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ORIGINAL ARTICLE

Combined hypotensive treatment with ≥ 3 hypotensive drugs in patients with recurrent atrial fibrillation and arterial hypertension ensures more effective arrhythmia control than using less drugs

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Abstract

Background: Combined arterial hypertension (AH) therapy ensures the effectiveness of treatment and improves haemodynamic parameters of cardiac function.

Aim: The evaluation of therapeutic regimens in the prevention of recurrence of atrial fibrillation (AF) episodes in hypertensive patients with paroxysmal/persistent forms of AF.

Methods: Prospective observation included patients (n = 164), without and with AH, grade I and II, with paroxysmal (51.3%) or persistent (48.7%) recurrent form of arrhythmia. Mean duration of AF was 4.0 years, (Q1:2; Q3:7). The anti-arrhythmic drugs were ineffective in prevention of AF episodes or non tolerated and were not used. In all patients precise control of blood pressure (BP) was implemented: patients were treated with beta-blockers: 100%; ACE-I: 65%, spironolactone: 47%, thiazide diuretics: 34%, loop-diuretics: 7%, calcium antagonists: 26.5% and alpha-blockers: 14.5%. Evaluation of symptomatic and confirmed AF episodes was performed every 3 months during 1-year follow-up.

Results: AH, grade I and II, was diagnosed in 115, 75%, of patients; (74% men, mean age 65.5 ± 9.7 years). Persistent form of arrhythmia was more frequent in patients with AH: 83% in comparison with patients without AH: 67% ($p < 0.05$). BP values were similar in normotensive and hypertensive patients after completing the study: 123 ± 9/79 ± 4 vs. 124 ± ± 10/80 ± 0.5 mm Hg. One hypotensive drug was used in 6 patients, 2 drugs in 38 patients, 3 in 37, 4 in 27, 5 in 7. Patients treated with ≥ 3 drugs had more AF episodes in 3 months prior to evaluation: 4.7 ± 0.8 vs. 2.9 ± 0.4, $p = 0.0444$. But during 1-year follow-up, observed in 3-months periods, they had significant reduction in every 3-months period, $p = 0.0001$. Patients treated with 1–2 drugs had significant reduction after 3 months: $p = 0.0029$, 6 months: $p = 0.04$ and 12 months: $p = 0.0012$, but not after 9 months.

Conclusions: AH promotes more advanced AF forms occurrence. Combined hypotensive therapy with minimum 3 drugs, including RAA inhibitors, may be effective in terms of BP control and reduction of arrhythmia episodes.

Key words: atrial fibrillation, arterial hypertension, pharmacotherapy

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INTRODUCTION

The effective management of cardiovascular disease and the extending life-span of patients, promote the occurrence of atrial fibrillation (AF). Arrhythmia is diagnosed in 10% (5–15%) of octagenarians and in 1–2% of the general population [1]. Currently arterial hypertension (AH) is becoming increasingly recognised as an important AF risk factor, also because of its high prevalence. In the Euro Heart Survey on Atrial Fibrilla-

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tion, the age of the patients with AF was 64–71 years, and AH occurred in 62–66% of the patients [2]. In the Polish part of the RecordAF registry, including patients with newly diagnosed AF, aged 63 ± 12 (range 22–88) years, AH was found in 71.5% [3]. In prospective and retrospective studies it was shown that AH causes 20–72% AF attacks. AF risk in patients with AH is 1.42 times bigger than in human normotensive population. It was observed that up to 40% of AF cases in this group of patients may become permanent [4, 5]. Effective treatment of AH with use of selective inhibitors of rennin–angiotensin–aldosterone system (RAA) and adrenergic system among others, may be a form of an upstream therapy for patients with AH and AF [1, 6, 7].

The aim of the study was to evaluate the effect of combination therapy with hypotensive drugs of various mechanisms of action, on AF recurrence rates in hypertensive patients with paroxysmal/persistent AF. The study represents an additional analysis of a group of hypertensive patients, a part of the population evaluated in SPIR-AF study [8].

METHODS

Design and course of the study

The study was performed as an open, prospective observation between 1.01.2005 and 1.01.2009, including the randomisation period: up to 30.04.2007. The study population consisted of patients with recurrent AF episodes, referred to 2nd Ischaemic Heart Disease Department or Outpatient Clinic of the Institute of Cardiology in Warsaw. Current anti-arrhythmic treatment was not effective in prevention of AF episodes or was not tolerated in the study patients. The observation period lasted typically 12 months. After obtaining an informed consent, the patients were randomised to 4 types of treatment: A — treatment with an aldosterone antagonist, an angiotensin converting enzyme inhibitor (ACE-I), a beta-adrenolytic drug, B — treatment with an aldosterone antagonist, a beta-adrenolytic drug, C — treatment with ACE-I, a beta-adrenolytic drug, D — treatment with a beta-adrenolytic drug. In the study the following drugs were used: an aldosterone antagonist (spironolactone), ACE-I (enalapril), a beta-adrenolytic drug (bisoprololol or metoprolol or propranolol). In hypertensive patients the treatment was performed to control the blood pressure (BP) at level under 140/90 mm Hg. In case of treatment failure, diuretic agents (thiazides or loop diuretic), dihydropyridine calcium antagonists and optionally alpha-adrenolytic drugs were used. Spironolactone was used at the dose of 25 mg/day in the morning. Enalapril was used at the highest tolerated dose, depending on arterial BP and renal parameters: 2 × 5 mg, 2 × 10 mg or 2 × 20 mg, minimum 10 mg/day. A mean dose was 12.5 mg. Beta-adrenolytic drug — bisoprolol or metoprolol or propranolol was used at the dose allowing for heart rate control at the level of 55–70/min. Beta-adrenolytic drugs had been previously taken by 90% of the patients. In the remaining 10%, a beta-adrenolytic drug was included during the randomisation visit.

Before patient inclusion in the study, after considering inclusion and exclusion criteria, detailed history taking (according to predefined questionnaire) and physical examination, echocardiography and ECG were performed, blood samples were drawn for biochemical tests. Control visits were repeated every 3 months, but after the initial 2 weeks, biochemical tests were performed to analyse electrolyte concentrations and renal parameters (this adds up to 6 visits). During the visits, general examinations were performed and ECG tracings were recorded. Information and documentation regarding patient's recent history of AF episodes (ECG tracings, discharge reports from emergency or hospital departments) were collected. The patients included in the study were frequently controlled and treated because of recurrent AF and were aware of the need to document all the AF episodes. The AF episodes that lasted over 1 h and verified by ECG, were registered. The therapy for concomitant diseases and the anticoagulant treatment were continued according to recent recommendations, conforming to the CHADS2 risk scale. Statin treatment was continued, at doses unchanged. During the program, longer-lasting administration of anti-arrhythmic drugs was not permitted. Direct pharmacological intervention (oral or intravenous administration of amiodarone, propafenone, potassium or magnesium supplementation), or cardioversion were allowed in case of AF episode occurrence.

Study group

The research included a group of 164 patients with history of recurrent paroxysmal or persistent AF, aged 40–80 years. Inclusion criteria were as follows: sinus rhythm on the day of inclusion, minimum 2 AF (paroxysmal or persistent) episodes verified by ECG tracing during the preceding 6 months, the awareness of AF episode occurrence, intolerance or ineffectiveness of recently used anti-arrhythmic drugs: class I according to Vaughan-Williams — propafenone, and class III — sotalol, amiodarone. The patients could not have been treated during the preceding 6 months with ACE-I, with antagonists of angiotensin receptors and with aldosterone antagonists. Exclusion criteria included: asymptomatic AF, angina pectoris of class higher than II according to CCS, myocardial infarction < 6 months, heart failure (HF), left ventricular ejection fraction < 55%, higher level diastolic dysfunction of the left ventricle, such as restriction and pseudo-normalisation, organic valvular congenital and acquired heart disease, renal failure (creatinine concentration > 1.2 mg/dL) and electrolyte disturbances, chronic systemic and inflammatory diseases, use of drugs influencing RAA system activity and anti-arrhythmic drugs different from the study drugs, generally agreed upon contraindications for ACE-I, aldosterone antagonists and beta-adrenolytic drugs, lack of patient's consent for participation. Metabolic syndrome was diagnosed according to the 2005 definition: waist circumference in men ≥ 94 cm, in women ≥ 80 cm and co-existence of min. 2 of the following: triglyceride concentration ≥ 150 mg/dL; HDL < 40 mg/dL in men and < 50 mg/dL in women or dysli-

pidaemia treatment; arterial BP ≥ 130/85 mm Hg or treatment for arterial hypertension; fasting glycaemia ≥ 100 mg/dL or treatment of type 2 diabetes.

Definition of atrial fibrillation forms

According to 2006 guidelines of American College of Cardiology, American Heart Association and European Society do Cardiology, recurrent AF was defined as a history of at least 2 arrhythmia episodes, paroxysmal AF — self-terminating, lasting typically up to 7 days, persistent AF — non-self-terminating, lasting longer than 7 days, permanent AF — long-lasting AF, the cardioversion not attempted or ineffective [9]. It was assumed in the study that the occurrence of minimum 1 episode of persistent AF, qualified the patient to the persistent AF group. The study was performed as a statutory work of the Institute of Cardiology, funded by The Scientific Research Committee grant (2.8/IV/2005). The permission of Bioethical Commission of the Institute of Cardiology was given on the 7th December, 2004 (865).

Statistical analysis

Statistical analysis was performed with use of the SAS package, ver. 9.2. Continuos variables with normal distribution were presented as mean values and standard deviations or as medians and interquartile ranges (IQR1, IQR3) in case of essential aberrations of data distribution (obliquity > 1.5). Normality of distribution was verified by Shapiro-Wilk test. To compare the differences in the clinical parameter values between the groups spironolactone (+), spironolactone (–) and enalapril (+), enalapril (–) the t test or the two-way analysis of variance (ANOVA) were used. Categorical variables were shown as a number and percentage. A χ^2 test with Yates correction was used to analyse the distribution of categorical data. To evaluate the differences between AF occurrence the ANOVA model with repeated measures was used. The main effects were analysed: between the measurements (time effect), between patients (the intervention effect: spironolactone and enalapril) and interactions between two types of effects (time*intervention). The model included: (1) variable related to the order of measurement: "visit"; (2) intervention: spironolactone or enalapril, (3) interaction between the time and the action of spironolactone or interaction between the time and the action of enalapril. Multivariate analysis of variance was performed (Wilks' Lambda, Pillai's trace). Because of small dispersion from normal distribution, to verify the results, nonparametric Wilcoxon tests were performed. The size of examined groups was stated for ANOVA with the assumption of constant effects, error of the 1st kind alpha = 0.05, power = = 90% and RMSSE (square root of a standardised effect) = 0.20 for the main effects and = 0.25 for interaction. The calculated sample size was n = 160. The actual statistical power of the study reached: 0.90 for the action of ACE-I (enalapril), 1.0 for spironolactone and 0.96 for interaction between enalapril and spironolactone.

Verification of all the hypotheses was performed at statistical significance level of alpha ≤ 0.05 (two-way testing was used).

RESULTS

Characteristics of the study group

The groups of 115 patients with AH of 1st and 2nd degree and 49 patients without AH were analysed. Persistent form of AF occurred significantly more frequently in patients with AH: 83% as compared with the population without hypertension: 67% ($p < 0.05$). Patients with AH had higher body mass index at randomisation: 27.8 ± 3.7 vs. 26.1 ± 2.9 kg/m^2, $p < 0.05$, higher rates of history of stroke: 15% vs. 2.5%, $p < 0.05$, hyperlipidaemia: 60% vs. 27%, $p < 0.0005$ and metabolic syndrome: 51% vs. 15%, $p < 0.0001$. Characteristics of the patients with AH and AF are presented in Table 1. In 14 (93%) of patients from the study group AF turned per-

Table 1. Clinical and demographic characteristics of patients with AF and arterial hypertension (n = 115). The results are presented as categorical values: n (%), continuous variables: mean value ± SD, time of AF as a median (interquartile range)

Age [years]	65.5 ± 9.7
BMI [kg/m^2]	27.8 ± 3.7
Sex, men	65 (57%)
Duration of AF history (Q1–Q3)	4 (2–7)
Persistent AF	83 (95%)
Pacemaker implanted	9 (8%)
Ablations	1%
LVH	9 (8%)
Stroke	17 (15%)
CAD	33 (28.6%)
History of MI	17 (14.8%)
Diabetes, type 2	15 (13.0%)
Hyperlipidaemia	69 (60%)
Metabolic syndrome	59 (51%)
Thyroid disorders	23 (20%)
Prostate hypertrophy (men)	17 (26%)
HRT (women)	11 (22%)
Peptic ulcer	14 (12%)
GERD	12 (10%)
Fainting	35 (30%)
Dizziness	6 (5%)
Caffeine intake > 2 cups/day	44 (38%)
Alcohol intake > 50 g/40%/day	10 (9%)
Sleep disorders	43 (37%)
Neurosis	44 (38%)

AF — atrial fibrillation; BMI — body mass index; LVH — left ventricular hypertrophy; CAD — coronary artery disease; MI — myocardial infarction; HRT — hormonal replacement therapy; GERD — gastrointestinal reflux disease

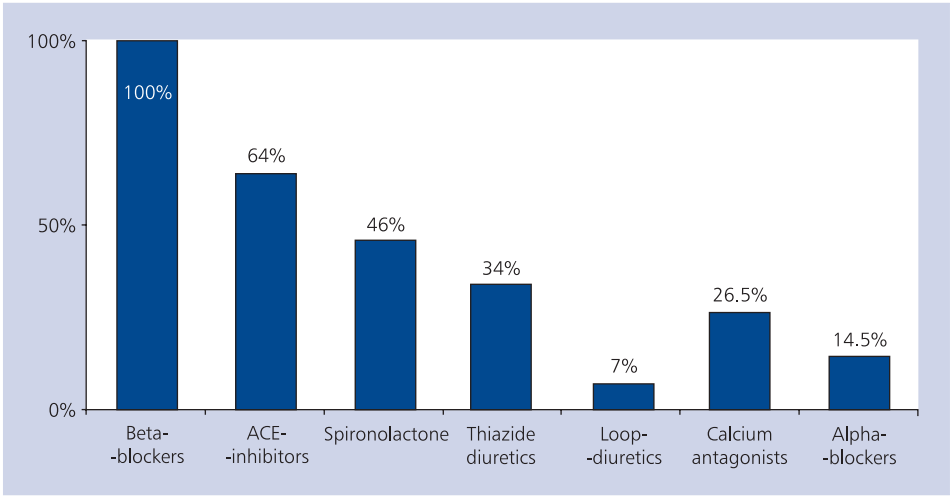

Figure 1. Pharmacological treatment: classes of hypotensive drugs in patients (n = 115) with atrial fibrillation and arterial hypertension

manent within a year. In patients without hypertension 1 case was diagnosed ($p < 0.05$).

Blood pressure values

The BP values before the inclusion to the study and after 1 year didn't differ significantly in patients with AF and AH — before the inclusion: 127 ± 11/80 ± 7 mm Hg and after the study completion: 124 ± 10/80 ± 5 mm Hg, NS. Similarly, the pressure values did not differ in relation to the number of episodes. In patients that had 0–1 AF attacks during the observation period, BP values after 12 months were: 124.7 ± ± 11.4/79.3 ± 5.7 mm Hg, and in patients with more than 1 AF attack: 123.4 ± 8.8/79.8 ± 4.4 mm Hg, NS.

The treatment

The frequency of applying specific classes of hypotensive drugs in patients with AF and AH is presented in Figure 1. Six of the AH patients received a single hypotensive drug, 38 patients received 2 drugs, 37 — 3 drugs, 27 — 4 drugs, 7 — 5 drugs (n = 115). In patients taking ≥ 3 drugs, 29% were taking spironolactone and 24% were taking other diuretics (thiazide diuretics and loop-diuretics). No statistically significant differences were found in the values of systolic and diastolic BP in patients taking in relation to the number of hypotensive drugs used. In patients taking 3 or more drugs in the program, for 3 months before the actual inclusion to the study, more AF episodes occurred than in the remaining patients: 4.7 ± 0.8 vs. 2.9 ± 0.4 ($p = 0.0444$). However, during 12 months of treatment, divided into 3-month-long observation intervals, it was observed that patients from that group showed a significant reduction of AF episodes ($p < 0.0001$). In patients treated with 1–2 drugs, a significant reduction of symptomatic AF episodes was observed after 3 months ($p = 0.0029$), 6 months ($p = 0.04$ and after 12 months ($p = 0.0012$) but

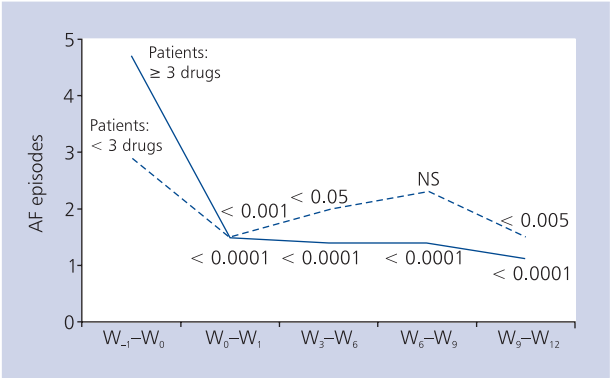

Figure 2. The number of atrial fibrillation episodes (AF, n = 0–5) in relation to the number of hypotensive drugs used during the study period (< 3 or ≥ 3) in 3-month intervals during one-year follow-up; W — visit

not after 9 months (Fig. 2, Table 2 and 3). Application of spironolactone as the 3rd or subsequent: 4th or 5th hypotensive drug, was related to a significant, progressive reduction of AF episodes but starting from the 4th month of treatment what may be due to increasing effectiveness of treatment in terms of arrhythmia reduction (Table 2). Those relationships were not confirmed for enalapril, despite its co-administration with a smaller (< 3) or bigger (≥ 3) number of drugs (Table 3). Statins were used in 19% of patients: that many patients were taking these drugs before the inclusion and that was not changed during the study. Multifactorial analysis did not confirm any relationship between the use of statins and BP values and the course of arrhythmia episodes. Angiotensin receptor blockers (ARB) were not used. In 3 patients cases of gynecomastia occurred and in 1 patient — spironolactone intolerance (dyspeptic symptoms) and in 1 case — nonfatal stroke.

Table 2. The number of atrial fibrillation (AF) episodes in relation to the number (< 3 or ≥ 3) of hypotensive drugs, including spironolacton (SPIR) in patients with arterial hypertension. The results were expressed as an arithmetic mean (SEM); median [min–max]. Multivariate analysis if variance, categorical data

Number of AF in period	< 3			≥ 3		
	SPIR– (n = 36)	SPIR+ (n = 8)	P	SPIR– (n = 25)	SPIR+ (n = 46)	P
3 months prior to randomisation	2.5 (0.4) 2 [1–15]	4.0 (1.2) 3 [1–10]	0.1868	3.6 (1.1) 1.5 [1–24]	5.3 (1.1) 2 [1–30]	0.3356
0–3 months	1.7 (0.5) 1 [0–13]	0.6 (0.6) 0 [0–4]	0.3234	2.2 (1.0) 0.5 [0–21]	1.1 (0.5) 0 [0–18]	0.2823
4–6 months	2.2 (0.6) 1 [0–16]	0.4 (0.4) 0 [0–3]	0.1923	2.8 (1.0) 0 [0–21]	0.7 (0.2) 0 [0–6]	0.0144
7–9 months	2.6 (0.7) 1 [0–24]	0.7 (0.7) 0 [0–5]	0.2822	3.0 (1.1) 0 [0–22]	0.6 (0.2) 0 [0–7]	0.0087
9–12 months	1.7 (0.4) 1 [0–12]	0.6 (0.4) 0 [0–3]	0.2870	2.4 (0.8) 0.5 [0–12]	0.4 (0.1) 0 [0–3]	0.0013
Effect time		MANOVA: 0.0055 ANOVA: 0.04321			MANOVA: 0.0033 ANOVA: < 0.0002	
Effect time*SPIR		MANOVA: 0.2733 ANOVA: 0.1757			MANOVA: 0.1828 ANOVA: 0.0194	
Effect SPIR		0.3261			0.1262	

Table 3. The number of atrial fibrillation (AF) episodes in relation the number (< 3 or ≥ 3) of hypotensive drugs, including enalapril (ENAL) in patients with arterial hypertension. Multivariate analysis if variance, categorical data. The results were expressed as an arithmetic mean (SEM); median [min-max]

Number of AF in period	< 3			≥ 3		
	ENAL– (n = 24)	ENAL+ (n = 20)	P	ENAL– (n = 16)	ENAL+ (n = 55)	P
3 months prior to randomisation	3.4 (0.7) 2 [1–15]	1.9 (0.2) 2 [1–4]	0.0675	4.4 (2.0) 2 [1–30]	4.8 (0.9) 2 [1–29]	0.8725
0–3 months	1.5 (0.6) 0 [0–13]	1.5 (0.6) 1 [0–10]	0.9814	1.6 (0.9) 0.5 [0–12]	1.5 (0.6) 0 [0–21]	0.9580
4–6 months	1.6 (0.7) 0 [0–16]	2.4 (0.7) 1 [0–10]	0.4467	1.4 (0.8) 0 [0–10]	1.4 (0.5) 0 [0–21]	0.9895
7–9 months	2.2 (1.0) 0 [0–24]	2.5 (0.6) 1.5 [0–10]	0.7981	1.4 (0.9) 0 [0–12]	1.5 (0.5) 0 [0–22]	0.9183
9–12 months	1.4 (0.5) 0 [0–12]	1.6 (0.5) 0 [0–7]	0.8815	1.1 (0.9) 0 [0–12]	1.1 (0.3) 0 [0–12]	0.9572
Effect time		MANOVA: 0.0125 ANOVA: 0.1912			MANOVA: 0.0109 ANOVA: 0.0005	
Effect time*ENAL		MANOVA: 0.2432 ANOVA: 0.3048			MANOVA: 0.9991 ANOVA: 0.9769	
Effect ENAL		0.9328			0.9300	

DISCUSSION

The rate of AH in the study group of patients with paroxysmal/persistent AF (75%) was similar to the data of European and Polish registries [2, 3]. Persistent AF occurred significantly more frequently in patients with AH.

From among 15 patients in whom AF turned permanent within 1 year, AH was found in as much as 93%. The putative pathophysiological mechanisms of AF occurrence in patients with AH include atrial activation disturbances, atrial enlargement leading to refraction period shortening and prolonged

activation and sympatho-vagal balance disturbances. In the long term, these changes can lead to left ventricular enlargement and development of HF. In a prospective, 16-year observation of 2482 patients with AH, the first AF episode occurred at a rate of 0.46 per 1000 patient-years. The main risk factors for AF occurrence were age, increased left ventricular mass (hypertrophy) and left atrial enlargement [10, 11].

Based on prospective analysis of 34221 women of the Women's Health Study it was demonstrated that increased systolic BP in the range of 130–139 mm Hg was closer related to AF occurrence than diastolic and that it significantly increased the risk of AF even if it did not yet meet the AH criteria [12].

Potentially beneficial influence of RAA inhibiting drugs substantiated the European Society of Hypertension and European Society of Cardiology 2007 guidelines and their 2009 update [6, 7]. These guidelines point to ACE-I and ARB as the preferred drugs in patients with AH and risk of AF occurrence. The results of one of the first meta-analyses, published in 1995, that included 11 studies of 56 308 patients with AH, HF and coronary artery disease showed that ACE-I and ARB use reduce the risk of AF occurrence by 28% on average (15–40%), $p = 0.0002$ [13]. A recently published analysis of 682 993 patients with AH, among whom AF occurred in 4661, demonstrated that long-term treatment with drugs inhibiting RAA: ACE-I, ARB and beta-adrenolytics was related to lower risk of AF in comparison with calcium channel blockers [14]. The results of another meta-analysis of 23 randomised studies of 87 048 patients, in whom ACE-I and ARB were used, confirms their effectiveness in primary prevention of HF in patients with AH as well as in secondary prevention of AF, also on top of antiarrhythmic drugs after cardioversion or in patients receiving pharmacological treatment with antiarrhythmics (reduction by 33%, $p < 0.0001$) [15].

Retrospective analyses of administration databases from the United States (8 million patients) and Great Britain (5 million) demonstrated higher effectiveness of hypotensive drugs inhibiting the RAA and the adrenergic systems in the prevention of the first AF episode in comparison to calcium channel blockers [14, 16]. In J-RHYTHM II study, effectiveness of candesartan (max. dose 12 mg) and amlodipine (max. dose 5 mg) were compared in 318 patients with AH and paroxysmal AF in the Japanese population. After 1-year follow-up better BP control was found in the amlodipine group, whereas no differences were noted in terms of AF episode rates. It can be due to the fact that more effective BP control counterbalanced the favourable effect of RAA inhibition [17].

The relationship between left atrial enlargement and left ventricular hypertrophy is commonly underlined. Also the effectiveness of RAA inhibition in patients with HF and AH is frequently pointed to. In one of the meta-analyses the results of 12 000 patients were summarised. It showed that beta-adrenolytic drugs significantly reduced the risk of AF occurrence — by 27% on average [18].

In comparison of the influence of the number of hypotensive drugs on the number of recurrences of paroxysmal AF it was found that in patients receiving 3 or more drugs the recurrences were less frequent at 6 months. All patients received beta-adrenolytics and vast majority received RAA inhibiting drugs: enalapril (65%) and spironolactone (47%); both drugs — 29%, none — 19% patients.

The analyses showed that the influence of spironolactone in terms of reduction of AF recurrences could have been stronger, what can be due to its wider spectrum of action and that it revealed itself only after 6 months of treatment [8]. This could have been related not only with effective BP control but with improved endothelial and smooth muscle cell function, increased potassium concentrations, left atrial wall fibrosis inhibition and reduction of cardiac muscle preload [19, 20].

It is possible, that both high effectiveness of antihypertensive treatment and concomitant favourable effect on arrhythmia recurrence can be due to wide therapeutic approach taking into account several mechanisms of hypotensive activity as part of "upstream therapy". Idiopathic AH (90% cases) is a net effect of many causes. Effectiveness and safety of treatment increase following the introduction of combination therapy, i.e. using compounds of various mechanisms of action at reduced doses.

It has been demonstrated that the more (> 3) hypotensive drugs are used, the more effective the therapy in terms of BP control and prevention of arrhythmia. This was subsequently confirmed in multivariate analysis. This finding seems to be an entirely new one — to the best of our knowledge, in the literature to date there are no studies prospectively addressing this issue.

Limitations of the study

The study limitations are, among others: single-centre type of study and small sample size. Only symptomatic, documented AF episodes were recorded, due to the lack of technical feasibility of long term (implantable devices) arrhythmia recording over the 12-month follow-up period. We did not perform detailed analysis of the patients pre-selected for the study prior to inclusion (screening phase) and not finally randomised.

CONCLUSIONS

The presence of AH promotes the occurrence of more advanced forms of recurrent AF. Combination therapy with at least 3 drugs with various mechanisms of action, including RAA activity inhibitors, can more effectively reduce the risk of arrhythmia recurrences.

Conflict of interest: *none declared*

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Stosowanie ≥ 3 leków hipotensyjnych u chorych z nawracającym migotaniem przedsionków i nadciśnieniem tętniczym skuteczniej kontroluje arytmię niż terapia mniejszą liczbą leków hipotensyjnych

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Streszczenie

Wstęp: Skojarzona terapia nadciśnienia tętniczego (AH) zapewnia prawidłową kontrolę ciśnienia i korzystnie wpływa na wskaźniki hemodynamiczne pracy serca. Skuteczne leczenie AH z zastosowaniem m.in. leków hamujących aktywność układu renina–angiotensyna–aldosteron (RAA) oraz układu adrenergicznego może być formą *upstream therapy* u chorych z AH i migotaniem przedsionków (AF).

Cel: Celem badania była analiza wpływu skojarzonej terapii hipotensyjnej z wykorzystaniem różnych mechanizmów działania leków na częstość nawrotów AF u pacjentów z AH i napadowym/przetrwałym AF.

Metody: Analizowano grupę 164 osób z nawracającymi epizodami AF, bez i z AH stopnia I i II, z napadową (51,3%) lub przetrwałą (48,7%) formą arytmii. Średni czas trwania AF wynosił 4 lata (Q1:2; Q3:7). Wcześniej stosowane leki antyarytmiczne były nieskuteczne w prewencji napadów AF lub nie były tolerowane. U wszystkich pacjentów osiągnięto dobrą kontrolę ciśnienia tętniczego. W leczeniu stosowano: leki beta-adrenolityczne: 100% osób, inhibitory konwertazy angiotensyny: 65%, spironolakton: 47%, diuretyki tiazydowe: 34%, diuretyki pętlowe: 7%, antagonistów wapnia: 26,5% i leki alfa-adrenolityczne: 14,5%. Oceny liczby objawowych i potwierdzonych epizodów AF dokonywano co 3 miesiące w trakcie rocznej obserwacji.

Wyniki: U 115 (75%) chorych (74% mężczyzn) stwierdzono AH stopnia I i II, średni wiek pacjentów wynosił 65,5 ± 9,7 roku. Przetrwała forma AF istotnie częściej występowała u osób z AH (83%) w porównaniu z populacją bez AH (67%; $p < 0,05$). Po zakończeniu obserwacji wartości ciśnienia tętniczego były zbliżone u osób z wyjściowo prawidłowym ciśnieniem oraz u pacjentów z AH i wynosiły odpowiednio: 123 ± 9/79 ± 4 *v.* 124 ± 10/80 ± 0,5 mm Hg; NS. Normalizację ciśnienia tętniczego uzyskano, stosując 1 lek hipotensyjny u 6 chorych; 2 leki u 39 pacjentów; 3 leki u 37; 4 leki u 27; a u 7 osób była konieczna terapia skojarzona za pomocą 5 leków. Wyjściowo pacjenci przyjmujący po włączeniu do badania ≥ 3 leków hipotensyjnych charakteryzowali się większą częstością epizodów AF: 4,7 ± 0,8 *v.* 2,9 ± 0,4; $p = 0,0444$. Jednak w ciągu rocznej obserwacji stwierdzono u nich istotne zmniejszenie liczby napadów AF po każdym z 3-miesięcznych podokresów badania ($p = 0,0001$). U pacjentów leczonych 1–2 lekami zanotowano istotną redukcję epizodów AF po 3 ($p = 0,0029$), 6 ($p = 0,04$) i 12 ($p = 0,0012$) miesiącach, natomiast zmniejszenie po 9 miesiącach nie było istotne statystycznie.

Wnioski: Nadciśnienie tętnicze wpływa na progresję AF do złożonych form arytmii. Skojarzona terapia hipotensyjna z zastosowaniem co najmniej 3 leków, w tym inhibitorów aktywności układu RAA, może być skuteczna w aspekcie kontroli ciśnienia i redukcji epizodów arytmii.

Słowa kluczowe: migotanie przedsionków, nadciśnienie tętnicze, farmakoterapia

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