.8% vs 10.4%, p<0.001) and calcified plaques (43.8% vs 23.9%, p=0.04; Table 2). The presence of any form of CAD on CT was associated with a higher cumulative incidence of CVD (Log-rank p = 0.006; Fig 1, Panel 2).

## Prediction of CVD development in iAF

Univariable Cox regression analysis showed a relation with CVD development for the following parameters (Table 3): age (HR1.12(1.05–1.20),p=0.001), statin use (HR3.10(1.01–9.40),p=0.048), LA diameter (HR1.17(1.05–1.30),p=0.005), LVPWd (HR1.87(1.01–3.50),p=0.047), Agatston score>0 (HR3.13(1.22–8.02),p=0.017), Agatston score continuous (HR/10 units 1.02(1.004–1.04),p=0.01), presence of any soft plaque (HR4.56(1.79–11.60),p=0.001), number of soft plaques (HR2.91(1.55–5.47),p=0.001), any calcified plaque (HR2.50(1.02–6.19),p=0.05), number of calcified plaques (HR1.37(1.02–1.83),p=0.03), any plaque (HR2.89(1.09–7.71),p=0.03), and SIS (HR1.34(1.17–1.59),p=0.001). Multivariable Cox analysis regression in which only clinical and echocardiographic parameters were tested, revealed that from these parameters only age (HR1.12(1.04–1.21),p=0.004) and LA-diameter (HR1.12(1.01–1.24),p=0.03) were independently associated with CVD development. Addition of CT parameters to this model, showed that the SIS (HR1.43(1.09–1.89),p=0.01) and number of calcified plaques (HR0.53(0.30–0.92),p=0.01) were independently associated with incident CVD on top of age (HR1.12(1.03–1.20),p=0.006) and LA diameter (HR1.16(1.03–1.31),p=0.01).

## Discussion

This study shows that a significant proportion of clinically healthy iAF patients - over one third - develops cardiovascular disease within 5 years of follow-up, most frequently hypertension. Independent predictors of CVD development include age, LA diameter, and the

**Table 3: Univariable and multivariable Cox-regression analysis of factors associated with development of cardiovascular disease in idiopathic AF patients.**

| | Univariable | | Model 1 | | Model 2 | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | P | HR (95% CI) | P | HR (95% CI) | P |
| Age | 1.12 (1.05–1.20) | 0.001 | 1.12 (1.04–1.21) | 0.004 | 1.12 (1.03–1.20) | 0.006 |
| Statin | 3.1 (1.01–9.4) | 0.048 | | | | |
| Left atrial diameter (per mm) | 1.17 (1.05–1.30) | 0.005 | 1.12 (1.01–1.24) | 0.03 | 1.16 (1.03–1.31) | 0.01 |
| Left ventricular posterior wall thickness at end diastole (per mm) | 1.87 (1.01–3.5) | 0.047 | | | | |
| Coronary Agatston>0 | 3.13 (1.22–8.02) | 0.017 | | | | |
| Coronary Agatston (per 10) | 1.02 (1.004–1.04) | 0.01 | | | | |
| Soft plaque | 4.56 (1.79–11.60) | 0.001 | | | | |
| Number of soft plaques | 2.91 (1.55–5.47) | 0.001 | | | | |
| Calcified plaque | 2.50 (1.02–6.19) | 0.05 | | | | |
| Number of calcified plaques | 1.37 (1.02–1.83) | 0.03 | | | 0.53 (0.30–0.92) | 0.01 |
| Any plaque | 2.89 (1.09–7.71) | 0.03 | | | | |
| Segment Involvement Score | 1.34 (1.17–1.59) | 0.001 | | | 1.43 (1.09–1.89) | 0.01 |

Model 1 included clinical parameters only, Model 2 includes parameters derived from CT angiography.

extent of CAD on CTA expressed as a higher SIS, mainly when caused by non-calcified plaques. This study therefore suggests that CTA in combination with clinical measures may enhance identification of iAF patients - currently considered to have a low CV risk - who are prone to develop CVD. This allows timely initiation of individualized follow-up programs as well as the start of adequate cardiovascular preventive therapy. This includes repeated thromboembolic risk assessment over time as iAF patients, once they emerge with hypertension, are in need of anticoagulation on top of other prevention measures[7,8].

The natural course of risk factor development in AF patients may best be studied in those patients originally diagnosed with idiopathic AF. The definition of iAF used in this study was very strict, which, based on the Euro Heart Survey on Atrial Fibrillation, corresponds to a prevalence of 3% of all AF patients[9]. Notwithstanding this strict definition of iAF, a significant proportion of the patients developed CVD. In the first study on this subject, Katritsis et al.[10] found an incidence of hypertension of 44% within 3 years of follow-up, which is higher than the 24.2% in 5 years in our study, which may be attributed to the inclusion of patients with persistent iAF instead of paroxysmal iAF in the study by Katritsis et al. Potpara et al.[11] found a lower incidence of CVD in patients with iAF, which may be related to the younger age at inclusion. Also, Weijs et al.[12,13] previously showed an incidence of CVD of almost 50% in patients with first detected iAF during the same duration of follow-up of 5 years – which is higher than the 32.3% in 5 years found in this study. This might be explained by the observation that patients with first detected AF harbour a high short term risk of CVD development[14]. Patients in our study had gone through a median of 29 months of AF without developing CVD at inclusion, which may have selected those patients who went through the initial phase of AF - in which they may have had the highest propensity of developing CVD - without developing CVD.

The iAF and iSR patients included in this study were matched on future vascular risk, yet as reported before, the iAF patients had a significantly higher prevalence of subclinical CAD on CTA[4] and associated biomarker profiles[15,16]. Surprisingly, in this report we show that – in contrast to our hypothesis – this higher prevalence of subclinical CAD is not associated with a higher incidence of CVD in the iAF patients as compared to the iSR patients. Apparently, in iAF patients, there are processes that lead to the development of AF and to progression of plaque burden, but are not associated with the development of hypertension. Results from the Bruneck Study have shown that there are distinct processes leading to initiation and to progression of atherosclerosis[17]: risk factors for initiation of atherosclerosis lie in traditional risk factors, such as hypertension, hyperlipidemia, and cigarette smoking – factors that are comparable between the iAF and iSR group. In contrast, risk factors for progression of atherosclerosis lie in markers of a hypercoagulable state. A prothrombotic state is already present very early in AF patients as compared to controls without AF[18], or may even be the reason AF has developed[19]. From these observations, it may be hypothesized that atherosclerosis is initiated to the same extent in both iAF and iSR, yet early plaques in iAF patients progress more rapidly to forms that are detected by CTA due to the prothrombotic state, while this prothrombotic state does not yet increase the incidence of other forms of early CVD.

Interestingly, multivariable analysis within the group of iAF patients showed that a greater burden of CAD, and especially soft not fully calcified plaques, associates with imminent CVD. In general, soft plaques are an early form of atherosclerosis[20] which fits with the notion that iAF associates with early subclinical vascular disease and imminent overt CVD. Based on the present study design, one cannot tell whether early coronary abnormalities – subclinical - CVD leads to subclinical angiographic abnormalities or vice versa, or that they share a common pathophysiological mechanism. Furthermore, it is of interest to note that the presence of plaques on CT was shown to associate with incident CVD on top of LA size. LA enlargement has been shown previously to be an early marker of vascular disease[21], as it is a sign of atrial remodelling, reflecting a state of pressure and volume overload[22], endothelial dysfunction[23], inflammation, and oxidative stress[24]. Although coronary artery calcification is a well-established risk factor for MACCE[25,26], and decreased systemic vascular compliance enhances the development of hypertension, this is to our knowledge for the first time that the association between plaques on CT angiography and development of CVD in apparently healthy AF patients is shown.

## Clinical implications of this study

Patients scheduled for AF ablation frequently undergo a diagnostic CT-angiography. This study suggests to use this CTA not only for pulmonary vein anatomy to guide the ablation, but also for triggering more intense follow-up to detect CVD and timely instalment of appropriate prophylactic vascular therapy, including antithrombotic

treatment[27]. All iAF patients in this study who are under 65 years of age at inclusion, have by definition a $CHA_2DS_2$-VASc-score of 0 (males) or 1 (females) and are thus considered low-risk and to have no indication for anticoagulation[28], yet all patients developing the endpoint of CVD in this study receive one (hypertension, diabetes, ACS/PCI/CABG, CHF) or two (TIA/CVA) extra points on the $CHA_2DS_2$-VASc-score, leading to an indication for the use of anti-coagulant therapy, with a NOAC and in selected cases in combination with antithrombotics [29, 30]. Whether CTA could help fine tune risk scores – for example whether CAD or aortic calfication[31] on CT should be scored as a $CHA_2DS_2$-VASc-point for vascular disease – remains to be determined. CTA will help to broaden the focus of clinical electrophysiologists to also include an integrated vascular approach in addition to rhythm control, and timely initiation of anticoagulation – or continuation after PVI. Furthermore, patients without abnormalities on CTA may be discharged with and taken off anticoagulation after PVI with more confidence.

## Study limitations

Firstly, these results were obtained in a selected population as it only includes patients with iAF referred for PVI and iSR patients that were referred for screening purposes. Due to the strict definition of idiopathic AF, during the first 5 years of follow-up mainly early forms of vascular disease occurred, and very low rates of MACCE. Longer follow-up may reveal the use of CTA in predicting MACCE. Lastly, since follow-up was not predefined and thus 24-hour blood pressure monitoring was not used consistently, subclinical forms of hypertension may have been missed.

## Conclusion

One third of idiopathic AF patients develop cardiovascular disease within 5 years of follow-up. Independent predictors of cardiovascular disease development in iAF patients include age, LA-diameter, and the extent of CAD on CTA expressed as higher SIS, mainly when caused by non-calcified plaques. CTA may be used to identify those patients with idiopathic AF that harbour concealed cardiovascular risk factors and thus need close surveillance.

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