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Authors: Michał Peller, Agnieszka Kapłon-Cieślicka, Marek Rosiak, Agata Tymińska, Krzysztof Ozierański, Ceren Eyileten, Agnieszka Kondracka, Dagmara Mirowska-Guzel, Grzegorz Opolski, Marek Postuła, Krzysztof J Filipiak

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Michał Peller[1], Agnieszka Kapłon-Cieślicka[1], Marek Rosiak[2], Agata Tymińska[1], Krzysztof Ozierański[1], Ceren Eyileten[3], Agnieszka Kondracka[4], Dagmara Mirowska-Guzel[3], Grzegorz Opolski[1], Marek Postuła[3], Krzysztof J. Filipiak[1]

[1] *1st Chair and Department of Cardiology, Medical University of Warsaw*
[2] *Department of Cardiology and Hypertension, Central Clinical Hospital, the Ministry of the Interior and Administration*
[3] *Centre for Preclinical Research and Technology (CePT), Department of Experimental and Clinical Pharmacology, Medical University of Warsaw*

Correspondence to:
Agnieszka Kapłon-Cieślicka, MD, PhD, I Katedra i Klinika Kardiologii Warszawskiego Uniwersytetu Medycznego, ul. Banacha 1a, 02–097 Warszawa, Polska; e-mail: agnieszka.kaplon@gmail.com

Abstract

Introduction: The potential effect of adipokines on the development of AF is yet to be established. The aim of this study was to investigate the association of baseline serum adipokines with 1) the presence of AF at baseline and 2) future risk of AF development.

Material and methods: The current study is a sub-analysis of the prospective, randomised AVOCADO (Aspirin Vs./Or Clopidogrel in Aspirin-resistant Diabetics inflammation Outcomes) trial. The AVOCADO study included patients with type 2 DM burdened with at least two additional cardiovascular risk factors and receiving acetylsalicylic acid. In patients included in the current analysis adipokines and inflammatory biomarker levels were measured. Information on the subsequent AF diagnosis was collected after a median of 5.4 years of follow-up.

Results: A total of 273 patients with type 2 DM (median age 68 years; 52% male) were included in the initial analysis comparing patients with and without AF at baseline. Patients with diagnosed AF (12%) had higher levels of serum resistin (8.5 [5.8–10.5] vs. 6.9 [5.6–8.7] ng/mL; p = 0.034), adiponectin (6.9 [5.6–8.7] vs. 2.7 [1.8–4.2] ng/mL; p = 0.032), and N-terminal pro-B-type natriuretic peptide (336 [148–473] vs. 108 [45–217]; p < 0.001) than non-AF patients. There were no significant differences in serum leptin, IL-6, and TNF-α concentrations between the two groups. From subjects without known AF at study entry, 19% developed AF at follow-up. In logistic regression analysis, baseline adipokine levels did not predict AF development.

Conclusion: In type 2 DM, patients with AF have higher resistin and adiponectin concentrations than patients with no AF. None of the studied adipokines proved a predictor of future AF development.

Key words: atrial fibrillation; diabetes mellitus; adipokines; resistin; adiponectin; leptin

Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias, with a prevalence of 3% among adults [1]. Due to its increasing incidence, in the coming decades we are expected to face a pandemic of AF. Diagnosis and treatment of AF are crucial to reduce the risk of thromboembolic events [2, 3]. Nowadays, the most challenging task seems to be establishing an AF diagnosis in asymptomatic patients. Therefore, many studies aim to assess risk factors of arrhythmia development and to identify subpopulations with higher risk of AF occurrence. Such subpopulations might benefit from a more rigorous screening for arrhythmia.

Diabetes mellitus (DM) is a well-known risk factor of AF development [4, 5]. Moreover, previous studies demonstrated that DM elevates the risk of thromboembolic events in patients with diagnosed AF [3]. This risk remains increased even during anticoagulation therapy [6]. Due to similar risk factors contributing to the onset of DM and cardiovascular diseases, AF is diagnosed in up to 15% of patients with DM [7]. The Framingham study revealed that DM patients have 1.6-times (male) and 1.4-times (female) higher risk of AF, irrespective of other risk factors [5]. The association between DM and AF seems to be bi-directional. This complex relation includes ionic abnormalities, myocardium hypertrophy, and autonomic nervous system disturbances.

Recent studies revealed that adipokines might play an important role in risk assessment in patients with diagnosed DM [8, 9]. Adipokines are involved in the regulation of insulin sensitivity, endothelial function, inflammatory response, and serum lipid levels [10, 11].

Although the association between DM and AF is well-proven, the potential effect of adipokines on the development of AF is yet to be established.

The aim of this study was to investigate the association of baseline serum adipokine concentrations with 1) the presence of AF at baseline and 2) future risk of AF development in type 2 DM patients. We focused on four key adipokines: two "classic" adipokines (leptin and resistin) and two inflammatory cytokines released from adipose tissue (interleukin-6 [IL-6] and tumour necrosis factor alpha [TNF-α]).

Material and methods

Study group

The current study is a sub-analysis of the prospective, randomised AVOCADO (Aspirin Vs./Or Clopidogrel in Aspirin-resistant Diabetics inflammation Outcomes) trial. The complete design of the AVOCADO trial, along with its inclusion and exclusion criteria, was described previously [12]. In brief, the AVOCADO study included patients aged between 30 and 80 years, with type 2 DM, irrespective of the type of antidiabetic treatment (with the exception of diet-only treated patients), burdened with at least two additional cardiovascular risk factors, and receiving 75 mg of acetylsalicylic acid (ASA) daily. Patients on anticoagulation or other antiplatelet regimens were excluded from the AVOCADO study. The aim of the AVOCADO trial was to assess the effect of an eight-week course of clopidogrel or an increased ASA dose (150 mg) in patients with type 2 DM and high platelet reactivity on lower ASA dose (75 mg). Patients who did not exhibit high platelet reactivity on ASA 75 mg daily continued this treatment. All laboratory assessments included in the present analysis were performed at study entry, i.e. before randomisation to clopidogrel or an increased ASA dose. Data on baseline clinical characteristics (including AF status at enrolment) were obtained during the initial visit in the AVOCADO study by interview, physical examination, electrocardiogram (ECG), and a thorough analysis of all previous medical records (including previous ECGs and Holter-ECGs, if available).

The current study included only those participants of the AVOCADO trial for whom information on baseline AF status as well as measurements of baseline leptin, resistin, IL-6, and TNF-α concentrations were available. These patients were divided into two groups: 1) patients with known paroxysmal, persistent, or permanent AF at baseline and 2) patients with no known AF at enrolment. These two groups were compared with respect to clinical and laboratory characteristics (including adipokine levels).

After a median of 5.4 years, patients with no known AF at study entry were contacted by telephone, and information on the diagnosis of AF at follow-up was collected. During the telephone call, a thorough analysis of the patient's medical documentation and current pharmacotherapy was carried out in order to establish a credible diagnosis of AF. Data on survival were obtained from the National ID Number Database. Patients who died during follow-up were excluded from the final analysis.

The AVOCADO study protocol was accepted by the Local Ethical Review Board, and every patient signed an informed consent form to participate in the study.

Laboratory assessments

All laboratory parameters were measured in blood samples collected from all subjects in the morning after overnight fasting during an outpatient visit. Haematology and biochemical parameters were measured, including complete blood count, ions, creatinine, lipid profile, glucose, glycated haemoglobin, and high-sensitivity C-reactive protein (CRP).

Additionally, in all patients included in the current analysis, leptin, resistin, IL-6, and TNF-α levels were assessed. All serum samples were stored at a temperature of –80°C before the laboratory assessment. The following kits were used for evaluation of adipokine levels: Human Leptin Quantikine ELISA Kit® (R&D Systems Inc., Minneapolis, Minnesota, United States), Human Resistin Quantikine ELISA Kit® (R&D Systems Inc.), Quantikine HS ELISA Human TNF-α Immunoassay® (R&D Systems Inc.), and Quantikine HS ELISA Human IL-6 Immunoassay® (R&D Systems Inc.). The baseline high-molecular weight (HMW) adiponectin concentration was assessed for 190 patients using Human HMW Adiponectin Quantikine ELISA Kit ® (R&D Systems Inc.).

Study endpoint

The study endpoint was AF diagnosed during the follow-up period. Only an AF diagnosis confirmed by the patient's medical documentation was considered as an endpoint.

Statistical analysis

All categorical and continuous variables were presented as percentages and median values with interquartile ranges (IQR), respectively. Continuous variables were non-normally distributed, which was calculated with the Shapiro-Wilk test. Differences between subgroups were assessed with Fisher's exact test and the Mann-Whitney U test, respectively, for categorical and continuous variables. Univariate logistic regression was used to identify

predictors of AF onset. A multivariate logistic regression model was developed including risk factors with $p < 0.1$ in univariate logistic regression. Tests were considered significant for p-values < 0.05. Statistical analysis was calculated using SAS® software, version 9.4.

Results

A total of 273 patients with type 2 DM (median age: 68 years, IQR: 61–74 years, 52% male) were included in the initial analysis comparing patients with and without AF at baseline. Complete follow-up for subjects without known AF at study entry, with a median duration of 5.4 years (IQR 4.8–5.9 years), was obtained for 171 patients. A flowchart of patient selection in the present analysis is shown in Figure 1.

Comparison of patients with and without AF at baseline

At study entry, 30 patients (11%) had known AF. Comparison between patients with and without AF at study entry revealed higher levels of serum resistin, adiponectin, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) in patients with diagnosed AF. A trend towards higher serum level of IL-6 was noted in patients with AF. There was no difference in serum leptin and TNF-α concentrations between the two groups. We observed higher prevalence of heart failure and a trend towards older age in patients with diagnosed AF compared to patients without AF. Baseline characteristics of analysed groups are presented in Table 1.

Predictors of AF development at follow-up

Out of 171 patients with no AF at baseline and a complete follow-up, AF was diagnosed in 33 (19%) patients. In univariate analysis, baseline adipokine levels did not predict AF development. We observed higher risk of AF onset in patients with a history of myocardial infarction. There were trends towards a higher risk of AF onset in patients with higher NT-proBNP concentration, a history of ischaemic heart disease, and longer DM history (Tab. II). In multivariate logistic regression analysis, only a history of myocardial infarction proved an independent risk factor of AF development (Tab. III).

Discussion

In the studied group of type 2 DM patients, serum concentrations of adipokines were not associated with future AF development. However, patients with a diagnosis of AF at

baseline had higher serum levels of resistin and adiponectin, and a trend towards higher IL-6 concentration compared with patients without known AF.

Baseline adipokine levels and future atrial fibrillation development

In contrast to our study, Ermakov at al. revealed that in a group of postmenopausal women (50–79 years-old), during over 11 years of observation, serum resistin levels were independently associated with new AF onset [13]. The authors concluded that resistin may be considered as a biomarker that partially mediates the relationship between obesity and AF. Notably, the incidence of new AF onset in the group of postmenopausal women was similar to that seen in our study (18.1% vs. 19.3%, respectively), but the duration of follow-up was twice as long. This shows that DM and other cardiovascular diseases requiring antiplatelet treatment (present in our study group) should be considered strong risk factors of AF development. So far, there are no data on resistin or its receptors as potential targets for intervention to reduce the incidence of AF.

Similar results were presented in a sub-analysis of the Framingham study [14]. During a follow-up of 7.6 ± 2.0 years new AF development was observed in 8.3% of patients. However, the effect of resistin lost significance after adjustment for CRP. The authors did not observe any relationship between serum adiponectin level and the risk of AF development.

The potential role of resistin in the pathophysiology of AF is not clear. Resistin is associated with other risk factors of AF, such as DM and coronary artery disease, but in the presented studies the effect of resistin on AF onset was observed even after adjustment for traditional risk factors of AF development. High serum resistin level may reflect increased systemic inflammatory response. Previous studies revealed strong correlation between resistin and CRP, IL-6, and TNF-α levels. Secretion of all these substances is regulated by nuclear factor-κB pathway [15]. Resistin is also related to reduced contractility and hypertrophy of cardiomyocytes [16]. Moreover, resistin is an independent risk factor of unfavourable outcome in patients with type 2 DM [17].

The effect of adiponectin and leptin on AF development has not yet been established. The study of Ermakov et. al, cited above, revealed no relationship between serum leptin level and AF development. A different study showed a strong relationship between serum leptin concentration and risk of heart failure and other cardiovascular diseases [18]. However, this effect was attenuated after adjustment for body mass index. In an animal model, leptin was involved in cardiac fibrosis [19]. This effect was not fully proven in humans. The lack of relationship between serum adiponectin level and new AF onset in our study contrasts with that

of Ermakov et al. [13]. In the whole cohort, no effect of adiponectin level on AF development was noted. However, in a subgroup of patients with treated DM, adiponectin was a strong predictor of subsequent AF diagnosis. Patients in the fourth quartile of serum adiponectin levels had an over six-fold higher risk of AF development compared with patients in the first quartile. Similarly, Macheret et al. revealed that in a group of 2376 elderly patients (mean age: 74 ± 5 years) with no chronic cardiovascular disease, higher serum adiponectin level was related to an increased risk of new AF [20]. The presented relationship contrasts with the well-described protective role of adiponectin, which is considered an anti-inflammatory and insulin-sensitising hormone [21]. This adiponectin "paradox" might be explained by possible adiponectin resistance and related to higher serum adiponectin level in older patients and in patients with diagnosed cardiovascular diseases [22, 23].

Other risk factors of atrial fibrillation development

The association of prior myocardial infarction with subsequent AF development, observed in our study, was also shown in other studies. In the analysis of 4764 Framingham Heart Study participants, after adjustment for age and gender, myocardial infarction was associated with an almost 1.5-fold higher risk of new AF onset [24]. This relationship seems to be complex and may be partially explained by a more intense inflammatory response and a higher risk of heart failure in patients with a history of myocardial infarction [25].

Adipokine levels in patients with a current diagnosis of atrial fibrillation

Despite no effect of analysed adipokines on future AF development, our study showed higher serum levels of resistin and adiponectin in patients with diagnosed AF compared with non-AF patients. In a study by Özcan et al., when compared with a control group matched for demographics and clinical characteristics, patients with AF had higher serum resistin levels [26]. In the AF group, higher serum levels of CRP were also observed. These results suggest a relationship between resistin and systemic inflammatory response. Another study showed higher serum adiponectin levels in patients with persistent AF compared with patients with paroxysmal AF and a control group [27]. This relationship might be explained by hyposensitivity of adiponectin receptors in AF patients and higher secretion of adiponectin in this group. In a study by Kim et al., higher serum adiponectin level was associated with recurrences of AF after pulmonary vein isolation [28]. This observation implies unfavourable atrial remodelling in patients with higher adiponectin levels. In our study, we observed a trend towards higher serum levels of IL-6 in patients with AF compared to patients without AF. This

finding confirms the role of inflammation in the pathogenesis of AF. Similarly, Marcus et al. analysed a group of patients with coronary artery disease and showed elevated levels of IL-6 in patients with AF compared to patients without AF [29]. Interestingly, no association between CRP and AF was found. This observation proved that inflammation affects AF development via a CRP-independent pathway. In our analysis, we did not observe differences in the levels of CRP or TNF-α between patients with and without AF. However, a previous study showed that higher TNF-α may be related to larger left atrium and involved in AF development [30]. In an animal model, TNF-α was associated with atrial fibrosis mainly through the influence on TNF-β signalling pathway [31].

Study group considerations

One of the exclusion criteria in the AVOCADO study was anticoagulation therapy. This decreased the number of patients with AF at baseline in the studied population. Nonetheless, at the time of patient recruitment to the AVOCADO study, ASA was approved for stroke prevention in moderate-risk patients (i.e. with 1 point in the $CHADS_2$ score) or in patients with contraindications to oral anticoagulation [32]. In an observational study, including over 17,000 DM patients aged between 65 and 74 years old, Nichols et al. reported AF with a prevalence of 7% [33]. Baseline AF prevalence in our study was 11%. Importantly, despite differences in resistin and adiponectin concentrations, we observed comparable values of body mass index and waist-hip ratio in patients with and without AF at baseline.

Study limitations

An important limitation of our analysis is that the AVOCADO study was primarily designed to assess laboratory response to antiplatelet treatment, which affected baseline characteristics of the study population. Secondly, the analysed group was quite heterogenous, with an interquartile range of DM duration ranging from 3 to 15 years, and with a wide spectrum of antidiabetic and cardiovascular pharmacological regimens. Furthermore, a larger study group and a longer follow-up might have revealed possible associations between adipokine levels and the risk of subsequent AF development. Almost 17% of patients were lost to follow-up. Finally, our analysis was based on a currently known diagnosis of AF (and in follow-up, this information was obtained from the patients via telephone). No additional tests, such as Holter ECG monitoring, were used to detect asymptomatic AF episodes. This might have resulted in a false classification of some patients with silent AF as non-AF patients.

Conclusion

In type 2 DM, patients with AF have higher resistin and adiponectin concentrations than patients with no AF. Among patients with no AF at baseline who survived to follow-up, one in five developed AF at five years. In this group, none of the studied adipokines proved to be a predictor of future AF development.

Key messages

Patients with a diagnosis of atrial fibrillation (AF) at baseline had higher serum levels of resistin and adiponectin compared with patients without known AF.

In the studied group of type 2 diabetes mellitus patients, serum concentrations of adipokines were not associated with future AF development

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Author contributions

M.Pe. and A.K.-C. designed the present study and conducted data analysis and interpretation. M.Pe. and A.K.-C. wrote the manuscript. A.K.- C., A.T., M.Po., M.R., K.O., C.E. conducted data research. M.Pe. performed statistical analysis. A.K. performed laboratory tests. D. M.-G., M.Po., K.J.F., and G.O. designed the AVOCADO study. All authors reviewed the manuscript and approved its final version.

Author disclosures

Conflicts of interest: None.

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Figure 1. Flowchart of subgroups selection. AF — atrial fibrillation; DM — diabetes mellitus; pts — patients

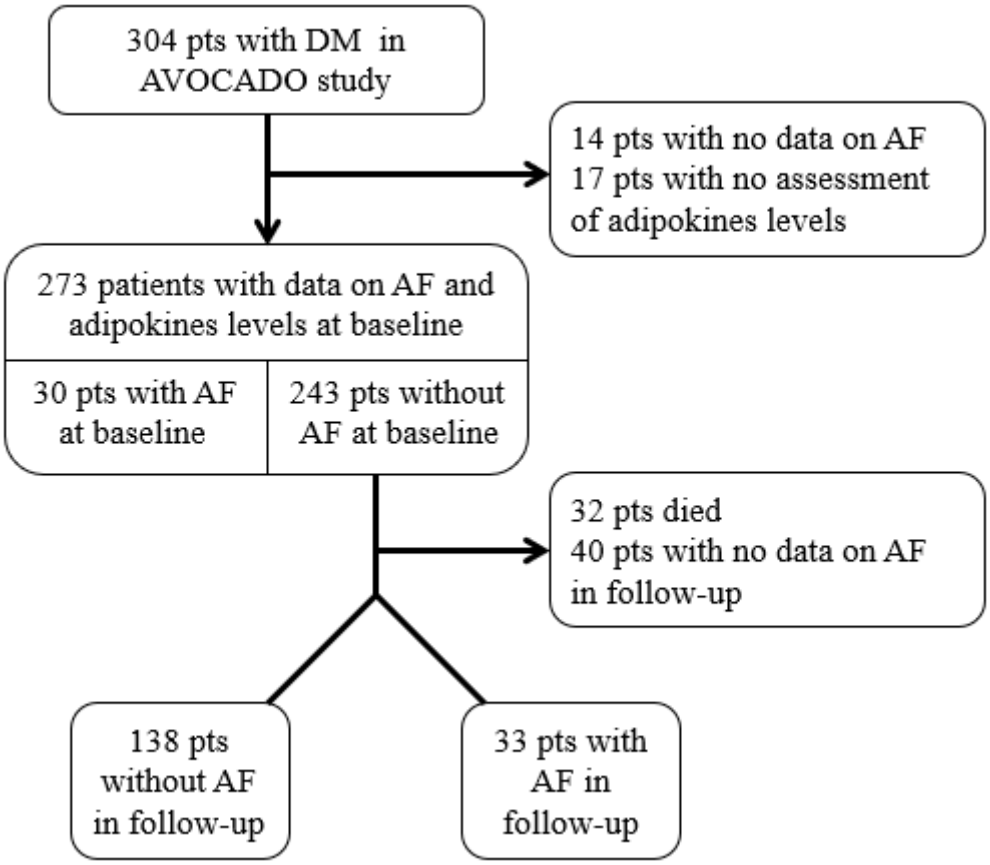

Table I. Baseline characteristics of patients with and without atrial fibrillation (AF) at study entry

	Total (n = 273)	**No AF at baseline (n = 243)**	**AF at baseline (n = 30)**	**p-value**
Demographics				
Age [years]	68 (61–74)	68 (60–74)	71 (64–76)	0.08
Male	52%	52%	53%	1.00
Clinical assessment				
Body mass index [kg/m^2]	30.3 (27.1–33.1)	30.3 (27.1–33.1)	30.2 (26.8–33.0)	0.73
Waist–hip ratio	0.97 (0.91–1.03)	0.97 (0.91–1.03)	0.96 (0.90–1.01)	0.38
Systolic blood pressure [mmHg]	140 (130–150)	140 (130–150)	138 (120–155)	0.29

Diastolic blood pressure [mmHg]	80 (70–86)	80 (70–86)	80 (70–86)	0.43
Heart rate [beats/min]	70 (65–78)	72 (65–79)	70 (64–71)	0.053
Medical history				
Diabetes mellitus duration [years]	8 (3–15)	8 (3–15)	6 (2–14)	0.24
Diabetes mellitus treated with oral antidiabetic drugs	86%	86%	90.0%	0.80
Metformin	61%	62%	50.5%	0.24
Diabetes mellitus treated with insulin	29%	30%	20.0%	0.29
Hypertension	93%	93%	93%	1.00
Ischaemic heart disease	55%	55%	53%	0.85
Dyslipidaemia	82%	83%	73%	0.21
Prior myocardial infarction	30%	30%	37%	0.53
Chronic heart failure	37%	35%	55%	0.042
Prior ischaemic stroke	7.0%	6.6%	10%	0.45
History of smoking	57%	58%	53%	0.70
Laboratory findings				
White blood cells [1000/mcL]	6.7 (5.7–7.8)	6.7 (5.8–7.7)	6.8 (5.4–9.3)	0.66
Haemoglobin [g/dL]	13.9 (13.0–14.7)	13.9 (13.0–14.8)	14.0 (13.1–14.4)	0.87
Estimated glomerular filtration rate [ml/min/1.73 m^2]	69.2 (56.6–83.7)	69.5 (56.7–84.9)	65.6 (54.8–77.3)	0.37
Sodium [mmol/L]	141.2 (139.1–142.9)	141.1 (138.8–142.9)	142.1 (140.3–142.9)	0.07
Potassium [mmol/L]	4.5 (4.2–4.7)	4.4 (4.2–4.7)	4.5 (4.2–4.6)	0.95
Total cholesterol [mg/dL]	160 (139–186)	161 (140–186)	158 (134–198)	0.75
Low-density lipoprotein [mg/dL]	85 (65–107)	85 (66–106)	79 (63–116)	0.94

High-density lipoprotein [mg/dL]	47 (39–56)	47 (39–56)	46 (40–57)	1.00
Triglycerides [mg/dL]	123 (91–164)	124 (92–165)	114 (89–153)	0.48
Glycated haemoglobin (%)	6.6 (6.1–7.6)	6.7 (6.2–7.7)	6.4 (5.7–7.1)	0.018
Leptin [ng/mL]	18.0 (9.4–32.4)	18.0 (9.4–32.4)	18.8 (7.8–36.0)	0.93
Resistin [ng/mL]	7.0 (5.6–9.0)	6.9 (5.6–8.7)	8.5 (5.8–10.5)	0.034
Adiponectin [ng/mL]	2.9 (1.9–4.4) [n = 190]	2.7 (1.8–4.2) [n = 167]	3.6 (2.7–6.0) [n = 23]	0.032
Tumour necrosis factor alpha [pg/mL]	1.8 (1.2–2.3)	1.8 (1.2–2.3)	2.0 (1.3–2.5)	0.39
Interleukin-6 [pg/mL]	2.4 (1.5–4.2)	2.3 (1.5–4.0)	3.3 (1.6–5.4)	0.09
High sensitivity C-reactive protein [mg/L]	2.6 (1.4–4.5)	2.6 (1.5–4.5)	3.1 (1.3–5.0)	0.74
N-terminal pro-B-type natriuretic peptide [pg/mL]	117 (53–252)	108 (45–217)	336 (148–473)	< 0.001
Concomitant medications				
Beta-blockers	73%	71%	86%	0.12
Angiotensin-converting enzyme inhibitors	66%	67%	52%	0.10
Calcium channel blockers	39%	41%	24%	0.10
Nitrates	5.9%	5.0%	14%	0.08
Loop diuretics	17%	16%	32%	0.038
Thiazide diuretics	7.4%	7.0%	10%	0.46
Indapamide	29%	30%	17%	0.19
Mineralocorticoid receptor antagonists	5.9%	5.8%	6.9%	0.68
Angiotensin receptor blockers	20%	19%	28%	0.32
Statins	73%	74%	73%	1.00
Fenofibrate	13%	13%	14%	1.00
Digoxin	1.5%	0.8%	6.9%	0.06

Table II. Univariate logistic regression analysis of predictors of atrial fibrillation development at follow-up

	OR (95% CI)	**p-value**
Demographics		
Age [per 10 years]	1.07 (0.69–1.67)	0.759
Male	0.89 (0.42–1.90)	0.760
Clinical assessment		
Body mass index [per kg/m^2]	1.02 (0.94–1.11)	0.618
Waist-hip ratio [per 0.1]	1.31 (0.87–1.97)	0.198
Systolic blood pressure [per 10 mmHg]	0.91 (0.74–1.11)	0.346
Diastolic blood pressure [per 10 mmHg]	0.79 (0.57–1.10)	0.162
Heart rate [per 10 beats/min]	0.77 (0.52–1.15)	0.203
Medical history		
Diabetes mellitus duration [per 10 years]	1.44 (0.98–2.12)	0.065
Diabetes mellitus treated with oral antidiabetic drugs	0.47 (0.16–1.34)	0.158
Diabetes mellitus treated with insulin	1.14 (0.50–2.63)	0.751
Hypertension	0.79 (0.21–3.06)	0.737
Ischaemic heart disease	2.00 (0.90–4.44)	0.089
Dyslipidaemia	0.50 (0.20–1.23)	0.144
Prior myocardial infarction	3.52 (1.60–7.75)	0.002
Chronic heart failure	1.56 (0.72–3.43)	0.253
Prior ischaemic stroke	1.28 (0.33–4.94)	0.720
History of smoking	1.12 (0.51–2.42)	0.783
Laboratory findings		
White blood cells [per 1000/mcL]	1.11 (0.92–1.35)	0.281
Haemoglobin [per g/dL]	0.81 (0.61–1.09)	0.162
Estimated glomerular filtration rate [per 10 ml/min/1.73 m^2]	1.03 (0.86–1.22)	0.786
Sodium [per mmol/L]	0.89 (0.78–1.03)	0.108
Potassium [per mmol/L]	0.60 (0.24–1.48)	0.268
Total cholesterol [per 10 mg/dL]	0.96 (0.86–1.07)	0.477

Low-density lipoprotein [per 10 mg/dL]	0.97 (0.85–1.11)	0.668
High-density lipoprotein [per 10 mg/dL]	0.89 (0.66–1.20)	0.441
Triglycerides [per 10 mg/dL]	1.03 (0.97–1.08)	0.322
Glycated haemoglobin [per %]	1.20 (0.91–1.59)	0.201
Leptin [per ng/mL]	0.99 (0.97–1.02)	0.535
Resistin [per ng/mL]	1.07 (0.96–1.20)	0.199
Adiponectin [ng/mL]	0.94 (0.74–1.12)	0.597
Tumour necrosis factor alpha [per 0.1 pg/mL]	1.02 (0.99–1.05)	0.160
Interleukin-6 [per 0.1 pg/mL]	1.01 (0.99–1.02)	0.224
High sensitivity C-reactive protein [per mg/L]	1.03 (0.98–1.09)	0.228
N-terminal pro-B-type natriuretic peptide [per 100 pg/mL]	1.10 (0.99–1.22)	0.077

OR — odds ratio; CI — confidence interval

Table III. Multivariate logistic regression analysis of predictors of atrial fibrillation development at follow-up

	OR (95% CI)	**p-value**
Diabetes mellitus duration [per year]	1.02 (0.98–1.06)	0.342
Ischaemic heart disease	1.06 (0.38–2.94)	0.911
Prior myocardial infarction	3.11 (1.16–8.34)	0.025
N-terminal pro-B-type natriuretic peptide [per 100 pg/mL]	1.08 (0.92–1.33)	0.158

CI — confidence interval