Atrial fibrillation indicates nonobstructive coronary lesions

Atrial fibrillation is more frequently associated with nonobstructive coronary lesions: the Bialystok Coronary Project

Anna Tomaszuk-Kazberuk¹, Marek Koziński², Łukasz Kuźma³, Elżbieta Bujno⁴, Paulina Łopatowska⁴, Ewelina Rogalska⁵, Sławomir Dobrzycki³, Bożena Sobkowicz¹, Gregory Y. H. Lip⁵,⁶

¹ Department of Cardiology, Medical University of Bialystok, Białystok, Poland
² Department of Cardiology and Internal Medicine, Medical University of Gdańsk, Gdynia, Poland
³ Department of Invasive Cardiology, Medical University of Bialystok, Białystok, Poland
⁴ Department of Cardiology, University Hospital in Bialystok, Białystok, Poland
⁵ Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom
⁶ Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

KEY WORDS
atrial fibrillation, coronary angiography, coronary artery disease

ABSTRACT
INTRODUCTION Atrial fibrillation (AF) and chronic coronary syndrome (CCS) share common risk factors and frequently coexist. Additionally, AF symptoms may mimic CCS.

OBJECTIVES The aim of the study was to investigate the hypothesis indicating absence of significant coronary lesions in patients with AF as compared with those with sinus rhythm.

PATIENTS AND METHODS We conducted a single-center retrospective study including consecutive patients referred for elective coronary angiography between 2007 and 2016.

RESULTS The study population included 8288 patients out of whom 1674 had AF. There were substantial differences between groups with and without AF. Patients with AF were significantly older, more often were men and had diabetes, and more frequently were diagnosed with both chronic kidney disease and heart failure. On the other hand, they had history of hyperlipidemia less often. CCS was less frequently detected in patients with AF as compared with those with sinus rhythm (37.5% vs 41.1%; P < 0.001). Additionally, the latter group more often underwent subsequent coronary angioplasty (19.2% vs 22.3%; P = 0.004). Multivariable analysis identified AF as an independent factor associated with absence of significant coronary lesions (odds ratio, 1.57; 95% CI, 1.32–1.87; P < 0.001). Moreover, a comparison between patients with and without angiographically significant CCS revealed a higher prevalence of AF in the latter group (18.7% vs 21.2%; P = 0.006).

CONCLUSIONS In our study, AF was associated with the absence of significant coronary lesions on angiography, reflecting difficulties with qualifying patients with AF for invasive CCS diagnostic workup. Our findings suggest the need for more efficacious noninvasive diagnostic approach for patients with AF and suspected CCS.

INTRODUCTION Atrial fibrillation (AF) is the most common cardiac arrhythmia associated with excessive risk of ischemic stroke and heart failure as well as reduced life expectancy.⁴,⁵ On the other hand, chronic coronary syndrome (CCS) remains the main cause of morbidity and mortality in an aging population. Both disease entities share common risk factors such as hypertension, diabetes, and obesity.³,⁵ The prevalence of CCS in patients with AF varies from 17% to 47%,³,⁶,⁷ whereas AF in patients with CCS is much less common, ranging from 0.2% to 5%.⁸,¹⁰ Patients with AF more often have concomitant CCS as compared with sinus rhythm controls.¹³,¹⁴ Additionally, AF is more frequently present in patients with either peripheral or cerebrovascular artery disease than in nonatherosclerotic individuals.¹⁵
WHAT’S NEW?

In this study, the number of nonsignificant findings on coronary angiography was 1.6-fold higher in patients with atrial fibrillation (AF) than in patients without AF. Atrial fibrillation was associated with absence of significant coronary lesions and patients with AF less frequently underwent coronary angioplasty as compared with those with sinus rhythm. This raises the possibility that it may be difficult to select patients with AF for invasive procedures, given the increased findings of nonsignificant chronic coronary syndromes (CCS) on coronary angiography. The reason for these findings might be multifactorial: AF symptoms mimic CCS symptoms, ST-segment depression during AF poorly predicts obstructive CCS, stress tests are rarely proceeded in patients with AF, and rapid rhythm makes computed tomography scan difficult to interpret. A more efficacious noninvasive diagnostic approach is needed in patients with AF and suspected CCS.

Patients with AF in the course of arrhythmia may present with chest pain, which can be accompanied by transient ischemic-type ST-segment changes, sometimes with marginally elevated cardiac necrosis markers, thus mimicking symptoms of CCS. There are contradictory data on angiographic findings among patients with AF. It is important to look at the prevalence of significant CCS lesions in patients with AF compared with those with sinus rhythm to prevent unnecessary coronary angiography in patients with AF.

On the other hand, there are several studies including the ARIC (the Atherosclerosis Risk in Communities) study, the MESA (Multi-Ethnic Study of Atherosclerosis), and the Rotterdam Study which found an association between subclinical atherosclerosis and incident AF. The aim of the present study was to investigate the hypothesis indicating the absence of significant coronary lesions in patients with AF as compared with those with sinus rhythm referred for elective coronary angiography. This indicates that some patients with AF may have undergone coronary angiography needlessly.

PATIENTS AND METHODS  We reviewed medical records of 26,985 patients hospitalized in the Department of Invasive Cardiology of the Medical University of Bialystok, Poland, who had coronary angiography performed because of exacerbated angina (recurrent chest pain, classical stable angina, long history of chest pain/angina, or other symptoms such as dyspnea) between 2007 and 2016. The Bialystok Coronary Project is an observational research project that includes hospitalized patients with AF and CCS. It is focused on diagnostics and therapy of this population. We excluded patients with acute coronary syndromes (ACS), Takotsubo cardiomyopathy, and history of ischemic heart disease, as well as those referred for coronary angiography before heart valve surgery. Prior cardiac surgery valve replacement was also the exclusion criterion. The set of extracted variables included demographic data, medical history, physical examination, resting electrocardiogram, routine transthoracic echocardiogram, coronary angiogram, and percutaneous coronary intervention (PCI). Eventually, our final study cohort included 8288 patients. Concomitant diseases were defined via the International Statistical Classification of Diseases, Tenth Revision (ICD-10) codes, not prescription claims.

We analyzed whether history of AF was associated with the absence of significant coronary lesions on coronary angiography. We also investigated factors connected with the absence of significant coronary lesions on angiography. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the local ethics committee.

Coronary angiography  All patients underwent coronary angiography and the number of diseased vessels were assessed. Coronary angiography was performed according to the Judkins technique. Diagnosis of CCS and indication for PCI was performed according to the current European guidelines. Significant stenosis of the coronary vessel was defined as more than 50% in the main stem of the left coronary artery and 70% in the rest of the epicardial arteries. The degree of CCS was classified as single-, double-, or triple-vessel disease.

Echocardiographic analysis  Left ventricular ejection fraction (LVEF) was assessed in transthoracic echocardiography using the modified biplane Simpson method (Philips Ultrasound System, Sonos 5500, Aalborg, Denmark, equipped for harmonic imaging with a 3.6 MHz transducer) and was derived in accordance with the recommendations of the European Society of Echocardiography.

Definition of atrial fibrillation  Atrial fibrillation was defined as the presence of AF on electrocardiogram during the index hospitalization and/or as indicated by a diagnosis found in medical records, the hospital inpatient database, or outpatient databases. Electrocardiographic AF was defined as an irregular rhythm with fibrillatory waves and no defined P waves. Diagnoses and AF classification were based on physician-assigned diagnoses in the medical records and/or the presence of corresponding codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) for AF (427.31) in the hospital discharge or outpatient databases. Atrial fibrillation was further divided into the following categories: paroxysmal AF or chronic AF (persistent and permanent).

Statistical analysis  Continuous data were expressed as means (SD) or medians and interquartile ranges (IQRs) when appropriate. Relative frequencies were used to present categorical variables. Normality of the distribution was assessed with the Kolmogorov-Smirnov test, while the 2-tailed t test was applied for
Out of 26,985 patients admitted for elective coronary angiography, a total of 8,288 patients were included in the final analysis (Figure 1, Table 1). Over 80% of study participants had hypertension, 66.9% had hyperlipidemia, and 25.7% had diabetes. Chronic kidney disease (CKD) and chronic heart failure (CHF) were diagnosed in 32.5% and 20.6% of the study population, respectively. Detailed characteristics of the study population is provided in Table 2.

A total of 1,674 (20.2%) patients had AF. Paroxysmal AF was the most frequent type of the analyzed arrhythmia. However, we found only a marginally lower prevalence of permanent AF (Figure 1).

**RESULTS**

**Atrial fibrillation population** There were substantial differences in terms of clinical characteristics between groups with and without AF. Patients with AF were older, more often men, and more often had diabetes, and had higher body mass index and more frequently were diagnosed with both CKD and CHF. On the other hand, they were less likely to have history of hyperlipidemia. Mean (SD) HAS-BLED score was 2.14 (0.87), CHA2DS2-VASc score was 3.99 (1.6).

The highest mean (SD) HAS-BLED and CHA2DS2-VASc scores were noted in patients with permanent AF: 2.2 (0.91) and 4.3 (1.6), respectively. In patients with paroxysmal AF, the mean (SD) HAS-BLED was 2.15 (0.84) and in persistent AF, it was 1.9 (0.81).
| Variable | All study participants (n = 8288) | Patients with AF (n = 1674) | Patients without AF (n = 6614) | P value |
|----------|----------------------------------|-----------------------------|------------------------------|---------|
| **Male sex, n (%)** | 4500 (54) | 1018 (61) | 3482 (53) | <0.001 |
| **Age, y, mean (SD)** | 65.2 (10.2) | 68.6 (9.6) | 64.3 (10.2) | <0.001 |
| **BMI, kg/m², mean (SD)** | 29.1 (4.9) | 30 (5.2) | 28.9 (4.7) | <0.001 |
| **NYHA class, median (IQR)** | 2 (2–3) | 3 (2–3) | 2 (2–3) | 0.22 |
| **CCS class, median (IQR)** | 2 (2–2) | 2 (2–2) | 2 (2–2) | 0.26 |
| **CAD with significant stenosis on coronary angiography** | 3345 (40.4) | 627 (37.5) | 2718 (41.1) | <0.001 |
| **Single-vessel CAD** | 1507 (18.2) | 342 (20.4) | 1165 (17.6) | <0.001 |
| **Double-vessel CAD** | 807 (9.7) | 126 (7.5) | 681 (10.3) | <0.001 |
| **Triple-vessel and/or significant LM stenosis** | 1031 (12.4) | 159 (9.5) | 872 (13.2) | <0.001 |
| **Hyperlipidemia** | 5548 (66.9) | 961 (57.4) | 4587 (69.4) | <0.001 |
| **Hypertension** | 6886 (83.1) | 1370 (81.8) | 5516 (83.4) | 0.14 |
| **Diabetes mellitus** | 2132 (25.7) | 477 (28.5) | 1655 (25) | 0.005 |
| **Chronic heart failure** | 2690 (32.5) | 1038 (62) | 1652 (24.9) | <0.001 |
| **HFrEF** | 1381 (51.3) | 621 (59.8) | 760 (46) | <0.001 |
| **HFmrEF** | 599 (22.3) | 220 (21.2) | 379 (22.9) | <0.001 |
| **HFpEF** | 710 (26.4) | 197 (18.9) | 513 (31.1) | <0.001 |
| **Left ventricular ejection fraction, %, median (IQR)** | 55 (42–60) | 45 (30–55) | 56 (50–60) | <0.001 |
| **Chronic kidney disease** | 1706 (20.6) | 556 (33.2) | 1150 (17.4) | <0.001 |
| **Creatinine, mg/dl, median (IQR)** | 0.89 (0.78–1.05) | 0.97 (0.82–1.17) | 0.87 (0.78–1.02) | <0.001 |
| **eGFR, ml/min/1.73 m², mean (SD)** | 76.4 (19.1) | 70 (20) | 77.9 (18.5) | <0.001 |
| **eGFR > 90 ml/min/1.73 m²** | 2095 (26) | 266 (16.4) | 1829 (28.6) | <0.001 |
| **eGFR 60–90 ml/min/1.73 m²** | 4455 (55.2) | 855 (52.8) | 3600 (55.9) | <0.001 |
| **eGFR 45–60 ml/min/1.73 m²** | 967 (12) | 302 (18.6) | 665 (10.3) | <0.001 |
| **eGFR 30–45 ml/min/1.73 m²** | 406 (5) | 161 (9.9) | 245 (3.8) | <0.001 |
| **eGFR 15–30 ml/min/1.73 m²** | 79 (0.9) | 27 (1.7) | 52 (0.1) | <0.001 |
| **eGFR <15 ml/min/1.73 m²** | 63 (0.8) | 10 (0.6) | 53 (0.9) | <0.001 |
| **RBC, 10⁶/mm³, median (IQR)** | 4.58 (4.28–4.88) | 4.58 (4.23–4.89) | 4.58 (4.29–4.8) | <0.001 |
| **Total cholesterol, mg/dl, median (IQR)** | 171 (146–203) | 167 (141–198) | 172 (148–204) | 0.006 |
| **High-density lipoprotein cholesterol, mg/dl, median (IQR)** | 46 (39–55) | 45 (38–53) | 47 (39–56) | <0.001 |
| **Low-density lipoprotein cholesterol, mg/dl, median (IQR)** | 99 (77–127) | 97 (75–124) | 99 (78–128) | 0.037 |
| **Triglycerides, mg/dl, median (IQR)** | 117 (85–165) | 113 (82–159) | 118 (85–167) | 0.4 |
| **Presence of any significant stenosis on coronary angiography** | 3345 (40.4) | 627 (37.5) | 2718 (41.1) | <0.001 |
| **LM stenosis** | 245 (3) | 42 (2.5) | 203 (3.1) | 0.2 |
| **LAD stenosis** | 2013 (24.3) | 336 (20.1) | 1677 (25.3) | <0.001 |
| **DIAG stenosis** | 735 (8.9) | 132 (7.9) | 603 (9.1) | 0.09 |
| **Cx stenosis** | 1096 (13.2) | 174 (10.4) | 922 (14) | <0.001 |
| **OM stenosis** | 664 (8) | 104 (6.2) | 560 (8.5) | <0.001 |
| **RCA stenosis** | 1481 (17.9) | 224 (13.4) | 1257 (19) | <0.001 |
| **Patients qualified for conservative management** | 5330 (64.3) | 1126 (67.3) | 4204 (63.6) | 0.004 |
| **Patients qualified for the Heart Team discussion** | 1161 (14) | 227 (13.6) | 934 (14.1) | 0.55 |
| **Patients treated with PCI** | 1796 (21.7) | 321 (19.2) | 1475 (22.3) | 0.004 |
| **PCI LM** | 34 (0.4) | 7 (0.4) | 27 (0.4) | 0.95 |
| **PCI LAD** | 1115 (13.4) | 206 (12.3) | 909 (13.7) | 0.11 |
| **PCI DIAG** | 182 (2.2) | 34 (2) | 148 (2.2) | 0.6 |
| **PCI Cx** | 451 (5.4) | 81 (4.9) | 370 (5.6) | 0.2 |
| **PCI OM** | 61 (0.7) | 13 (0.8) | 48 (0.7) | 0.83 |
| **PCI RCA** | 404 (4.9) | 64 (3.8) | 340 (5.1) | 0.015 |
The lowest mean (SD) CHA₂DS₂-VASc score was noted in the group of patients with paroxysmal AF (3.74 [1.5]). In the group of patients with persistent AF, the mean (SD) CHA₂DS₂-VASc score was 3.87 (1.5). A detailed comparison between the 2 groups is shown in Table 2.

### Coronary angiography

Out of 8288 patients who underwent coronary angiography, significant lesions were found in 3345 study participants (40.4%). Importantly, patients without significant CCS were more frequently women and more commonly presented with AF (Table 3). Additionally, CCS was markedly less frequently detected on coronary angiography in patients with AF than in those with sinus rhythm. Furthermore, the latter group significantly more often underwent subsequent coronary angioplasty (Table 2).

### Predictors of nonsignificant coronary findings in the multivariable analysis

In the logistic regression model, the odds ratio of nonsignificant findings on coronary angiography were 1.6-fold higher in patients with AF than in those without AF (OR, 1.57; 95% CI, 1.32–1.87; P < 0.001). The indexed OR for a 5-kg/m² increase in body mass index was 1.24 (95% CI, 1.15–1.35; P < 0.001), and for a 5-mg/ml increase in high-density lipoprotein cholesterol concentration, 1.16 (95% CI, 1.1–1.24; P < 0.001). The OR for CHF was 0.68 (95% CI, 0.56–0.83; P < 0.001), other cardiovascular risk factors such as hypercholesterolemia, 0.64 (95% CI, 0.55–0.75; P < 0.001), diabetes, 0.69 (95% CI, 0.59–0.81; P < 0.001), hypertension, 0.68 (95% CI, 0.56–0.82; P < 0.001), CKD, 0.79 (95% CI, 0.66–0.94; P < 0.001) and women as compared with men, 0.39 (95% CI, 0.34–0.46; P < 0.001). Additionally, for a 10-year increase in age, the OR was 0.71 (95% CI, 0.65–0.76; P < 0.001; Figure 2)

### Complications of coronary angiography

There were 48 cases of significant vascular complications related to the puncture of the site (0.5%). In 75% of complications, the femoral artery was affected, and in 25% of cases, it was the radial artery. Out of those cases, 16 (1%) were patients with AF and 32 (0.4%) had sinus rhythm (P = 0.004).

In 9 patients (0.11%), neurological disorders associated with the procedure were recorded in 7 patients (0.1%) with sinus rhythm and in 2 patients (0.12%) with AF. All computed tomography (CT) examinations performed in these patients failed to show any signs of intracranial bleeding. In 19 patients, cardiac arrest occurred during hospitalization: 7 patients (0.4%) with AF and 12 patients with sinus rhythm (0.2%). Overall, composite complications were more common in patients with AF.

### DISCUSSION

In this study, nonsignificant findings on coronary angiography were 1.6-fold higher in patients with AF than in patients without AF. Second, AF was associated with significantly less atherosclerotic narrowing on coronary angiography (627 [37.5%] vs 2718 [41.1%] in patients without AF; P < 0.001) and patients with AF less frequently underwent coronary angioplasty as compared with the population with sinus rhythm. This raises the possibility that AF may result in difficulties in selecting patients with AF for invasive procedures, given the increased findings of nonsignificant CCS on coronary angiography.

The reason for these findings might be complex and multifactorial. Patients with AF often present with typical or atypical chest pain, transient ST-segment depression, and elevated cardiac markers. These findings may mimic symptoms of CCS. Moreover, rapid tachycardia is often observed in patients with AF, and ST-segment changes at these rates have been linked with myocardial ischemia. For example, Tsikgas et al reported ST-segment depression in 38% of patients with AF and rapid rhythm and only about 50% of these patients had significant CCS on coronary angiography. ST-segment depression may frequently occur during significant tachycardia, even without CCS, and it is not necessarily typical for cardiac ischemia if the ST segment depression is less than 2 mm.

Moreover, ST-segment depression during rapid AF has less significant value than ST-segment depression during exercise tests in patients with sinus rhythm. Only 4% of patients without ST-segment depression during rapid AF had positive noninvasive tests for myocardial ischemia and CCS on angiography. Troponin release was shown in 15% of patients with AF and symptoms of ischemia, although CCS at angiography was absent. In a database of patients referred for coronary angiography, history of AF correlated with no obstructive CCS.

On the other hand, Kraler et al showed that left main stem and right coronary artery (RCA) disease was present more frequently in patients with AF compared with controls. They also suggested that significant atherosclerotic narrowing
that in patients with AF, ischemia at the level of microcirculation of the myocardial muscle (rather than epicardial vessels) is responsible for the presence of typical angina. Unfortunately, our study did not explore the impact of cardiac ischemia induced by coronary small-vessel disease.

Our findings reflect difficulties with selecting AF patients for invasive coronary investigations. In the general population, the sensitivity of exercise testing ranges from 60% to 70% and specificity is approximately 85%.

As mentioned before, ST-segment depression is a common finding in AF patients, and ST-depression during rapid AF has relatively higher sensitivity and lower specificity, when compared with exercise testing. Thus, the absence of ST-depression during rapid AF has satisfactory sensitivity for excluding significant CCS.

Table 3: Comparison between patients with and without angiographically significant coronary artery disease

| Variable | Patients with CAD (n = 3345) | Patients without CAD (n = 5483) | P value |
|----------|-------------------------------|---------------------------------|---------|
| Male sex | 2238 (67)                     | 2262 (46)                       | <0.001  |
| Age, y, mean (SD) | 66.9 (9.7)                     | 64 (10.3)                       | <0.001  |
| BMI, kg/m², mean (SD) | 28.8 (4.6)                     | 29.33 (5)                       | <0.001  |
| NYHA class, median (IQR) | 3 (4–3)                        | 2 (2–3)                         | 0.04    |
| CCS class, median (IQR) | 2 (2–2)                        | 2 (2–2)                         | 0.03    |
| Left ventricular ejection fraction, %, median (IQR) | 55 (44–60)                     | 55 (42–60)                      | 0.5     |
| Chronic heart failure | 1247 (37.3)                    | 1443 (29.2)                     | <0.001  |
| HFrEF | 601 (48.2)                     | 780 (54.1)                      | <0.001  |
| HFmrEF | 301 (24.1)                     | 298 (20.6)                      |         |
| HfPEF | 345 (27.7)                     | 365 (25.3)                      |         |
| Hyperlipidemia | 2348 (70.2)                    | 3200 (64.7)                     | 0.001   |
| Hypertension | 2891 (86.4)                    | 3995 (80.8)                     | <0.001  |
| Diabetes mellitus | 1014 (30.3)                    | 1118 (22.6)                     | <0.001  |
| AF Any | 627 (18.7)                     | 1047 (21.2)                     | 0.006   |
| Paroxysmal | 267 (42.6)%                    | 490 (46.8)%                     | 0.09    |
| Persistent | 69 (11)%                       | 125 (11.9)%                     | 0.56    |
| Chronic kidney disease | 824 (24.6)                     | 882 (17.9)                      | <0.001  |
| Creatinine, mg/dl, median (IQR) | 0.93 (0.81–1.1)                | 0.86 (0.77–1.01)                | <0.001  |
| eGFR, ml/min/1.73 m², mean (SD) | 70 (20)                        | 77.8 (18.6)                     | <0.001  |
| eGFR >90 ml/min/1.73 m² | 754 (23.2)                     | 1341 (27.9)                     | <0.001  |
| eGFR 60–90 ml/min/1.73 m² | 1775 (54.5)                    | 2680 (55.7)                     | <0.001  |
| eGFR 45–60 ml/min/1.73 m² | 441 (13.6)                     | 526 (10.9)                      |         |
| eGFR 30–45 ml/min/1.73 m² | 214 (6.6)                      | 192 (4)                         |         |
| eGFR 15–30 ml/min/1.73 m² | 37 (1.1)                       | 42 (0.1)                        |         |
| eGFR <15 ml/min/1.73 m² | 32 (1)                         | 31 (0.6)                        |         |
| RBC, 10⁶/mm³, median (IQR) | 4.58 (4.26–4.89)               | 4.58 (4.28–4.87)                | 0.55    |
| Total cholesterol, mg/dl, median (IQR) | 169 (144–200)                  | 173 (147–204)                   | 0.008   |
| High-density lipoprotein cholesterol, mg/dl, median (IQR) | 44 (38–52)                     | 48 (40–57)                      | 0.075   |
| Low-density lipoprotein cholesterol, mg/dl, median (IQR) | 99 (77–125)                    | 99 (77–128)                     | 0.006   |
| Triglycerides, mg/dl, median (IQR) | 121 (87–170)                   | 114 (83–162)                    | 0.34    |

Data are presented as number (percentage) of patients unless otherwise indicated.

a The percentage is calculated within the subgroup.

Abbreviations: see Figure 1 and Table 2

in the proximal RCA and the circumflex artery (Cx) prior to the takeoff of the atrial arteries raises the risk of AF. In our study, significant RCA and Cx disease were less common than in patients with sinus rhythm. Another analysis of 3220 patients referred for coronary angiography revealed that only 43% of patients with CCS and AF had a diseased RCA or Cx.

Does AF contribute to CCS or vice versa? There is a debate on this topic and opinions are often contradictory. Motloch et al. found that the anatomical distribution of coronary artery stenoses did not contribute to AF in CCS patients; however, AF was linked to worse CCS severity, which might predispose individuals to AF by driving ischemic heart disease and changes in left ventricular function. In our study, patients with AF had less prevalent multivessel CCS. It is possible that in patients with AF, ischemia at the level of microcirculation of the myocardial muscle (rather than epicardial vessels) is responsible for the presence of typical angina. Unfortunately, our study did not explore the impact of cardiac ischemia induced by coronary small-vessel disease.

Our findings reflect difficulties with selecting AF patients for invasive coronary investigations. In the general population, the sensitivity of exercise testing ranges from 60% to 70% and specificity is approximately 85%.

As mentioned before, ST-segment depression is a common finding in AF patients, and ST-depression during rapid AF has relatively higher sensitivity and lower specificity, when compared with exercise testing. Thus, the absence of ST-depression during rapid AF has satisfactory sensitivity for excluding significant CCS. Low positive predictive values
Atrial fibrillation indicates nonobstructive coronary lesions

Limitations

Our study has several limitations. First, our findings were obtained in a retrospective single-center study and should be confirmed in a multicenter prospective study. However, our data represent real life, as they were obtained during daily clinical practice. Second, we excluded from our analysis patients with ACS. Third, fractional flow reserve measurements were not performed on regular basis. This could cause an inaccurate assessment of the significance of coronary stenosis. Therefore, only cases of stenosis with a reduction of 70% were defined as significant. Fourth, we were able neither to reliably assess stress tests before invasive diagnostics nor to measure concentrations of natriuretic peptides. Fifth, our study did not explore the impact of myocardial ischemia induced by coronary microvascular disease. Six, patients with AF were less likely to have lipid disorders, which may affect the results. Seven, due to a very large group of patients included in the study (nearly 10 000) and nearly 10 years of analysis (2007–2016), we were unable to obtain reliable data on smoking in the analyzed group. Over the years, the approach to smoking addiction and the way it is coded has changed. Our diagnoses were based on the diagnoses established by the physicians in charge and were not verified again. Additionally, it would be interesting to perform more detailed echocardiographic examinations of all study participants. Furthermore, retrospective chart databases provide easy and cheap access to large numbers of patients although limitations such as potential selection bias should be taken into consideration. The last thing, one of the subtypes of AF is newly diagnosed AF. As there is no specific ICD code for it, we were not able to distinguish this type of AF.

Conclusions

In our study, AF was associated with the absence of significant coronary lesions on angiography and less frequent need for revascularization, reflecting difficulties with qualifying AF patients for invasive CCS diagnostic workup. Multiple factors might be the reason for these findings, namely, AF symptoms may mimic CCS symptoms, ST-segment depression during AF poorly
predicts obstructive CCS, stress tests are rarely proceeded in patients with AF, and rapid rhythm makes CT scan difficult to interpret. Our findings suggest the need for a more efficacious noninvasive diagnostic approach for patients with AF and suspected CCS.

ARTICLE INFORMATION

CONTRIBUTION STATEMENT ATK, MK, EB, and PL conceived the idea for the study and contributed to the design of the research. ATK, EB, LK, ER, SD, and PL were involved in data collection. ATK, MK, LK, and GHY ana-
lyzed the data. ATK, MK, MG, AS, BS, and GHY edited the manuscript. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST None declared.

OPEN ACCESS This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0), allowing third parties to copy and re-
distribute the material in any medium or format and to remix, transform, and build upon the material, provided the original work is properly cited, distrib-
uted under the same license, and used for noncommercial purposes only. For commercial use, please contact the journal office at pami@mp.pl.

HOW TO CITE Tomaszuk-Kasberuk A, Kozinski M, Kulma L, et al. Atrial fibrillation is more frequently associated with nonobstructive coronary le-
sions: the Białystok Coronary Project. Pol Arch Intern Med. 2020; 130: 1029-1036. doi:10.24052/pami.15635

REFERENCES

1. Kirchfeld F, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the man-
agement of atrial fibrillation developed in collaboration with EACTS. Europe-
ce. 2016; 18: 1609-1673.

2. Potpara TS, Mujovic N, Lip GYH. Meeting the unmet needs to improve management and outcomes of patients with atrial fibrillation: fitting glob-
 al solutions to local settings. Pol Arch Intern Med. 2019; 129: 574-576.

3. Michnicewicz E, Młodawska E, Lopatowska P, et al. Patients with atrial-
al fibrillation and coronary artery disease – double trouble. Adv Med Sci. 2018; 63: 30-35.

4. Bednarski J, Balsam P, Tyminiska A, et al. District versus academic hos-
 pitals: differences in the clinical characteristics of patients with atrial fibrilla-
tion without valvular heart disease treated with oral anticoagulants. Pol Arch Intern Med. 2018; 128: 274-279.

5. Knutj J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diag-
nosis and management of chronic coronary syndromes. Eur Heart J. 2020; 41: 407-477.

6. AFFIRM Investigators. Atrial Fibrillation Follow-up Investigation of Rhythm Management. Baseline characteristics of patients with atrial fibril-
lation: the AFFIRM study. Am Heart J. 2002; 143: 991-1001.

7. Lip GYH, Beesing GD. History, epidemiology and importance of atrial fi-
brillation. BMJ. 1995; 311: 1361-1363.

8. Krah A, Höfling J, Schirmer M, et al. The natural history of atrial fibrill-
ation: incidence, risk factors and prognosis in the Mannheim follow-up study. Am J Med. 1996; 98: 476-484.

9. Ottesen JE, Kirva BA, Lusen J, et al. Action Investigators. Incidence and outcome of atrial fibrillation in stable symptomatic coronary disease. Scand Cardiovasc J. 2006; 40: 152-159.

10. Cameron A, Schwartz MJ, Knuuti J, et al. Prevalence and signifi-
cance of atrial fibrillation in coronary artery disease (CASS Registry). Am J Cardiol. 1988; 61: 714-717.

11. Haddad AH, Prabhavat Y, Dean DC. Chronic atrial fibrillation and coro-
nary artery disease. J Electrocardiol. 1978; 11: 67-69.

12. Cheng TD. Coronary artery disease as an uncommon cause of chronic atrial fibrillation. Clin Res. 1974; 22: 268A.

13. Weis B, Pisters R, Haest RJ, et al. Patients originally diagnosed with idiopathic atrial fibrillation more often suffer frominsidious coronary artery disease compared to healthy sinus rhythm controls. Heart Rhythm. 2012; 9: 1923-1929.

14. Kakkar AK, Mueller I, Bassand JP, et al. GARFIELD Registry Investi-
gators. Risk profiles and antithrombotic treatment of patients newly diag-
nosed with atrial fibrillation at risk of stroke: perspectives from the inter-
national, observational, prospective GARFIELD registry. PLoS ONE. 2013; 8: e63478.

15. Goto S, Bhatt DL, Röther J, et al. Prevalence, clinical profile, and car-
diovascular outcomes of atrial fibrillation patients with atherosclerosis. Am Heart J. 2008; 156: 855-863.

16. Kapwai K, Inram N, Grubb B, et al. Troponin elevation in patients with various tachycardias and normal epicardial coronaries. Indian Pacing Elect-
rophysiol J. 2008; 8: 172-174.

17. Chen LY, Leening MJ, Nfiby FL, et al. Carotid intima-media thickness and arterial stiffness and the risk of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study, Multi-Ethnic Study of Atherosclerosis (MESA), and the Rotterdam Study. J Am Heart Assoc. 2016; 5: e002907.

18. Judkins MP. Percutaneous transfemoral selective coronary arteriogra-
phy. Radiol Clin North Am. 1986; 6: 467-492.

19. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines for the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013; 34: 2949-3003.

20. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardi-
ac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Associa-
tion of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015; 16: 233-270.

21. Tarigkas G, Kippsia G, Xanthopoulou I, et al. Diagnostic accuracy of electrophysiologic ST-segment depression in patients with rapid atrial fi-
brillation for the prediction of coronary artery disease. Can J Cardiol. 2014; 30: 907-924.

22. Androuakis A, Ammoura A, Micali M, et al. Transient ST-segment depression during paroxysms of atrial fibrillation in otherwise normal indi-
viduals: relation with underlying coronary artery disease. J Am Coll Cardiol. 2007; 6: 1909-1911.

23. Mendes LA, Connelly GP, McKenney PA, et al. Right coronary artery stenosis: an independent predictor of atrial fibrillation after coronary artery bypass surgery. J Am Coll Cardiol. 1995; 25: 198-202.

24. Pradhan R, Chaudhary A, Donato AA. Predictive accuracy of ST de-
pression during rapid atrial fibrillation on the presence of obstructive coro-
nary artery disease. Am J Emerg Med. 2012; 30: 1042-1047.

25. Wierzbowska-Dražík K, Cygulska K, Cieśluk-Guerra U, et al. Circumfer-
ential strain of carotid arteries does not differ between patients with ad-
cvanced coronary artery disease and group without coronary stenoses. Adv Med Sci. 2016; 61: 203-206.

26. Abidov A, Hachamovitch R, Rozanski A, et al. prognostic implica-
tions of atrial fibrillation in patients undergoing myocardial perfusion single-
photon emission computed tomography. J Am Coll Cardiol. 2004; 44: 1062-1070.

27. Kravla S, Schneider K, Lang S, et al. Incidence and severity of coronary artery disease in patients with atrial fibrillation undergoing first-time coro-
nary angiography. PLoS One. 2011; 6: e24946.

28. Mottochet LJ, Reda S, Larbig R, et al. Characteristics of coronary artery disease among patients with atrial fibrillation compared to patients with si-
nus rhythm. Hellenic J Cardiol. 2017; 58: 204-212.

29. Morise AP, Damodar GA. Comparison of the sensitivity and specificity of exercise electrocardiography in biased and unbiased populations of men and women. Am Heart J. 1995; 130: 741-747.

30. Lopatowska P, Tomaszuk-Kasberuk A, Młodawska E, et al. Manage-
ment of patients with valvular and non-valvular atrial fibrillation in Poland: Results from Reference Cardiology University Center. Cardiol J. 2015; 22: 296-305.

31. Zimetbaum PJ, Josephson ME, McDonald MJ, et al. Incidence and pre-
dictors of myocardial infarction among patients with atrial fibrillation. J Am Coll Cardiol. 2000; 36: 1223-1227.

32. Sutton NR, Seth M, Bouveng C, et al. Outcomes of patients with atrial-
al fibrillation undergoing percutaneous coronary intervention. J Am Coll Car-
diol. 2016; 68: 895-904.

33. Lopes RD, Elliott LE, White HD, et al. Antithrombotic therapy and out-
comes of patients with atrial fibrillation following primary percutaneous coro-
nary intervention: results from the APEX-AMI trial. Eur Heart J. 2009; 30: 2019-2028.

34. Tonino PA, Fearon WF, De Bruyne B, et al. Angiographic versus func-
tional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. J Am Coll Cardiol. 2010; 55: 2816-2821.

35. Düzel B, Erenir SV, Berilgen R. Effect of atrial fibrillation on contrast-
duced nephropathy development in patients with non-ST-segment eleva-
tion myocardial infarction. Angiology. 2017; 68: 871-876.