

Research Article

Control of arterial hypertension and risk of new-onset of atrial fibrillation in patients with metabolic syndrome

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Abstract

Background: An association between Atrial Fibrillation (AF) and Metabolic Syndrome (MS) a constellation of abnormalities (high blood pressure, hyperglycemia, dyslipidemia, and abdominal obesity), has been demonstrated. There have been many studies that have shown that elevated blood pressure (BP), was significantly associated with an increased risk of AF. It is uncertain whether maintaining the optimal BP levels can prevent AF in the patients with MS categorized as 'high-risk' patients.

Objective: The aim of this study was to evaluate the influence of control of BP on the occurrence of new-onset atrial fibrillation in patients with Metabolic Syndrome.

Methods: Into this observational study, was enrolled 435 consecutive patients (210 males and 225 females) aged 45-79 years who fulfilled criteria for MS. Participants were selected among primary and secondary care patients, who were receiving ongoing care for arterial hypertension in the period from November 2018 till November 2021. The study was conducted at outpatients in 5 Health Care Clinics (3 Secondary Health Care Clinics and 2 Primary Health Clinics). Patient were categorized according to their BP levels as Group 1-patients with controlled BP, {(patients aged < 65 years Systolic Blood Pressure (SBP) of 120 - 130 mmHg, patients aged ≥ 65 years SBP of 130 - 139 mmHg)} and Diastolic Blood Pressure (DBP), {(patients aged < 65 years of < 80 mmHg, but not < 70 mmHg; patients aged ≥ 65 years of 85 - 89 mmHg)}, or Group 2-patients with uncontrolled BP (> 130/80 mmHg), and in patients aged ≥ 65 years BP (≥ 140/90 mmHg).

Results: New-onset of AF, was more frequent in participants with uncontrolled BP, respectively (34.7% vs. 19.5%, $p = 0.009$). Patients with uncontrolled BP have more frequent persistent AF (15.2% vs. 0.04%) and permanent AF (0.08% vs. 0.02%), whereas there was not significant changes between groups in relation to frequency of paroxysmal AF, respectively (12.8% vs. 10.9%, $p = 0.29$). There was observed significant association of uncontrolled BP with: increased frequency of AF (OR = 2.193; 95% CI 1.390 - 3.439), persistent AF (OR = 3.931; 95% CI 1.771 - 8.084), permanent AF (OR = 4.138; 95% CI 1.383-12.381), LA. Dimension ≥ 2.2 cm/m² (OR = 2.089, 95% CI 1.330 - 3.252), BMI (OR = 5.226, 95% CI 3.155 - 8.659) and 5-risk factors for MS, respectively (OR = 2.998, 95% CI 1.833 - 4.901).

Conclusion: Optimal BP levels, can reduce the frequency of new-onset AF in patients with MS categorized as 'high-risk' patients. Uncontrolled BP was associated with an increased risk of both subtypes of AF (persistent and permanent) in the patients with MS categorized as 'high-risk' patients.

More Information

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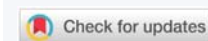
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Keywords: Controlled blood pressure; Metabolic syndrome and atrial fibrillation

Abbreviations: MS: Metabolic Syndrome; BW: Bodyweight; BH: Body Height; BMI: Body Mass Index; BP: Blood Pressure; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; T2DM: Diabetes Mellitus Type 2; WCI: Waist Circumference; LDL.Chol.: Serum Low-Density Lipoprotein Cholesterol; HDL-C: Serum High-Density Lipoproteins Cholesterol; TG: Serum Triglycerides; AF: Atrial Fibrillation; LVEF: LV Ejection Fraction; LAVI: Left Atrial Volume Index; ESC: European Society of Cardiology; ASE: American Society of Echocardiography





Background

Atrial fibrillation (AF), the most common arrhythmia, is a medical problem of increasing prevalence often associated with multiple comorbidities and adverse outcomes [1]. An association between AF and Metabolic Syndrome (MS) a constellation of abnormalities (high blood pressure, hyperglycemia, dyslipidemia, and abdominal obesity), has been demonstrated [2-4]. AF appears to be more closely related to a specific component of MS compared with others [5]. There have been many studies that have shown that elevated BP was significantly associated with an increased risk of AF [6]. According to new findings [7], strong evidence of a causal relationship between blood pressure (BP) and AF has been found. High BP can directly lead to AF, establishing that elevated BP causes AF, provides further impetus for public health strategies aimed at improving BP control [7]. It is not clear whether the risk of AF increases linearly with BP or whether there is a BP threshold above which the risk of this condition definitely increases [8], also it is uncertain whether maintaining the optimal BP levels can prevent AF in the patients with MS [9,10] categorized as 'high-risk' patients. We sought to test the hypothesis that: optimal BP levels can reduce the frequency of new-onset AF in the patients with MS categorized as 'high-risk' patients.

Objective

The aim of this study was to evaluate the influence of control of blood pressure on the occurrence of new-onset atrial fibrillation in patients with Metabolic Syndrome.

Material and methods

Into this observational study, was enrolled 435 consecutive patients (210 males and 225 females) aged 45-79 years who fulfilled the criteria for MS [11]. Participants were selected among primary and secondary care patients, who were receiving ongoing care for arterial hypertension in the period from November 2018 till November 2021. The study was conducted at outpatients in 5 Health Care Clinics (3 Secondary Health Care Clinics and 2 Primary Health Clinics).

Subjects with: AF and other cardiac arrhythmias at baseline, secondary hypertension, those on hemodialysis, congenital and acquired valvular heart disease, left/right bundle branch block, pre-excitation syndrome, patients with a pacemaker, patients treated with drugs that prolong QT-interval, were excluded.

All the patients underwent medical history, clinical and anthropometric evaluation, the survey obtained data on age, gender, and calculated body mass index (BMI) as weight (kg) divided by the square of the height (m^2). Weight was measured with weight balance scales and height with a stadiometer. Waist circumference (WCi) was reported in cm. All participants in the study were subjected to a resting external electrocardiogram (ECG with Lab. version 3.0).

Routine laboratory tests from blood samples the value of glycemia, creatinine, electrolyte (Na^+ , K^+ , Ca^+), lipid status: total cholesterol (TC), LDL-cholesterol, HDL-cholesterol, Triglycerides (TG), in the morning post 12-hour fasting period were determined.

Metabolic Syndrome, was defined according to the harmonized definition of the International Diabetes Federation and other organizations [12]. On the basis of the baseline examination, the metabolic syndrome was diagnosed when at least 3 of the following criteria were met.

- (1) Central adiposity {Waist circumference (WC)} > 102 cm in men and > 88 cm in women);
- (2) Serum HDL-C < 50 mg/dL in women or < 40 mg/dL in men;
- (3) Serum triglyceride levels > 150 mg/dL;
- (4) Arterial hypertension or use of antihypertensive drugs;
- (5) The presence of diabetes mellitus (DM) or use of anti-diabetic drugs [13].

Office BP measurements, Measuring of blood pressure according to standard protocol [14]. Clinic systolic (SBP) and diastolic (DBP), were recorded by a physician using a mercury sphygmomanometer and appropriate-sized cuffs. The BP was determined with the individual sitting for at least 5 min. The individuals had not smoked or taken any coffee, tea, or alcohol for at least 3 h, nor had they undertaken any physical exercise for half an hour before the BP measurements were taken. Measurements were performed in triplicate, 2 min apart, and the mean value was used as the BP for the visit. The mean SBP and mean (DBP) recorded during the study period were calculated. According to guidelines of ESC/ESH [14], SBP was target to (120 - 130 mmHg) and in older patients (aged ≥ 65 years aged) to target 130 - 139 mmHg), to target the DBP (< 80 mm Hg. but not < 70 mmHg).

Patients were categorized according to their BP levels as Group 1-patients with controlled BP (SBP of 120 - 130 mmHg, patients aged ≥ 65 years SBP of 130 - 139 mmHg and DBP of < 80 mmHg. but not < 70 mmHg; aged ≥ 65 years of 85 - 89 mmHg), or Group 2-patients with uncontrolled BP (>130/80 mmHg).and in patients aged ≥ 65 years BP ($\geq 140/90$ mmHg).

Echocardiography

Left atrial (LA) and left ventricular (LV) measurements and calculation of LV mass were made according to standardized methods [15]. LA diameter (cm) was indexed by body surface area (m^2), and LA enlargement was defined as LA diameter/body surface area ≥ 2.2 cm/ m^2 [16]. LV ejection fraction was calculated using the Teichholz formula or the Simpson rule and defined as low when it was < 50% [15]. LV mass was indexed by height and LV hypertrophy was defined as LV mass/height > 50 g/m in men and > 47 g/m in women [17].

Follow-up

Subjects were followed-up in outpatient clinics. The occurrence of the event, that is AF, was recorded during follow-up visits. Data were collected by the authors of this study. Those reviewing the endpoint were blinded to other patients' data. In this report, we evaluated the occurrence of new-onset AF, either paroxysmal, persistent, or permanent, in patients with baseline sinus rhythm. AF was documented by ECG performed at follow-up visits or the time of hospitalization. Each ECG was evaluated by two independent cardiologists. The incidence date of AF was defined as the date of the first ECG showing AF.

The study was conducted in agreement with the Declaration of Helsinki. Informed written consent was given by all participants before they were enrolled in the study.

Statistical analysis

A statistical software program ((SPSS 19.0), was applied for the statistical analysis. Results are expressed as mean and \pm SD, or as a percentage. A simple descriptive analysis was performed for the general characterization of the sample and distribution of variables. The distribution of variables was tested for normality using the Kolmogorov-Smirnov test, and the heterogeneity of variances was evaluated by Levene's test. To compare baseline characteristics and findings between groups, we used Student's unpaired t - test for continuous data, Mann-Whitney U - test for continuous data with abnormal distribution, and χ^2 - test for categorical data. The association between variables was analyzed using logistic regression. Odds Ratio (OR) and 95% confidence interval (CI) were estimated by logistic regression. A p - value < 0.05 was considered statistically significant for a confidence interval of 95%.

Results

According to control of Blood Pressure, in patients

with MS, there were no significant changes in relation to baseline characteristics. Data are presented in Table 1. Echocardiographic data of cardiac structure and function according to control of BP, are presented in Table 1A. There were no significant changes between groups in relation to left ventricular dimensions and ejection fraction, however, in relation to LVMI, there was a significant difference. Participants who had uncontrolled BP had higher LVMI than participants with controlled BP, respectively (53.6 ± 12.1 vs. 49.1 ± 7.4 , $p = 0.03$). Also participants with uncontrolled BP, have increased LA Dimension ($LA \geq 2.2$ cm/m²): (36% vs. 20% $p = 0.006$).

New-onset of AF, was more frequent in participants with uncontrolled BP, respectively (34.7% vs. 19.5%, $p = 0.009$). Patients with uncontrolled BP have more frequent persistent AF (15.2% vs. 0.04%) and permanent AF (0.08% vs. 0.02%), whereas there was not significant changes between groups in relation to frequency of paroxysmal AF, respectively {(12.8% vs. 10.9%, $p = 0.29$), (Table 2, Figures 1,2)}.

Association of uncontrolled blood pressure with: Frequency of AF, Type of AF (persistens and permanent), association of AF with features of cardiac structures (LA. Dimension, ≥ 2.2 cm/m²); BMI, number of risk factors for Metabolic Syndrome, are presented in Table 3. There was observed significant association of uncontrolled BP with: increased frequency of AF (OR = 2.193; 95% CI 1.390 - 3.439), persistent AF (OR = 3.931; 95% CI 1.771 - 8.084), permanent AF (OR = 4.138; 95% CI 1.383 - 12.381), LA. Dimension ≥ 2.2 cm/m² (OR = 2.089, 95% CI 1.330 - 3.252), BMI (OR = 5.226, 95% CI 3.155 - 8.659) and 5-risk factors for MS, respectively (OR = 2.998, 95% CI 1.833 - 4.901).

Discussion

In the present study, we demonstrated that the participants with MS and uncontrolled BP, have a 34,7% increase in the

Table 1: Baseline characteristics of patients with MS (n.435), according to control of Blood Pressure.

Variables		MS (N.435)						p - value
		Gr. with controlled B.P. (n- 179)			Gr. with uncontrolled B.P. (n. 256)			
		N. (%)	Mean	\pm SD	N. (%)	Mean	\pm SD	
Gender.	Females	79(42.2)			146(57.8)			0.1
	Males	100(57.8)			240(42.2)			0.1
Age (year)			62.6	± 6.9		63.3	± 5.0	0.9
Age (year)	> 65	99(55.3)			157(61.0)			0.5
	< 65	80(44.6)			99(38.6)			0.4
BMI (kg/m ²)			26.6	± 3.7		26.85	± 4.6	0.6
SBP (mmHg)			128.1	± 6.2		155.4	± 7.3	0.000
DBP (mmHg)			81	± 4		98.7	± 2.9	0.000
T2DM (presence)		148(79.1)			215(83.9)			0.9
WCi (presence)		140(78.2)			205(88)			0.8
HDL-chl (presence)		136(75.9)			189(73.8)			0.7
TG (presence)		125(69.8)			185 (72.2)			0.8
No. of measures BP.			16.3	± 1		16.8	± 2	0.6
Three MS risk factor		75(41.8)			80(31.2)			0.1
Four MS risk factor		65(36.3)			132(51.5)			0.05
Five MS risk factor		40(22.3)			45(17.5)			0.3

SPB: Systolic Blood Pressure; DPB: Diastolic Blood Pressure; T2D: Diabetes Mellitus; WCi: Weist Circumference; HDL-Chol: High-Density Cholesterol; TG: Triglycerides; No BP: Number of Measures Blood Pressure during the followed period; MS risk factors: Number of a risk factor for Metabolic Syndrome; Three, Four, Five (risk factors for MS).

Table 1A: Echocardiographic data of cardiac structure and function according to control of Blood Pressure.

Variables	Gr. with controlled B.P. (n.179)	Gr. with uncontrolled B.P. (n.256)	p - value
LA. Dimension (cm).	2.1 ± 1.7	2.3 ± 3.0	0.7
LA ≥ 2.2 cm/m ² ; (n;%)	36(20)	93(36)	0.006
LVEF,%	65 ± 0.5	67 ± 0.8	0.4
LVFS,%	37 ± 2.3	38 ± 0.4	0.7
EDD(cm)	4.83 ± 0.4	4.86 ± 0.3	0.7
ESD(cm)	2.8 ± 0.3	2.9 ± 0.6	0.6
THS(cm)	1.2 ± 2.5	1.3 ± 2.7	0.05
THPW(cm)	1.1 ± 0.5	1.1 ± 0.2	0.9
LVMI(g/m ²)	49.1 ± 7.4	53.6 ± 12.1	0.03

LA: Dimension; LA ≥ 2.2 cm/m² Dimension/m²; LVEF%: Left Ventricular Ejection Fraction; LVFS: Left Ventricular Fraction of Shortening; EDD: End Diastolic Dimension of Left Ventriculi; ESD: End Systolic Dimension of Left Ventriculi; THS: Thickening of the Septum; TPW: Thickening of the Posterior Wall; LVMI: Left Ventricular Mas/Index.

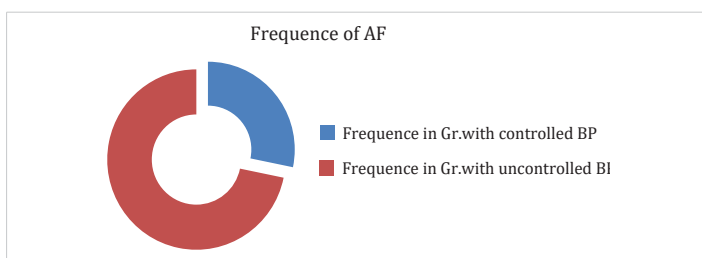
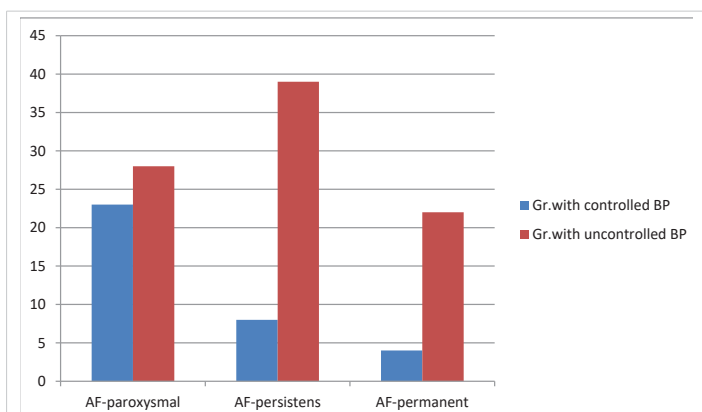
Table 2: Frequency and type of Atrial Fibrillation according to control of Blood Pressure.

Variables	Study Groups. (N.435)		p
	Gr. with controlled B.P. (N. 179)	Gr. with uncontrolled B.P. (N. 256)	
AF(No; %)	35(19.5)	89(34.7)	0.009
AF-paroxysmal (No; %)	23(12.8)	28(10.9)	0.29
AF-persistsens (No; %)	8(0.04)	39(15.2)	0.001
AF-permanent (No; %)	4(51.4)	22(30.9)	0.009

AF: Atrial Fibrillation; BP: Blood Pressure.

Table 3: Logistic Regression Model. Association of uncontrolled blood pressure with Frequency of AF, Type of AF (paroxysmal, persistent, and permanent). Association of AF with features of cardiac structures (LA. Dimension, ≥ 2.2 cm/m²).

characteristics: uncontrolled BP	OR	Significance	95% CI for Exp (B)	
			Lower	Upper
Frequency of AF	2.193	.000	1.390	3.439
Persistent AF	3.931	.000	1.771	8.094
Permanent AF	4.138	.000	1.383	12.381
LA.Dimension	2.089	.000	1.330	3.252
N.5-MS.RF	2.998	.000	1.833	4.901
BMI	5.226	.000	3.155	8.659

**Figure 1:** Frequency of Atrial Fibrillation according to control of Blood Pressure.**Figure 2:** Frequency of type of Atrial Fibrillation according to control of Blood Pressure.

frequency of new-onset of AF. Frequency that is significantly higher than among participants with MS and controlled BP. Results that confirmed our hypothesis and highlight the importance of optimal BP control to prevent AF in participants with MS categorized as 'high-risk' patients.

The link between blood pressure and atrial fibrillation in a patient with MS is not simply, furthermore AF appears to be more closely related to specific components of MS compared with others, however, elevated blood pressure was the most important contributor [18]. Recently, Georgios Georgiopoulos and co-authors [19], found that elevated blood pressure was associated with a heightened risk of AF. When a patient's systolic blood pressure rises just 1 mmHG, for instance, it was associated with a 1.8% relative increase of developing AF. The same increase in a patient's diastolic blood pressure is associated with a 2.6% relative increase. In our study, the results indicated that the participants with MS and uncontrolled BP, have a 34.7% increased rate of incident AF. It was consistent with the previous study demonstrating the relationship between arterial hypertension and incidence of AF [18]. However, in the present study, we had a much shorter follow-up time (a median of 4 years) and participants were with MS, while the previous surveyes [18-20], had a much longer follow-up time, and participants were without MS.

Previous studies demonstrate an epidemiological association between hypertension and increased risk of AF, however, it is not clear whether the risk of AF increases linearly with BP or whether there is a BP threshold above which the risk of this condition definitely increases [21,22]. Thus, the majority of clinical studies showed a direct and linear relation between BP levels and the risk of AF. Moreover, our aim was different, resulting in different patient classifications. Also, it is uncertain whether Standart (SBP < 140 mmHg) or intensive control of BP (SBP < 120 mmHg), reduces the risk of subsequent AF in hypertensive patients with MS, categorized as 'high-risk' patients. Thus, the most effective BP target in these patients is unknown. In the previous study by Verdecchia, and co-authors [9], demonstrate that the risk of new-onset AF was reduced in the intensive BP (SBP < 120 mmHg) lowering group, compared to the standard BP (SBP < 140 mmHg) lowering group with hypertension and diabetes [23]. Chen, and co-authors demonstrated that the intensive therapy group (target SBP < 120 mm Hg) did not show statistical significance with respect to the incidence of AF in patients with hypertension and diabetes [24]. Yet the current BP guidelines, including the recently released US guidelines [14,25], did not recommend more aggressive blood pressure targets for AF prevention. Based on epidemiological evidence, this suggestion might sound quite reasonable.

Previous studies have shown that hypertension promotes the progression from paroxysmal AF to more sustained forms of the disease [26]. Our study adds to this by showing the risk of developing different subtypes of AF in a population without AF at baseline. In our study, we found that the frequency of



persistent and permanent subtypes of AF was significantly increased in participants with uncontrolled BP. Longitudinal studies examining the association between blood pressure and AF subtypes are sparse [27,28].

Several pathophysiologic mechanisms could explain the relationship between HT and AF. Chronic exposure of the heart to elevated blood pressure leads to mechanical and electrical changes in LA anatomy and function that, over time, promote AF through a variety of electrophysiological mechanisms, some of which are unclear [29]. In the present study, we found a significant association of increased dimension of LA, LVMI, and: frequency of AF and subtype of AF (persistent and permanent AF), in participants with uncontrolled BP. Similar results have been found by other authors [30-32]. A recent study by Larsson SC and co-authors reported that Arterial Hypertension and AF share the same pathogenic factors. Higher BMI and a particularly fat mass index were associated with an increased risk of both HT and AF [33]. In our study, we found a significant association between increased BMI and increased frequency of AF in a patient with uncontrolled BP.

Future directions: Arterial Hypertension is the most common modifiable risk factor for atrial fibrillation, this indicates that optimal BP control, could be an effective strategy to stop AF and its complications.

Limitations

There are several limitations to our study. First, the cross-sectional design precludes the assessment of causal relationships between control of BP and AF. In spite of this, based on the epidemiology data and Mendelian randomization causality research, we believe the causality to HT and AF.

Second, the ascertainment of AF is not perfect, It is identified by ECGs performed during the examination, so the true prevalence of AF is probably higher than that indicated by the present study because prolonged electrocardiographic monitoring may detect clinically silent AF in a variable proportion of subjects who present in sinus rhythm, it may miss the paroxysmal AF, resulting in a lower AF incidence in the present study.

Third, the partial ability of clinic BP to detect real BP status/control unlike ambulatory BP might be helpful in order to find the best strategy to prevent AF in a patient with MS and uncontrolled BP.

Conclusion

We proved the hypothesis that optimal BP levels can reduce the frequency of new-onset AF in the patients with MS categorized as 'high-risk' patients. Uncontrolled BP was associated with an increased risk of both subtypes of AF (persistent and permanent) in the patients with MS categorized as 'high-risk' patients. These findings should clinicians encourage and prioritize blood pressure control in patients at high risk for new-onset atrial fibrillation as an effective strategy to reduce this common arrhythmia.

Declarations

Consent to participate: All patients were written informed, consent was obtained from all participating patients before they were enrolled in the study.

A local ethics committee ruled that no formal ethics approval was required in this particular case.

Authorship contributions

Concept: Ylber Jani, Design-Bekim Pocesta; *Supervision:* Atila Rexhepi; *Materials:* Fatmir Ferati, Agim Zeqiri; *Kastriot Haxhirexha;* *Data collection/processing:* Ylber Jani, Sotiraq Xhunga, Artur Serani, Ferizat Haxhirexha; *Analysis/interpretation:* Ylber Jani, Atila Rexhepi, Ahmet Kamberi; *Literature Search:* Fatmir Ferati, Ylber Jani, Artur Serani; *Critical Reviews:* Ahmet Kamberi, Atila Rexhepi, Lutfi Izeiri.

All authors read and approved the final manuscript.

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Conflict of interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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