Prevalence of Coronary Artery Disease Assessed by
Multislice Computed Tomography Coronary Angiography in
Patients With Paroxysmal or Persistent Atrial Fibrillation

Gaetano Nucifora, MD; Joanne D. Schuijf, PhD; Laurens F. Tops, MD; Jacob M. van Werkhoven, MSc; Sami Kajander, MD; J. Wouter Jukema, MD; Joop H.M. Schreur, MD; Mark W. Heijenbrok, MD; Serge A. Trines, MD; Oliver Gaemperli, MD; Olli Turta, BM; Philipp A. Kaufmann, MD; Juhani Knuuti, MD; Martin J. Schalij, MD; Jeroen J. Bax, MD

Background—Although atrial fibrillation (AF) has been linked to underlying coronary artery disease (CAD), data supporting this association have been based on ECG and clinical history for the definition of CAD rather than direct visualization of atherosclerosis.

Methods and Results—The prevalence of CAD among patients with paroxysmal or persistent AF and without history of CAD was evaluated using multislice computed tomography. Multislice computed tomography was performed in 150 patients with AF (61 ± 11 years, 67% males, 58% asymptomatic) with predominantly low (59%) or intermediate (25%) pretest likelihood of CAD. CAD was classified as obstructive (≥50% luminal narrowing) or not. A population of 148 patients without history of AF, similar to the AF group as to age, gender, symptomatic status, and pretest likelihood, served as a control group. Logistic regression analysis was applied to evaluate the relationship between demographic and clinical data and the presence of obstructive CAD. On the basis of multislice computed tomography, 18% of patients with AF were classified as having no CAD, whereas 41% showed nonobstructive CAD and the remaining 41% had obstructive CAD. Among patients without AF, 32% were classified as having no CAD, whereas 41% showed nonobstructive CAD and 27% had obstructive CAD (P = 0.010 compared with patients with AF). At logistic regression analysis, age, male gender, and the presence of AF were significantly related to obstructive CAD.

Conclusion—A higher prevalence of obstructive CAD was observed among patients with AF, confirming the hypothesis that AF could be a marker of advanced coronary atherosclerosis. (Circ Cardiovasc Imaging. 2009;2:100-106.)

Key Words: atrial fibrillation ■ coronary disease ■ multislice computed tomography ■ prevalence ■ risk stratification

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with an estimated prevalence of 0.4% to 1% in the general population. In addition, the mortality rate of patients with AF is almost double than that of patients in normal sinus rhythm. This observation has been attributed to an increased cardiac death rate due to underlying heart disease2-5 rather than to thromboembolism.6

Clinical Perspective see p 106

Coronary artery disease (CAD) is considered to be highly prevalent among patients with AF and may be one of its underlying causes.7 Furthermore, it has been suggested that AF may be the sole manifestation of CAD.8 However, most data supporting this association have been derived from studies using the presence of ECG abnormalities and a history of ischemic heart disease to define CAD9,10 rather than direct visualization of atherosclerosis. Thus far, only 2 cardiac imaging studies are available. In these investigations, stress myocardial perfusion single-photon emission computed tomography (SPECT) was applied to evaluate the prevalence of CAD in patients with AF.11,12 Abidov et al11 showed a significantly higher prevalence of abnormal myocardial perfusion SPECT studies in patients with AF as compared with patients without AF. However, in this study patients with symptoms and known CAD were included while investigation of a strictly asymptomatic population, as performed by Askew et al,12 failed to confirm this observation.
Recently, multislice computed tomography (MSCT) has been introduced as an alternative cardiac imaging modality. This technique allows noninvasive direct visualization of the coronary arteries, including detection of coronary atherosclerosis by assessing the coronary artery calcium burden (calcium scoring) and by performing noninvasive angiography. Accordingly, this technique allows evaluation of CAD at an early stage. The aim of the present study was to evaluate the prevalence of CAD, by means of MSCT, among patients with paroxysmal or persistent AF and compare findings to patients without a history of AF.

Methods

Study Population

The study population consisted of 150 patients from the outpatient clinic with a history of paroxysmal (n = 99, 66%) or persistent (n = 51, 34%) AF referred to MSCT for coronary evaluation, due to an elevated risk profile and/or chest pain. Patients with history of CAD and contraindications to MSCT were excluded, as well as patients who were not in sinus rhythm during MSCT examination. Paroxysmal and persistent AF were diagnosed according to the American Heart Association/American College of Cardiology/European Society of Cardiology criteria. Briefly, paroxysmal AF was defined as self-terminating episodes of AF lasting ≤7 days whereas persistent AF was defined as episodes lasting >7 days, requiring pharmacological or electric cardioversion, respectively. Accordingly, no patient with permanent (defined as long-lasting) AF was included in the study; all the patients were in sinus rhythm during the MSCT examination. A history of CAD was defined as the presence of previous acute coronary syndrome, percutaneous or surgical coronary revascularization, and/or one or more angiographically documented coronary stenosis ≥50% luminal diameter. Contraindications for MSCT were (1) known allergy to iodinated contrast agent, (2) renal failure, and (3) pregnancy.

For each patient, the presence of coronary risk factors (diabetes mellitus, systemic hypertension, hypercholesterolemia, positive family history, and cigarette smoking) and symptoms was recorded. In addition, the prevalence of ≥3 coronary risk factors and the pretest likelihood of obstructive CAD was evaluated using the Diamond and Forrester’s criteria. Using the same exclusion criteria, a population of 148 patients from the outpatient clinic without a history of AF, similar to the AF group as to age, gender, chest pain complaints, and pretest likelihood of obstructive CAD, who underwent MSCT for coronary evaluation due to an elevated risk profile and/or chest pain, was identified from the clinical database to serve as a control group for comparison purposes.

Patients were included at 4 centers in 3 different countries (Leiden University Medical Center, Leiden, the Netherlands; Medisch Centrum Haaglanden, Leidschendam, The Netherlands; Turku PET Center, Turku, Finland; University Hospital Zurich, Zurich, Switzerland).

MSCT Data Acquisition

MSCT coronary angiography was performed with 2 different 16-slice MSCT scanners (Aquilion 16, Toshiba Medical Systems, n = 39; and Discovery STE, GE Healthcare, n = 8) and 3 different 64-slice MSCT scanners (Aquilion 64, Toshiba Medical Systems, n = 202; LightSpeed VCT, GE Healthcare, n = 19; and Discovery VCT, GE Healthcare, n = 30). The heart rate and blood pressure were monitored before the examination in each patient. In the absence of contraindications, patients with a heart rate ≥65 bpm were administered β-blocking medication (50 to 100 mg metoprolol, oral or 5 to 10 mg metoprolol, intravenous). First, a prospective coronary calcium scan without contrast was performed, followed by 16- or 64-slice MSCT coronary angiography performed according to protocols described previously. Data were subsequently transferred to dedicated workstations for postprocessing and evaluation (Advantage, GE Healthcare; Vitrea 2, Vital Images; and Aquarius, TeraRecon).

MSCT Data Analysis

The MSCT data analysis was performed in each center by 2 experienced observers who had no knowledge of the patient’s medical history and symptom status; disagreement was solved by consensus or evaluation by a third observer. Standardized MSCT data evaluation methodology and scoring system described later were used in each center.

Coronary Artery Calcium Score

Coronary artery calcium was identified as a dense area in the coronary artery >130 Hounsfield units. A total coronary artery calcium score was recorded for each patient. In accordance to the value of total calcium score, the study population was then categorized as having no calcium (total score = 0) or minimal (total score = 1 to 10), mild (total score = 11 to 100), moderate (total score = 101 to 400), and severe (total score >400) coronary calcifications.

Coronary Angiography

MSCT coronary angiograms obtained with 16- and 64-slice scanners were evaluated for the presence of obstructive CAD (≥50% luminal narrowing) on a patient, vessel, and segment level. For this purpose, both the original axial dataset and curved multiplanar reconstructions were used. Coronary segments were evaluated in accordance to the 17 segments American Heart Association classification. First, each segment was classified as interpretable or not. Then, the interpretable segments were evaluated for the presence of any atherosclerotic plaque, 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, as described previously. One coronary plaque was assigned per coronary segment. Subsequently, segments were further classified as (1) completely normal, (2) having nonobstructive CAD when atherosclerotic lesions <50% of luminal diameter were present, or (3) having obstructive CAD when atherosclerotic lesions ≥50% of luminal diameter were present.

The prevalence of CAD (including obstructive and nonobstructive CAD), obstructive CAD, the presence of obstructive CAD in 1 vessel (single-vessel disease) or 2 or 3 vessels (multivessel disease) and location in the left main (LM) and/or proximal left anterior descending (LAD) coronary artery were evaluated. In addition, the number of diseased coronary segments (segments containing plaques) and the number of coronary segments with obstructive as well as nonobstructive plaques were determined for each patient.

Statistical Analysis

Continuous variables are expressed as mean and standard deviation. Categorical variables are expressed as absolute numbers and percentages. The differences in continuous variables were assessed using the Student t test when normally distributed and the Mann–Whitney test when not normally distributed. All continuous variables were normally distributed, except coronary artery calcium score, the number of diseased coronary segments, of segments with obstructive CAD and nonobstructive CAD per patient. χ² was computed to test for differences in categorical variables.

Multivariable logistic regression analyses (backward stepwise with retention level set at 0.1) were performed to evaluate the relationship between demographic and clinical data (age, gender, coronary risk factors, symptoms, pretest likelihood of CAD, and history of AF) and the presence of CAD and obstructive CAD at MSCT coronary angiography. Only significant univariate predictors were entered as covariates in the multivariable models. Odds ratios and 95% CI were calculated.

The diagnostic accuracy of MSCT coronary angiography for the detection of obstructive (≥50% luminal narrowing) coronary artery
stenoses was assessed in the subgroup of patients who underwent invasive coronary angiography. The sensitivity and specificity, including 95% CI, were calculated using invasive coronary angiography as the reference standard.

A probability value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software (version 14.0, SPSS Inc).

Statement of Responsibility
The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patient Characteristics
Baseline characteristics of each group are shown in Table 1. In accordance to the study design, AF and non-AF groups did not differ as to mean age (61 ± 11 versus 59 ± 10 years), male gender (67% versus 65%), symptomatic status, and pretest likelihood of CAD. In particular, a history of typical or atypical angina pectoris was present in 42% of patients with AF and in 43% of patients without AF and the pretest likelihood of CAD according to Diamond and Forrester was low, intermediate, and high, respectively, in 59%, 25%, and 16% of patients with AF and in 58%, 28%, and 14% of patients without AF.

Patients with AF, as compared with patients without AF, were less frequently diabetic (13% versus 28%, P = 0.001) and smoker (21% versus 31%, P = 0.027). Overall, the prevalence of ≥3 coronary risk factors was not statistically different between the 2 groups.

MSCT Calcium Scoring and Noninvasive Angiography
A total of 24 (16%) patients with AF and 23 (16%) patients without AF underwent examination with 16-slice MSCT, whereas the remaining study population underwent 64-slice MSCT. Table 2 and Figures 1 through 3 depict the results of calcium scoring and MSCT coronary angiography in the study population.

Coronary Artery Calcium Score
Coronary artery calcium score was effectively performed in 133 (89%) patients with AF and in all patients without AF. The median Agatston calcium score did not differ between patients with AF and patients without AF (27, interquartile range 0 to 308, versus 75, interquartile range 0 to 350; P = 0.19). The prevalence of no calcium and minimal, mild, moderate, and severe coronary calcifications was not statistically different between the 2 groups, although absence of any calcium was less frequently observed among patients with AF (Figure 1).

Noninvasive Coronary Angiography
Noninvasive coronary angiography was successfully performed in all the patients of the study population. Mean heart rate during the scan was 64 ± 6 bpm among patients with AF and 65 ± 9 bpm among patients without AF (P = 0.24).

As shown in Figure 2, 28 (18%) patients with AF were classified as having no CAD based on MSCT, whereas 61
(41%) showed nonobstructive CAD and at least 1 significant (≥50%) luminal narrowing was observed in the remaining 61 (41%) patients. The prevalence of CAD among patients without AF was significantly lower: 47 (32%) were classified as having no CAD, whereas 61 (41%) showed nonobstructive CAD and 40 (27%) had obstructive CAD, based on MSCT ($P=0.010$ compared with patients with AF).

Obstructive single-vessel disease was present in 35 (23%) patients with AF, whereas obstructive LM and/or proximal LAD disease was present in 37 (25%) patients with AF. Multivessel disease was observed in 26 (17%) (Figure 3).

As also indicated by Figure 3, patients without AF showed a significantly lower prevalence of obstructive single-vessel disease and obstructive LM and/or proximal LAD disease, as compared with patients with AF, but not a significantly lower prevalence of multivessel disease. Obstructive single-vessel disease was indeed observed in 19 (13%) patients without AF, obstructive CAD in the LM and/or proximal LAD in 15 (10%) and multivessel disease in 21 (14%) ($P=0.024$, $P=0.001$, and $P=0.53$, respectively, compared with patients with AF).

Because of motion artifacts, 39 (1.5%) segments in the AF group and 38 (1.5%) segments in the non-AF group were excluded from the segment-based analysis, respectively. A significantly higher number of diseased coronary segments, of segments with obstructive CAD and nonobstructive CAD per patient was present in the AF group, as compared with non-AF group (5.5±3.9 versus 4.0±4.0, $P=0.001$; 1.1±1.9 versus 0.8±1.7, $P=0.010$ and 4.4±3.2 versus 3.2±3.3, $P=0.001$, respectively).

Age ($P<0.001$), male gender ($P=0.002$), diabetes mellitus ($P=0.004$), hypertension ($P<0.001$), hypercholesterolemia ($P<0.001$), and history of AF ($P=0.010$) were selected as significant univariate predictors of (any) CAD. Age ($P<0.001$), male gender ($P=0.014$), hypertension ($P=0.006$), hypercholesterolemia ($P=0.026$), pretest likelihood of CAD ($P=0.021$), and history of AF ($P=0.013$) were selected as significant univariate predictors of obstructive CAD. At multivariable logistic regression analysis, age, history of AF, male gender, and hypercholesterolemia were identified as significantly associated to the presence of (any) CAD whereas the variables age, history of AF, and male gender were identified as significantly associated to obstructive CAD (Table 2).

Figure 4 shows an example of an asymptomatic patient with paroxysmal AF and evidence of extensive coronary atherosclerosis on MSCT.
Diagnostic Accuracy of MSCT Coronary Angiography

A total of 79 patients underwent invasive coronary angiography. The overall number of obstructive (>50% luminal narrowing) coronary artery stenoses was 151. The sensitivity/specificity of MSCT coronary angiography was 92.1% (95% CI, 86.5% to 95.8%) and 96.4% (95% CI, 95% to 97.4%), respectively.

Discussion

This is one of first studies using anatomic assessment to examine the prevalence of CAD among patients with paroxysmal or persistent AF and without a history of CAD. A higher prevalence of obstructive CAD was detected among patients with AF, as compared with a cohort of patients without AF, with similar age and pretest likelihood of CAD, but with a higher prevalence of diabetes mellitus. Moreover, LM and/or proximal LAD disease was more frequently identified (25% of patients with AF versus 10% of patients without AF). At logistic regression analysis, AF, together with age and male gender, was identified as an independent predictor of the presence of obstructive CAD.

Although a casual relationship between CAD and AF has not yet been established, CAD is considered to be highly prevalent among patients with AF and may be one of its potential etiologic factors. Indeed, AF and CAD may simply be different, concurrent consequences of long-lasting exposure to coronary risk factors, but, on the other hand, AF could be a consequence of CAD, directly or indirectly, through an increase of left atrial pressure secondary to episodes of left ventricular ischemia. Previous population studies such as the Framingham and Manitoba studies reported CAD to be one of the etiologic factors most commonly associated with the development of AF. Moreover, once diagnosed with AF, the presence of CAD has been shown to be related with recurrent AF episodes, presence of symptoms (including arrhythmic, heart failure, and angina symptoms) and increased risk of death. Interestingly, epidemiological data disclosed that ischemic heart disease is one of the most common underlying cause of death among patients with AF and a more recent community-based longitudinal cohort study showed that patients diagnosed with first AF but yet without established CAD constitute a high-risk group with increased risk for subsequent new coronary ischemic events and mortality.

Accordingly, these observations have lead to an increased interest in the evaluation of underlying CAD in patients with AF. Two recent studies assessed the value of cardiac imaging to detect CAD in patients with AF, using stress myocardial perfusion SPECT. Abidov et al reported that patients with AF have larger perfusion abnormalities on SPECT and a higher risk of cardiac death as compared with patients without AF. However, >50% of enrolled patients had symptoms and/or known CAD, and the reported difference in SPECT studies results was mostly due to a higher amount of hypoperfused myocardium at rest in the AF group. More recently, Askew et al showed a prevalence of abnormal myocardial perfusion SPECT studies of 51.6% among asymptomatic patients with AF. After an average follow-up of 5.7 years, a significantly higher mortality rate was observed in patients with AF as compared with patients without AF. Interestingly, no significant difference in the rate of abnormal SPECT studies between patients with and without AF was observed, suggesting that the increased mortality was not related to a higher prevalence of obstructive CAD.

However, SPECT reflects only indirectly the presence of CAD, because it is based on the detection of coronary lesions that result in compromised blood flow during stress, whereas the actual prevalence of atherosclerosis in patients with AF may be higher.

In this study, imaging of atherosclerosis with MSCT was used to determine the prevalence of CAD. By means of calcium scoring, the presence and extensions of coronary calcifications was not statistically different between patients with AF and patients without AF. However, using noninvasive coronary angiography, patients with AF were found to have more frequently coronary atherosclerosis (82%) and obstructive CAD (41%), as compared with patients without AF (68% and 27%, respectively). Furthermore, LM/proximal LAD disease was identified in 25% of patients with AF versus 10% of patients without AF. These findings are particular striking, when considering that the patients of the study population were mostly asymptomatic and with low pretest likelihood for CAD. In addition, a higher prevalence of diabetes, a condition that is generally associated with a significantly higher extent of CAD, was observed in patients without AF. Indeed, at multivariable logistic regression analysis, only AF, age and male gender were identified as significantly related to the presence of obstructive CAD.

Clinical Implications

Because of the lack of follow-up data, the clinical significance and implications of these findings are still unknown at this time. However, taking into account the suspected association between AF, underlying CAD and increased risk for coronary events, our observations suggest that patients with AF (despite the absence of symptoms) potentially may benefit from noninvasive diagnostic procedures to evaluate the presence of CAD. In this study, the feasibility of MSCT coronary angiography was evaluated, showing a higher prevalence of atherosclerosis and even obstructive CAD in patients with AF, as compared with patients without AF, confirming the hypothesis that AF could be a marker of advanced coronary atherosclerosis. However, in this regard, it remains important to realize that MSCT coronary angiography does not provide information about the hemodynamic consequences of observed coronary lesions. In patients with obstructive CAD on MSCT functional testing remains needed to determine the presence of ischemia and to guide further therapeutic decisions (aggressive medical therapy and risk factor modification or referral for invasive angiography with potentially revascularization).

Study Limitations

This study has several limitations that should be acknowledged. First, it is a case-control study, the limitations of which are well known. Moreover, no prognostic data were available. A larger study, with follow-up data, may provide
more conclusive information. Second, only patients with paroxysmal or persistent AF were studied. We preferred to exclude patients with permanent AF. Despite the introduction of 64-slice MSCT, the technique still suffers from limited diagnostic accuracy in case of irregular heart rate. With the more recent generations of dual source and 320-slice MSCT scanners, imaging in patients with permanent AF could potentially be possible, although no consistent data are available. Third, MSCT coronary angiography is not able to discriminate between flow-limiting and non–flow-limiting stenoses; accordingly, no data regarding the hemodynamic consequences of observed coronary lesions can be provided. Fourth, because the presence of history of paroxysmal or persistent AF was used to identify the study population, it is possible that some patients with unacknowledged episodes of paroxysmal AF have been included in the control group. In addition, although standardized MSCT evaluation protocols were used in the participating centers, acquisition protocols were not completely uniform as scanners from different generations and manufacturers were used. This, however, reflects the daily clinical routine and confers generalized applicability to our observations. In addition, no off-site reading of MSCT coronary angiography was performed, possibly influencing interobserver variability. Finally, MSCT coronary angiography still has a high radiation exposure, which limits its use in asymptomatic patients. However, the use of more recent generation scanners and the implementation of dose-saving algorithms is likely to result in substantial dose reduction, without degradation of image quality.32

Conclusions
A higher prevalence of obstructive CAD was detected among patients with AF, as compared with patients without AF, confirming the hypothesis that AF could be a marker of advanced coronary atherosclerosis. In addition, the presence of AF was identified as a significant and independent predictor of the presence of obstructive CAD.

Sources of Funding
This work was supported by the Research Fellowship of the European Association of Percutaneous Cardiovascular Interventions (to G.N.) and the Netherlands Society of Cardiology (to J.M.v.W.).

Disclosures
Dr Schalij has research grants from Biotronik (Berlin, Germany), Boston Scientific (Natick, Mass), and Medtronic (Minneapolis, Minn). Dr Bax has research grants from Biotronik, BMS Medical Imaging (North Billerica, Mass), Boston Scientific, Edwards Lifesciences (Irvine, Calif), GE Healthcare (Buckinghamshire, United Kingdom), Medtronic (Minneapolis, Minn), and St Jude Medical (St Paul, Minn). The other authors have nothing to disclose.

References


Coronary artery disease (CAD) is considered to be highly prevalent among patients with atrial fibrillation (AF) and may be one of its underlying causes. Furthermore, it has been suggested that AF may be the sole manifestation of CAD. However, most data supporting this association have been derived from studies using the presence of ECG abnormalities or a history of ischemic heart disease to define CAD rather than direct visualization of atherosclerosis. In this study, multislice computed tomography coronary angiography showed a higher prevalence of atherosclerosis and obstructive CAD in patients with AF, as compared with patients without AF, further supporting the hypothesis that AF could be a marker of advanced coronary atherosclerosis. It should be stressed, however, that multislice computed tomography coronary angiography does not provide information about the hemodynamic consequences of the observed coronary lesions (ie, ischemia or not). In patients with obstructive CAD on multislice computed tomography, functional testing remains needed to determine the presence of ischemia and to guide further therapeutic decisions.
Prevalence of Coronary Artery Disease Assessed by Multislice Computed Tomography Coronary Angiography in Patients With Paroxysmal or Persistent Atrial Fibrillation

Gaetano Nucifora, Joanne D. Schuijf, Laurens F. Tops, Jacob M. van Werkhoven, Sami Kajander, J. Wouter Jukema, Joop H.M. Schreur, Mark W. Heijenbrok, Serge A. Trines, Oliver Gaemperli, Olli Turta, Philipp A. Kaufmann, Juhani Knuuti, Martin J. Schalij and Jeroen J. Bax

_Circ Cardiovasc Imaging_. 2009;2:100-106; originally published online January 26, 2009; doi: 10.1161/CIRCIMAGING.108.795328

_Circulation: Cardiovascular Imaging_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2009 American Heart Association, Inc. All rights reserved.

Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://circimaging.ahajournals.org/content/2/2/100

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Cardiovascular Imaging_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Cardiovascular Imaging_ is online at:
http://circimaging.ahajournals.org//subscriptions/