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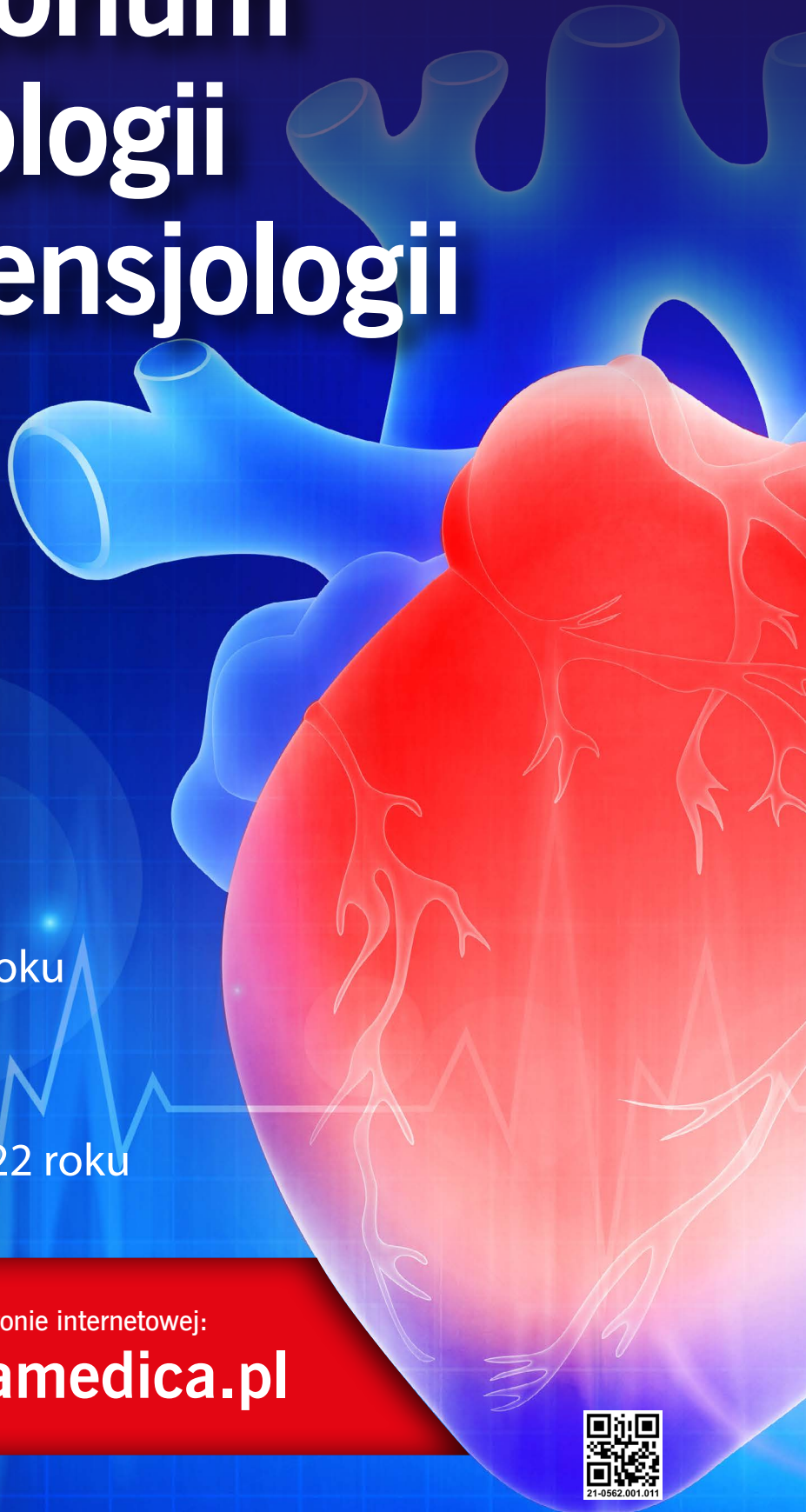

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The risk of a blood pressure increase during treatment with selected psychotropic drugs

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Abstract

Arterial hypertension is the most common cardiovascular risk factor in the general population. Increased mortality from arterial hypertension affects all ethnicities and ages, including those with mental disorders. Most people with arterial hypertension suffer from the primary form of the disease. The aim of this article was to analyze the influence of psychiatric drugs on blood pressure.

The articles for analysis were selected *via* the PubMed search engine in the Medline database using the names of individual drugs or a group of psychotropic drugs, the AND operator and the words "hypertension" or "blood pressure" or "cardiovascular system". The articles were then selected and 44 references were selected for analysis. Selected articles were archived on April 9, 2021.

Many medications with the potential to increase blood pressure are used to treat mental illness. These include venlafaxine, milnacipran, bupropion, esketamine, 1st and 2nd generation antipsychotics, tricyclic antidepressants and psychostimulants.

In patients using psychotropic drugs that may increase blood pressure, attention should be paid to monitoring it during treatment.

Key words: arterial hypertension; psychotropic drugs; cardiovascular risk

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Introduction

Arterial hypertension is one of the most common cardiovascular risk factors. About 45% of people worldwide suffer from hypertension, and the incidence increases with age [1]. According to a 2014 World Health Organization (WHO) report, hypertension accounted for 51% of stroke deaths and 45% of overall cardiovascular mortality, and it affected all age groups and ethnicities [1].

Blood pressure remains insufficiently controlled in approximately 50% of all treated hypertensive patients [2, 3]. The reason for such a high prevalence of hypertension and its poor control is, first of all, low public awareness of classical and non-classical risk factors for its occurrence and non-compliance with medical recommendations [4, 5]. Most patients with hypertension suffer from its primary form (90% of cases) or an identified secondary form (e.g. in the course of renal artery

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stenosis, chronic kidney disease, hyperaldosteronism, pheochromocytoma).

From a clinical point of view, the influence of psychiatric drugs on blood pressure and the interaction of these drugs with antihypertensive drugs are significant [7]. These drugs may affect both the risk of hypertension and the effectiveness of antihypertensive therapy [6]. The aim of the article was to analyze the effect of psychiatric drugs on blood pressure and to present potential interactions between these drugs and antihypertensive drugs.

Method

The analysis of available literature in English and Polish was carried out using the PubMed search engine in the Medline database. The search was performed by using the search terms with the name of the drug or group of drugs, the "AND" operator and the terms "hypertension" or "blood pressure" or "cardiovascular system". 162 abstracts were pre-selected. Those that did not refer to the research problem or contained methodological problems were excluded and 44 papers were selected for the review. Selected articles were archived on April 9, 2021.

Antidepressants

According to WHO, about 264 million people worldwide currently suffer from depressive disorders [8]. Antidepressants are among the most frequently prescribed medications [9]. The influence of these drugs on the cardiovascular system, and in particular on blood pressure, is a very important issue in the practice of practically every medical specialty. Antidepressants include tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants (NaSSA), serotonin antagonist and reuptake inhibitors (SARs) and esketamine, which opens a new group of fast-acting antidepressants, and older and less frequently used monoamine oxidase inhibitors (MAOIs).

Tricyclic antidepressants

Tricyclic antidepressants work by inhibiting the reuptake of serotonin (mainly amitriptyline, imipramine, and clomipramine) and noradrenaline (mainly nortriptyline and desipramine). However, they do not affect the dopaminergic system. Currently, they are used less frequently due to their side effects resulting from the antagonistic effect on muscarinic cholinergic receptors (dry mouth, constipation, tachycardia, urinary retention), histamine H1 (sedation, weight gain) and $\alpha 1$ adrenergic receptors (tachycardia, orthostatic hypotension) [10]. The most serious side effect of TCAs is its effect on the myocardial stimulus-conductive system. Overdosing of TCA may result in atrioventricular blocks or Hiss bundle branch blocks. Despite their unquestionable effectiveness in the treatment of depressive disorders, they should not be used in patients with cardiac risk [10]. The meta-analysis of Thase (1998), including 3744 depressed patients, assessed the effect of imipramine on blood pressure. The use of TCA in therapeutic doses was associated with a small but statistically significant increase in systolic blood pressure during the treatment of the acute phase of depression [11]. However, in elderly patients with concomitant cardiovascular diseases, more frequent occurrence of orthostatic hypotension was found during the use of TCAs [11].

In a study by Licht et al. (2009) including 2028 patients with depression (of whom 1384 were not taking antidepressants, mean age 42.0 ± 11.3 years), the impact of antidepressant drugs on the risk of hypertension was assessed. It has been shown that patients using TCAs were characterized by increased systolic and diastolic blood pressure and more often had stage 1 (OR: 1.90; 95% CI: 0.94–3.84; p = 0.07) and stage 2 hypertension (OR: 3.19; 95% CI: 1.35–7.59; p = 0.008). The risk of isolated systolic and diastolic hypertension was also increased in patients using TCAs, although the effect was not statistically significant (OR 1.43; 95% CI: 0.68–3.00, p = 0.34 and OR 2.12; 95% CI: 0.69–6.49, p = 0.19, respectively) [12]. The main cause of death in patients with TCAs was arrhythmia [13].

In conclusion, the presented studies indicate that the use of TCAs may be associated with an increased risk of hypertension in adults.

Serotonin reuptake inhibitors

Serotonin reuptake inhibitors increase the concentration of serotonin in the synaptic space by reducing its reuptake. Currently, 6 drugs from this group are registered in Poland: fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram and escitalopram. Due to the lack or low affinity of drugs from this group to muscarinic, histamine and adrenergic receptors, SSRI drugs show low behavioral toxicity and are well tolerated by patients.

Drugs from the SSRI group may have a certain antihypertensive effect in some groups of patients. In the study by Valclavik et al. (2018) covering 56

patients with phaeochromocytoma who started the use of sertraline, clinical improvement was observed in 75% of them. Mean systolic and diastolic blood pressure (measured in a doctor's office) in patients receiving sertraline decreased by 12.8/7.4 mm Hg ($p < 0.001$), and complete resolution of paroxysmal increases in blood pressure was observed in 50% of patients [14]. In a meta-analysis of 23 randomized clinical trials conducted by Zhong et al. (2017) involving 13,285 subjects, the effect of SSRIs on systolic and diastolic blood pressure was assessed. There was no statistically significant effect (weighted mean difference, WMD) of paroxetine, fluoxetine, sertraline, escitalopram and citalopram compared to placebo on systolic blood pressure (total WMD 0.04; 95% CI: –0.68–0.59) and diastolic blood pressure (total WMD 0.08; 95% CI: –0.43–0.60) [15].

In a randomized placebo-controlled clinical trial by Peixoto et al. (2019) involving 30 patients with depression and hypertension, the effect of escitalopram on blood pressure was assessed. Patients were divided into escitalopram (n = 15, dose 10–20 mg/day) and placebo (n = 15) group and were followed for 8 weeks. There was no statistically significant effect of escitalopram on systolic blood pressure (140.80 ± 16.48 mm Hg *vs.* 139.61 ± 18.92 mm Hg, p = 0.85) and diastolic blood pressure (80.55 ± 12.64 mm Hg *vs.* 80, 18 16.36 mm Hg, p = 0.94) [16].

The study by Humbert et al. (2019) obtained different results. In a study of these authors, two different types of investigations were performed: a comparative study in VigiBase® (n = 14824), which is the WHO pharmacovigilance database (PVDB), from where notifications of hypertension with six SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) were extracted [relationship between the suspected SSRIs and the occurrence of hypertension was assessed by calculating reporting odds ratio (ROR)] and a descriptive study of hypertension reports associated with SSRIs in the French pharmacovigilance database (FPVDB; n = 24). Based on the VigiBase® analysis, it was shown that the use of SSRIs significantly increased the ROR of hypertension (ROR 1.71; 95% CI: 1.68–1.74). In the FPVDB, 24 reports of hypertension were found with all six SSRIs used at standard doses, mainly in women (66.7%) with a mean age of 57.8 years and a median time of onset of 6 days. In 10 cases (42%), patients had a history of hypertension. This real-life study shows a significant pharmacovigilance safety signal between the use of SSRIs and the development or worsening of hypertension [17].

Overall, the impact of SSRIs on the risk of hypertension remains controversial and requires further research.

Serotonin and norepinephrine reuptake inhibitors

This group of drugs reduces the reuptake of serotonin and noradrenaline in the synaptic space. The SNRIs include desvenlafaxine, duloxetine, milnacipram and venlafaxine. Of the SNRIs, only venlafaxine and milnacipram seems to be able to increase blood pressure.

In the previously cited meta-analysis by Thase (1998), including 3744 depressed patients, the effect of venlafaxine on blood pressure was assessed. The use of venlafaxine compared with placebo has been shown to be associated with increased systolic blood pressure. The effect of venlafaxine was highly dose-dependent and the incidence of elevated diastolic blood pressure (> 90 mm Hg) was 3 times higher than in patients treated with the lower dose (9% *vs.* 3%). Importantly, however, the study concluded that venlafaxine did not adversely affect blood pressure control with antihypertensive drugs in patients with previously diagnosed hypertension. The previously cited meta-analysis by Zhong et al. (2017) showed that the use of SNRI compared to SSRI may cause a slight but statistically significant increase in systolic (WMD –1.50; 95% CI: –2.15– –0.84) and diastolic (WMD –1.34; 95% CI: –1.92– –0.75) blood pressure in both short-term (less than 8 weeks) and long-term (more than 8 weeks) therapy [15].

The negative effect of venlafaxine on blood pressure results from the stimulation of the sympathetic nervous system [11]. Moreover, in clinical practice the interaction between venlafaxine and amlodipine is important. It has been shown that the blood levels of venlafaxine metabolites increase in patients taking amlodipine. This effect may lead to an additional increase in the stimulation of the sympathetic nervous system and significantly increased blood pressure [18].

A meta-analysis of 17 randomized clinical trials by Park et al. (2020) assessed the effects of duloxetine on heart rate and blood pressure. Intervention time was up to 13 weeks and the daily dose of duloxetine was 30–120 mg. Duloxetine has been shown to increase heart rate by 2.22 beats/min (95% CI: 1.53–2.91), diastolic blood pressure by 0.82 mm Hg (95% CI: 0.17–1.47) and systolic blood pressure by 0.64 mm Hg (95% CI: –0.24–1.52). Thus, it was found that duloxetine did not increase the heart rate and blood pressure in the short term. However, studies are

needed to assess the long-term effects of duloxetine on the cardiovascular system [19].

The effects of duloxetine on heart rate and blood pressure appear to be dose dependent. A randomized, placebo-controlled, double-blind study by Derby et al. (2007) evaluated the effect of supra-therapeutic doses of duloxetine on heart rate and blood pressure in 117 healthy subjects. Dosages were escalated from 60 mg 2×/day to 200 mg 2×/day over 16 days. Duloxetine produced increases in supine systolic and diastolic blood pressures, which reached maximums of approximately 12 mm Hg and approximately 7 mm Hg above baseline, respectively, during dosing at 120 mg twice daily and then stabilized. Supine pulse rate increased gradually with dose, reaching 10 to 12 bpm above baseline after 4 days of dosing at 200 mg twice daily. Duloxetine caused changes in orthostatic blood pressures and pulse rate that reached plateau values after 3 to 4 days of dosing at 160 mg twice daily and were generally not associated with subjectively reported orthostatic-related adverse events. All vital signs normalized by 1 to 2 days after study drug discontinuation. Thus, duloxetine used in short-term supra-therapeutic doses may significantly increase heart rate and blood pressure [20].

The effect of milnacipran on blood pressure was assessed in a randomized, placebo-controlled, double-blind clinical study by Mease et al. (2009) in 888 patients with fibromyalgia. The safety of use of 100 and 200 mg milnacipran over 27 weeks was compared to placebo. After 27 weeks, supine systolic blood pressure was shown to increase by 3.3 mm Hg from baseline in both milnacipran groups. Mean diastolic blood pressure in the supine position increased by 2.5 mm Hg and 3.5 mm Hg from baseline in the milnacipran 200 and 100 mg/day groups, respectively [21]. The randomized, placebo-controlled, double-blind study by Trugman et al. (2014) in patients with fibromyalgia also assessed the effect of milnacipran on blood pressure. Patients were randomized to receive milnacipran (n = 210) or placebo (n = 111) for 7 weeks. Half of the patients suffered from hypertension. Analyzes were performed at weeks 4 and 7, after dose escalation of milnacipran to 100 and 200 mg/day, respectively. Blood pressure was measured by means of its 24-hour recording. Systolic and diastolic blood pressure increased on average by 4–5 mm Hg and 3–4 mm Hg, respectively, at the week 4 and week 7 visit. The mean increase in blood pressure was similar and comparable both in patients with hypertension and patients with normal blood pressure. A normal 24-hour blood pressure profile was maintained in patients receiving milnacipran. Researchers concluded that milnacipran slightly increases blood pressure in both normotensive people and those with hypertension [22].

In summary, among the SNRI drugs, venlafaxine and milnacipran have significant properties that increase the risk of hypertension. Therapeutic doses of duloxetine do not increase blood pressure in the short-term treatment.

Monoamine oxidase inhibitors

This group of drugs includes older drugs such as iproniazid, phenelzine, tranylcypromine and isocarboxazid (irreversible monoamine oxidase (MAO) antagonists, older and less frequently used drugs), and moclobemide, befloxatone and brofaromine (newer and reversible antagonists of MAO). Their mechanism of action is to reduce the breakdown of amine neurotransmitters (serotonin, noradrenaline, dopamine, tyramine and phenylalanine) in the central nervous system by reducing the activity of MAO. These drugs cannot be used together with drugs from the group of SSRIs, SNRIs or SSNRIs. Such a combination may result in serotonin syndrome, in which there may be both a dangerous increase and a decrease in blood pressure [7].

Increasing blood pressure by MAOIs results from the intensification of the intracellular transport of tyramine with a simultaneous increase in the concentration of norepinephrine in the vascular system (through the norepinephrine transporter). Noradrenaline, by narrowing the blood vessels, leads to an increase in blood pressure, and in extreme cases even a hypertensive crisis. This reaction is especially intensified with the use of older generation MAOIs (which irreversible block both MAO-A and MAO-B). Therefore, when taking drugs from this group, it is recommended to avoid excessive consumption of foods containing tyramine, such as cheese, red wine, fish, avocados, bananas or chocolate [7, 23]. In the literature, there are reports of patients with depression who used MAOIs and who experienced a hypertensive crisis after consuming red wine or long-aged cheese [24–26]. Increased blood pressure occurs rarely in patients using MAOIs and adhering to the aforementioned dietary recommendations, and most often up to 2 hours after administration of the drug; the observed increase in blood pressure is transient and no serious clinical consequences are found [27].

In order to reduce the risk of increased blood pressure while taking MAOIs, over-the-counter medications such as phenylephrine and pseudoephedrine, which may increase blood pressure, should also be avoided [27]. Orthostatic hypotension may also occur during the use of MAOIs [27]. Benzodiazepines

may be used to treat hypertension secondary to an increase in tyramine levels in the blood (unless systolic blood pressure is above 200 mm Hg). In such a case, antihypertensive drugs other than nifedipine should be used [23].

In summary, during the use of MAOIs, especially older, irreversibly blocking MAOIs, there is a risk of increasing blood pressure, largely dependent on the diet used during treatment and the concomitant medications used.

Other antidepressants

Trazodone is a drug that reduces the reuptake of serotonin and acts antagonistically on 5-HT2A receptors (serotonin antagonist and reuptake inhibitors, SARI). Its side effects are mainly somnolence, headache and nausea. As a side effect trazodone can also affect blood pressure. Orthostatic hypotension is the most commonly reported episode. Thus, when using this drug in patients with hypertension, the need to modify antihypertensive treatment should be considered [28, 29].

Another group of antidepressants are the NaSSA drugs, including mianserin and mitrazapine. The mechanism of the antidepressant action of these drugs is to reduce noradrenaline reuptake and block 5-HT2A receptors. Common side effects of these drugs are increased appetite and weight gain. Drugs from the NaSSA group can also cause changes in blood pressure, but to a lesser extent than TCAs. The safety profile of mitrazapine was assessed in a meta-analysis of 25 randomized and controlled trials by Watanabe et al. (2010) of 4,842 depressed patients. It has been shown that compared to TCAs, mitrazapine was characterized by a significantly lower risk of hypertension (RR: 0.51, 95% CI: 0.31–0.86; p = 0.01) [30].

Esketamine is a new antidepressant drug. The mechanism of action of esketamine is based on the blocking of NMDA (N-methyl-D-aspartate) glutamate receptors. Esketamine nasal spray has already been approved in many countries to augment the treatment of treatment-resistant depression in adults.

In 2020, a study by Doherty et al. was published, covering 1708 patients with treatment-resistant depression. Patients were divided into esketamine plus oral antidepressant and oral antidepressant plus placebo. It was shown that the increase in blood pressure was more frequent in patients receiving esketamine compared to placebo (3.9% *vs.* 11.6%). This indicates a greater risk of elevated blood pressure in patients receiving esketamine (OR: 3.2; 95% CI: 1.9–5.8). Hypertension occurred in 1.9% of patients receiving esketamine and in 0.6% of patients receiving placebo. On the other hand, no organ complications of the increased blood pressure were found. It was also found that the increase in blood pressure after administration of esketamine is generally transient (most often resolved 90 minutes after administration), asymptomatic and not associated with serious cardiovascular safety consequences [31].

Bupropion is a norepinephrine and dopamine reuptake inhibitor. It is used to treat depression (including seasonal depression), nicotine addiction and obesity. Data on the effects of bupropion on blood pressure are inconsistent. A randomized, double-blind, placebo-controlled study by Thase et al. (2008) of 300 patients with first degree hypertension investigated the effect of bupropion on blood pressure. Patients were randomized (four arms 1:1:1:1) to receive either placebo or prolonged-release bupropion (SR) 150, 300 or 400 mg/day for 4 weeks. Systolic and diastolic blood pressure decreased in all groups by –6.53, –6.46, –4.20, –4.87 mm Hg and –2.36, –2.27, –1.95, –1.55 mm Hg, respectively [32].

Slightly different results were obtained by Roose et al. (1991) in a study involving 32 patients with depression and cardiovascular diseases. These researchers showed that bupropion increased blood pressure in the supine (but not standing) position [33]. Similar results were obtained by Kiev et al. (1994) in a randomized, double-blind, placebo-controlled trial in 115 depressed patients. It has been shown that patients treated with bupropion (225–450 mg/day) experienced a slight but statistically significant increase in supine diastolic blood pressure by 5.6 mm Hg after the first week of treatment and by 7.5 mm Hg in the fourth week of treatment [34]. In conclusion, bupropion may increase diastolic blood pressure in supine patients [35].

Antipsychotic drugs

Antipsychotics are a group of drugs that have been used to treat mental illness since the 1950s. There are two main groups of antipsychotics: classic (older) antipsychotics (i.e. first-generation antipsychotics) and atypical neuroleptics. First-generation drugs, compared to atypical neuroleptics, more often cause extrapyramidal symptoms. In contrast to classic neuroleptics, second-generation drugs are more likely to cause symptoms of the metabolic syndrome, i.e. hypertension, insulin resistance, abdominal obesity, dyslipidemia and additionally — sexual dysfunction [36]. Side metabolic effects resulting from the use

of antipsychotic drugs are most pronounced in the first 6 weeks of their use, when the body mass index and waist circumference increase [36]. Clozapine and olanzapine are characterized by the highest average weight gain risk during antipsychotic treatment. Data from prospective studies indicate a possible increase of 6 to 12 kg in the first year of treatment and 3 to 12 kg in the later period [37]. In general, the symptoms of the metabolic syndrome are quite common (40%) in patients with schizophrenia treated with antipsychotics [38].

Hypertension in patients taking antipsychotic drugs is a consequence of the metabolic disorders caused by these drugs but many of them can also cause orthostatic hypotension [39]. A review of the literature by Gonsai et al. (2018) summarized the knowledge of the mechanism of the influence of antipsychotic drugs on blood pressure. All 5 dopamine receptor subtypes (D1, D2, D3, D4 and D5) regulate sodium excretion and blood pressure. The D1, D3 and D4 receptors interact directly with the renin–angiotensin–aldosterone system, whereas D2 and D5 receptors directly interact with the sympathetic nervous system to regulate blood pressure. The authors indicate that the use of dopamine receptor antagonists may disturb the regulation of blood pressure, leading to its increase [40].

The effect of clozapine or olanzapine administered for 8 weeks on blood pressure was analyzed in a retrospective study by Woo et al. (2009) involving patients with schizophrenia. A total of 167 patients were included in the study; 70 patients in clozapine group and 97 patients in olanzapine group. There was a significant increase in systolic (115.68 ± 8.64 mm Hg *vs.* 118.64 ± 11.65 mm Hg; p = 0.031) and diastolic (75.64 ± 6.52 mmHg *vs.* 79.36 ± 8.68 mm Hg; p = 0.001) blood pressure in the clozapine group. Moreover, a significant increase in body weight and serum triglycerides concentrations was found in this group of patients. Only significant weight gain was observed in patients treated with olanzapine. The researchers concluded that treatment with clozapine may lead to an increase blood pressure [41]. In a retrospective study by Norman et al. (2017) involving patients with a DSM IV diagnosis of schizophrenia or schizoaffective disorder, the effect of treatment with clozapine on blood pressure for 24 weeks was assessed. In this study participated 18 patients, and the mean stabilized clozapine dose was 441.7 ± 171.8 mg/day. It was shown that 22% of patients met criteria for hypertension before and 67% during clozapine treatment (p = 0.0124). No significant changes in weight or renal function occurred during clozapine treatment. Thus, this study also showed that clozapine may increase the risk of hypertension [42].

Valsartan, telmisartan and topiramate have been shown to be effective in blood pressure control in patients taking antipsychotic drugs [43].

In conclusion, when taking antipsychotics, due to the risk of both blood pressure increase and decrease, patients should be monitored regularly and, if necessary, existing antihypertensive therapy should be initiated or modified.

Mood stabilizers

Mood stabilizers include antiepileptic drugs, i.e. valproic acid, carbamazepine, lamotrigine and lithium salts with neuron membrane stabilizing activity. Mood-stabilizing drugs do not directly increase blood pressure, but they may contribute to the development of obesity, which may result in secondary dyslipidemia and hypertension. When using these medications, special attention should be paid to other medications taken by the patient, as mood stabilizers have numerous drug interactions.

When lithium salts are used concomitantly with thiazide diuretics or angiotensin converting enzyme inhibitors, the blood concentration of lithium may increase (should not be higher than 1.2 mmol/L). In the case of the use of thiazide diuretics, the increase is 20–40% of the blood pressure may occur and is due to the increase of lithium reabsorption in the proximal nephron coil. Moreover, spironolactone, which is an antagonist of the mineralocorticoid receptor, by increasing the amount of urine excreted may also increase the concentration of lithium in the body [44]. Excessive increase in the concentration of lithium (> 1.5 mmol/L) in the blood leads to intoxication and potentially life-threatening condition [44]. It has been shown in studies that the use of loop diuretics in patients over 66 years of age and taking lithium salts significantly increases the risk of hospitalization due to complications resulting from the toxicity of lithium [45].

The effect of lamotrigine on the risk of hypertension was assessed by Danielsson et al. (2018) in a study involving 1778 pregnant women with epilepsy and 221662 pregnant women without epilepsy. In the group of women taking lamotrigine (n = 280), this drug has not been shown to increase the risk of disorders associated with an increase in blood pressure in pregnancy (hypertension in pregnancy, mild to severe pre-eclampsia, early-onset pre-eclampsia). The total odds ratio of the disorders associated with the increase in blood pressure was 1.20 (95% CI:

0.76–1.88, p = 0.434) [46]. A review of the literature by Katsiki et al. (2014) analyzed the effect of different antiepileptic drugs on risk factors for cardiovascular disease. It was found that lamotrigine did not increase the risk of metabolic syndrome, body weight and tissue resistance to insulin [47]. Therefore, it seems that such properties of lamotrigine confirm its neutral influence on the risk of hypertension.

The presented data indicate that although mood stabilizers do not directly increase blood pressure, when using lithium salts, particular care should be taken in the case of concomitant use of antihypertensive drugs.

Psychostimulants

The mechanism of action of these psychostimulants is to increase the concentration of noradrenaline and dopamine in the synaptic space. A slight but statistically significant increase in systolic (by 3.3 mm Hg) and diastolic blood pressure (by 1.5 mm Hg) was demonstrated in the 1-year follow-up of 432 children with attention deficit hyperactivity disorder (ADHD) aged 6–13 years receiving methylphenidate (at a dose of 18–54 mg) [48]. The effect of methylphenidate on blood pressure was assessed in a randomized 6-week clinical trial in 141 patients with ADHD. A slight but statistically significant increase in systolic (3.5 ± 11.8 mm Hg) and diastolic (4.0 ± 8.5 mm Hg) blood pressure was demonstrated [49].

The long-term cardiovascular effects of methylphenidate intake (up to 60 mg/day) have also been extensively evaluated in adults with ADHD. A 24-month study involving 223 adult patients showed a small but statistically significant increase in systolic (2.3 ± 12.5 mm Hg; p = 0.006) and diastolic (1.3 ± 9.2 mm Hg; p = 0.042) blood pressure [50]. The short-term cardiovascular safety of lisdexamfetamine has been extensively assessed in a 4-week, randomized, controlled clinical trial in 420 adult ADHD patients. There was no statistically significant effect of this drug on both systolic and diastolic blood pressure [51].

A meta-analysis of six randomized, double-blind, placebo-controlled clinical trials (6–9 weeks duration) evaluated the effects of another psychostimulant — atomoxetine on blood pressure in a pediatric ADHD population, including 280 younger children (6–7 years old) and 256 older children (ages 6–7) at the age of 8–12). A statistically significant increase in systolic (2.1 mm Hg) and diastolic (2.9 mm Hg) blood pressure in the group of older children was found [52]. A meta-analysis by Hannissen et al. (2017) covering 18 clinical trials assessed the effects of methylphenidate, amphetamines, and atomoxetine on diastolic and systolic blood pressure in children and adolescents with ADHD (n = 5837). The mean duration of therapy was 28.7 weeks. All three medications were associated with a small, but statistically significant increase of systolic blood pressure (SMD: 0.18; 95% CI: 0.10–0.27, p < 0.01). The head-to-head comparison of the three medications did not reveal significant differences [53]. A more recent meta-analysis by Liang et al. (2018) assessed the effects of atomoxetine and methylphenidate on systolic blood pressure in young people and adults with ADHD. Twenty-two studies were included and the total number of participants was 46107. Children/adolescents and adults treated with methylphenidate had more significant increases in post- *vs.* pre-treatment SBP (pooled SMD with random-effects model: 1.40, 95% CI: 0.62–2.18, z = 3.52, p < 0.001) than those treated by placebo. Subgroup analysis showed no significant difference in systolic blood pressure between children/adolescents and adults in post- *vs.* pre-treatment. Children and adolescents treated with atomoxetine had more significant increases post- *vs.* pre-treatment SBP (pooled SMD with random-effects model: 0.366, 95% CI: 0.23–0.51, p < 0.001) than those treated with methylphenidate. The researchers conclude that during treatment with methylphenidate or atomoxetine, blood pressure should be monitored regularly [54].

In conclusion, psychostimulants to a slight but statistically significant degree may increase systolic and diastolic blood pressure [55].

Summary

As presented above, many groups of psychotropic drugs potentially influencing blood pressure are used in the treatment of mental diseases (Tab. 1) [6, 7, 56].

When planning treatment with the use of psychotropic drugs, it is first necessary to determine whether the patient has normal blood pressure. If the patient has hypertension, it should be determined whether it is well controlled and what antihypertensive drugs they are currently taking. In the case of treatment with psychotropic drugs, which potentially increase blood pressure, it should be monitored regularly and, if necessary, therapy with these drugs should be started or modified.

Conflict of interests

Authors declare no conflict of interest.

Table 1. Psychotropic drugs and their influence on blood pressure

Drug group	Subgroup	Risk of hypertension	Safety in patients with cardiac burden
Antidepressants	TCAs	Yes	They should be used with extreme caution. If possible, choose a drug from a different group
	SSRIs	Probably slight increase	They seem safe however, each case must be considered individually
	SNRIs	Probably yes (especially venlafaxine and milnacipran)	They seem relatively safe; however, attention should be paid to interactions e.g. venlafaxine–amlodipine
	IMAOs	Dependent on adherence to dietary restrictions and medications used	Dependent on adherence to dietary restrictions and medications used
	Trazodone (SARI)	Probably not	Treatment may need to be adjusted in patients with arterial hypertension (i.e. drug dose reduction)
	Bupropion (NDRI)	Increases blood pressure in supine position	Particular caution should be exercised in patients lying down
	Esketamine	Yes. The effect is temporary and most commonly occurs just after drug administration	Particular care should be taken in patients with unstable blood pressure values
Antipsychotics	First generation antipsychotics	Probably yes	Carefully, especially in patients treated with diuretics
	Second generation antipsychotics	Probably yes	Should be used with caution
Mood stabilizers	Carbamazepine, valproic acid	No	Seem safe
	Lithium carbonicum	No	Be careful due to interactions with diuretics
	Lamotrigine	No	The drug is cardiologically safe
Psychostimulants		Yes	Rather not recommended in patients with cardiac burden; they should be used with extreme caution

TCAs — tricyclic antidepressants; SSRIs — selective serotonin reuptake inhibitors; SNRIs — serotonin and norepinephrine reuptake inhibitors; SARI — serotonin antagonist and reuptake inhibitor; IMAOs — monoamine oxidase inhibitor; NDRI — norepinephrine-dopamine reuptake inhibitor

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Aortic knob width is associated with non-dipping blood pressure pattern

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Abstract

Background: Aortic knob width (AKW) is the measurement of the radiographic configuration composed of the foreshortened aortic arch and a part of the descending aorta. We investigated the relationship between the non-dipper pattern and AKW.

Material and methods: All patients' office blood pressure measurements and 24-hour ambulatory blood pressure readings were recorded. A blood pressure drop of less than 10% was defined as non-dipping. The patients were grouped into Group 1; dipper pattern (37 patients; 22F, and mean age 49.2 ± 11.7 yrs) and Group 2; non-dipper pattern (64 patients; 37F, and mean age 53.7 ± 13.1 yrs). On posteroanterior chest radiography, the widest point of the aortic knob was measured along the straight imaginary line from the lateral edge of the trachea to the left lateral wall of the aortic arch.

Results: AKW was significantly higher in Group 2 compared to group 1 (36.7 ± 5.7 *vs.* 30.7 ± 4.5 mm, $p < 0.001$). The mean daytime and night-time systolic blood pressures, the mean night-time diastolic blood pressure levels, 24-hour mean blood pressure and mean pulse pressures were higher; percentage of nocturnal drops was significantly lower in Group 2 compared to Group 1. AKW was determined to be the parameter that was mostly related to the non-dipper pattern. A ROC analysis revealed that the area under the curve values for AKW values of non-dippers were 0.796 (95% CI: 0.707–0.884, $p< 0.001$).

Conclusion: AKW is significantly higher in non-dipper individuals compared to dippers. AKW values above 32.6 mm on the chest radiograph may be associated with non-dipper pattern especially in hypertensive individuals.

Key words: aortic knob width, non-dipper pattern, hypertension, chest radiography

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Introduction

Widespread hypertension is known risk factor for the development of cardiovascular disease, renal failure, and cerebrovascular disease [1]. Blood pressure exhibits a circadian rhythm in healthy individuals; starting to decrease later in the evening, reaching its lowest value at midnight, and rising just after waking up in the morning [2]. Drops ≥ 10% in mean systolic and diastolic blood pressure at night compared to the

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daytime values constitutes a dipping pattern, whereas reductions of less than 10% are known as non- dipping [3]. It is known that patients who are characterized by non-dipping (non-dippers) are at increased cardiovascular risk, target organ damage, and future cardiac and cerebral events [4].

Chest radiography is an inexpensive and easy method contributing to the diagnosis and treatment of several cardiovascular diseases. Aortic knob width (AKW) is the measurement of the radiographic configuration composed of the foreshortened aortic arch and a part of the descending aorta. It has been demonstrated in several studies that there is a relationship between AKW and various cardiovascular diseases in hypertensive patients [5–8].

We sought to investigate the relationship between the non-dipping pattern and AKW.

Material and methods

Patient selection

We enrolled a total of 101 consecutive patients (42 males, 59 females; mean age: 52.2 ± 13.1 years) without known hypertension and not receiving blood lowering drugs . Patients presented to our outpatient clinics of internal diseases and cardiology. underwent ambulatory blood pressure measurements either to confirm or rule out the HTN diagnosis. Detailed medical history (history of the complaints, medication use, previous blood pressure levels, etc.) was obtained from all participants and a detailed physical examination was performed. Diabetes was diagnosed when fasting blood glucose levels was above 125 or a patient was receiving antidiabetic treatment. Family history of heart disease was considered positive in patients with a history of cardiovascular disease in their first-degree relatives. Body mass index was calculated by dividing the body weight in kilograms by the square of body height in meters (kg/m^2) [9]. The waist and hip circumferences were measured with an elastic tape. The circumference of the waist was measured at the level of the umbilicus and the subcostal plane, while the patient stands in an upright position with both arms open.

We defined the metabolic syndrome (MetS) according to ATP-III criteria. MetS criteria include the presence of central obesity (waist circumference in men > 102 cm and women > 88 cm), hyperglycemia [fasting plasma glucose ≥ 100 mg/dL (5.6 mmol/L)], low HDL-C [HDL-C ≤ 40 mg/dL (1.03 mmol/L) in men and 50 mg/dL (1.29 mmol/L in women)], hypertriglyceridemia [fasting plasma triglycerides 150 mg/dL (1.7 mmol/L)] and arterial hypertension (peripheral arterial blood pressure ≥140/90 mm Hg). According to the ATP-III criteria MS was defined as the presence of three or more components [10].

Detailed information was provided for all patients included in the study and their informed consents were received. The study was approved by the local ethics committee with the ID number 2338.

Aortic knob width measurement

On posteroanterior chest radiography, the widest point of the aortic knob was measured along the straight imaginary line from the lateral edge of the trachea to the left lateral wall of the aortic arch. To minimize interpersonal differences, a single reviewer blinded to the participants' demographic data measured all AKW on chest radiography [11].

Blood pressure and laboratory measurement

Blood pressure was measured with a sphygmomanometer (ERKA perfect aneroid sphygmomanometer, Germany) and heart rate was recorded in sitting position after resting for 5 minutes. The participants were advised to avoid caffeinated drinks and exercise for at least 30 minutes before the measurement. Blood pressure was measured at left arm. During the measurement, each participant was seated with their tested arm supported at the level of the heart. The mean of 3 BP measurements was calculated and used in all analyses.

Hypertension is defined as office SBP values ≥ 140 mm Hg and/or diastolic BP (DBP) values ≥ 90 mm Hg according to European hypertension management guidelines [12] [13]. Subjects with pregnancy, history of obstructive sleep apnea, acute infection, acute vascular event, malignancy, secondary hypertension, chronic renal failure, and uncontrolled thyroid dysfunction were excluded, as were those with resistant hypertension and those using medications elevating blood pressure. Patients' fasting blood glucose, total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), triglyceride, thyroid function tests, urea, creatinine, aspartate aminotransferase (AST), alanine transaminase (ALT), sodium and potassium levels were measured from venous blood samples after 8 hours of fasting.

Ambulatory blood pressure monitoring (ABPM)

Twenty-four hour blood pressure monitoring was performed with a portable digital recorder

(BPlab Blood pressure monitor, BPLAB Standart, Schwalbach, Germany) and placing an appropriately sized cuff to left upper arm. The device was set to perform blood pressure measurements every 15 minutes during daytime and every 30 minutes between 00:00 at night and 08:00 in the morning. The patients were asked to continue their normal daily activities, to avoid heavy exercise, and to remain still during blood pressure measurements. The default setting for daytime (07:00 to 23:00) and night-time (23:00 to 07:00) hours were modified appropriately based on the patient's feedback. A night-time blood pressure drop of at least 10% was labeled as dipper pattern and a drop of less than 10% as non-dipper pattern [3].

Transthoracic echocardiography

Echocardiogram procedures were performed using a Philips EPIQ 7 device (Philips Healthcare, Andover, MA, USA). A 2.5 MHz probe was used for the Doppler measurements and a 2.5–3.5 MHz probe was used for tissue Doppler measurements. Left ventricle (LV) dimensions and wall thickness were obtained from the parasternal long axis with an M-mode cursor positioned just beyond the mitral leaflet tips, perpendicular to the long axis of the ventricle. LV end-diastolic diameter and end-systolic diameter and thicknesses of the interventricular septum and posterior wall of the left ventricle were measured. LV ejection fraction (LVEF) was estimated by Simpson's rule. Mitral inflow velocities were evaluated by pulse-wave Doppler with the sample volume placed at the tip of the mitral leaflets from the apical 4-chamber view. Diastolic peak early (E), peak late transmitral flow velocity (A), and deceleration time of peak E velocity (EDT) were measured. Tissue Doppler velocities (Sm, Em, Am) were measured from lateral, septal and tricuspid annuli [14]. Measurements were calculated from 3 cardiac cycles.

Statistical analysis

The study data were analyzed using SPSS 22.0 software package. The numerical variables were expressed as mean ± standard deviation and non-normal distributed variables with median. Categoric variables were expressed as frequency (n) and percentage (%). Inter-group differences for categoric variables were tested using χ^2 test or, when the assumptions for χ^2 test were unmet, Fisher's exact test. The normality of distribution of numerical variables was tested with Kolmogorov-Smirnov test. The comparison of continuous variables between two independent groups was performed with independent samples t test when the parametric test assumptions were met, and with Mann Whitney-U test when the parametric test assumptions were unmet. Spearman correlation analysis was used to evaluate the relationship between AKW and ABPM measurements. To assess the independent contribution of each variable, except for ambulatory blood pressure parameters, we performed a multiple logistic regression analysis that included all clinical variables with a $p < 0.05$ in the univariate analysis. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A receiver operating characteristic (ROC) curve analysis was used to calculate the AKW value that predicted non-dippers with the best specificity and sensitivity. A p value of less than 0.05 was considered statistically significant.

Results

Using the data obtained via ambulatory blood pressure monitoring (ABPM); the study population was divided into 2 groups as follows: Group 1; dipper pattern, 37 patients, 22 females, and mean age 49.2 ± 11.7 years and Group 2; non-dipper pattern, 64 patients, 37 females, and mean age 53.7 ± 13.1 years. Table 1 shows the comparison of demographic data, laboratory findings, and office blood pressure measurement results between the groups. Systolic and diastolic blood pressure levels were significantly higher in Group 2 compared to Group 1 (Tab. 1). The frequencies of hypertension and MetS were significantly higher in Group 2 compared to Group 1 (Tab. 1). The measured values of AKW were significantly higher in Group 2 compared to Group 1 (36.7 ± 5.7 *vs.* 30.7 ± 4.5 mm, $p < 0.001$).

ABPM records are shown in Table 2. The mean daytime and night-time systolic blood pressure and the mean night-time diastolic blood pressure levels were higher in Group 2 compared to Group 1. The percentage of nocturnal drops was significantly lower in Group 2 compared to Group 1. The 24-hour mean blood pressure and mean pulse pressure were higher in Group 2 compared to Group 1.

Positive correlations were found between AKW and age, the mean daytime systolic and diastolic blood pressure levels, the night-time maximum systolic and diastolic blood pressure levels, the mean night-time systolic and diastolic blood pres-

Table 1. Demographic and laboratory features of the groups

	Group 1 (n = 37)	Group 2 (n = 64)	p
Age [years]	49.2 ± 11.7	53.7 ± 13.1	0.09
Gender [F, n]	22	37	0.87
BMI [kg/m^2]	30.9 ± 9.6	29.9 ± 5.4	0.46
Systolic blood pressure [mm Hg]	137.0 ± 15.1	147.2 ± 12.8	< 0.001
Diastolic blood pressure [mm Hg]	80.9 ± 10.9	74.1 ± 11.8	0.02
Heart rate [beats/min]	82.8 ± 9.5	80.8 ± 11.9	0.38
Hypertension [n]	21	45	0.008
Diabetes Mellitus [n]	7	15	0.57
Family history of CAD [n]	16	25	0.72
Smoking [n]	12	21	0.96
Metabolic syndrome [n]	8	28	0.02
Obesity [n]	14	30	0.33
Glucose [mg/dL]	107.5 ± 41.7	113.1 ± 51.1	0.59
Total cholesterol [mg/dL]	196.2 ± 64.8	185.9 ± 75.5	0.52
Triglyceride [mg/dL]	185.9 ± 75.5	203.7 ± 133.9	0.50
HDL [mg/dL]	43.5 ± 8.5	46.4 ± 9.9	0.17
LDL [mg/dL]	134.8 ± 40.6	135.9 ± 33.2	0.89

BMI — body mass index; CAD — coronary artery disease; HDL — high density lipoprotein; LDL — low density lipoprotein

Table 2. Comparison of ambulatory blood pressure measurements between the groups

	Group 1 (n = 37)	Group 2 (n = 64)	p
Mean daytime systolic BP [mm Hg]	124.7 ± 12.3	131.6 ± 15.5	< 0.03
Mean daytime diastolic BP [mm Hg]	80.3 ± 8.2	80.5 ± 10.0	< 0.91
Mean night systolic BP [mm Hg]	109.1 ± 10.7	128.0 ± 16.5	<0.001
Mean night diastolic BP [mm Hg]	68.0 ± 7.9	77.1 ± 10.2	< 0.001
24 hour mean systolic BP [mm Hg]	118.1 ± 9.6	128.8 ± 14.1	0.01
24 hour mean diastolic BP [mm Hg]	75.1 ± 5.9	79.5 ± 9.6	0.07
24 hour mean BP [mm Hg]	92.5 ± 11.2	99.0 ± 11.7	0.01
% nocturnal decrease systolic [mm Hg]	14.3 ± 4.9	4.6 ± 5.3	< 0.001
% nocturnal decrease diastolic [mm Hg]	13.5 ± 3.8	3.3 ± 5.6	< 0.001
Mean pulse pressure [mm Hg]	43.2 ± 7.8	48.2 ± 10.3	0.03

BP — blood pressure

sure levels, the mean 24-hour systolic and the mean blood pressure levels (Tab. 3). Similarly, there was a negative correlation between AKW and nocturnal drops in the systolic and diastolic blood pressure levels (Tab. 3). Of the echocardiographic parameters, the interventricular septum thickness and the aortic root diameter were significantly correlated ($r = 0.51$, $p < 0.001$; $r = 0.44$, $p = 0.001$, respectively). Also, there was a significant and positive correlation between AKW and age ($r = 0.50$, $p < 0.001$).

In order to study which parameter was associated with the non-dipper pattern; modelled univariate and multivariate regression analyses were applied, using the model which was created with the inclusion of AKW, age, gender, presence of hypertension, BMI, waist-height ratio, and the presence of MetS. AKW was determined to be the parameter that was most related to the non-dipper pattern (Tab. 4). A ROC analysis revealed that the area under the curve values for AKW values of non-dippers were 0.796

Table 3. Pearson's correlation analysis between the aortic knob width (AKW) and several ambulatory blood pressure monitoring (ABPM) recording parameters

	rho	p
Daytime mean systolic BP	0.32	0.003
Daytime mean diastolic BP	0.22	0.047
Night-time mean systolic BP	0.48	< 0.001
Night-time mean diastolic BP	0.40	< 0.001
% nocturnal decrease systolic	20.39	< 0.001
% nocturnal decrease diastolic	–0.38	< 0.001
24 hour mean systolic BP	0.41	0.007
24 hour mean diastolic BP	0.25	0.101
24 hour mean BP	0.33	0.02

BP — blood pressure

(95% CI: 0.707–0.884, p < 0.001) (Fig. 1). The cut-off value for AKW to predict non-dippers was 32.6 mm with a sensitivity of 71.9% and a specificity of 75.7%.

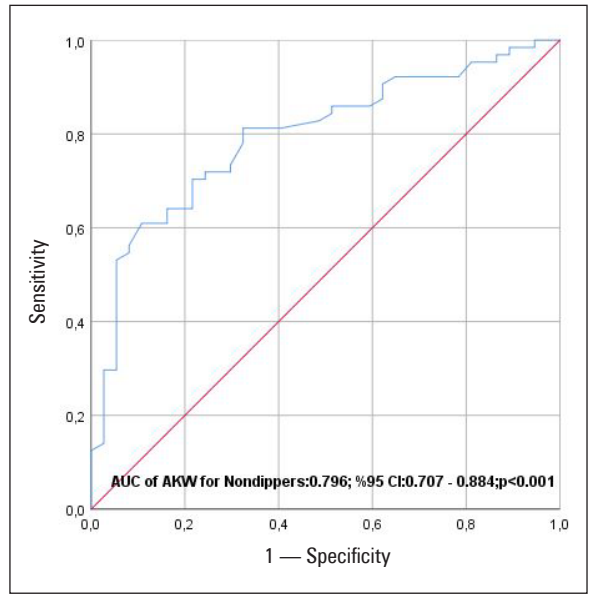

Figure 1. Receiver operating characteristics (ROC) curve used to calculate the aortic knob width (AKW) value that predicted non-dippers

Discussion

The main finding of our study is that AKW is associated with the non-dipper pattern in both hypertensive and non-hypertensive individuals. AKW correlates with blood pressure parameters obtained via ABPM.

In routine clinical practice, chest radiograms are obtained in the majority of cardiac patients. Information about many diseases and conditions can be obtained via chest radiographs. Elderly patients are known to have more dilated and tortuous aortas. Aneurysmal dilatation of the aorta or of the aortic arch can be observed with persistent high blood pressure [15]. Several studies are available, associating AKW with various cardiovascular disorders and hypertension.

In a 374 patient study, the relationship of AKW with subclinical atherosclerosis was investigated in hypertensive patients by using the cardio-ankle vascular index (CAVI) as a marker of subclinical atherosclerosis. The study demonstrated that AKW over 41 mm can predict subclinical atherosclerosis [7].

In a similar study that investigated the relationship between the carotid intima media thickness (CIMT) and AKW in patients with essential hypertension, Erkan et al. found a strong correlation between those two variables (r = 0.62, p < 0.001). By applying regression analysis, they also showed

Table 4. Univariate and multivariate regression analysis showing the parameters related with non-dipper pattern

	OR	Univariate		Multivariate	
		95% CI	p OR	95% CI	p
AKW	9.329	3.384–25.715	< 0.001 6.848	1.479–31.698	0.014
Metabolic syndrome	2.819	1.117–7.114	0.028		
Hypertension	3.109	1.338–7.222	0.008		
Waist to length ratio	2.729	1.168–6.380	0.020		
Gender	1.070	0.470–2.437	0.871		
Body mass index	1.561	1.050–2.320	0.028		
Age	1.029	0.996–1.064	0.088		

OR — odds ratio; CI — confidence interval

that AKW was one of the independent predictors to predict CIMT [6].

Sung et al. have conducted a study on 587 individuals to investigate whether there is a relationship between AKW and heart rate variability, which is used for the evaluation of the autonomic nervous system activity and which is recorded with an ambulatory Holter rhythm device. The study found that AKW was significantly associated with the values of the time domain, one of the parameters indicating heart rate variability. Considering the lack of association of AKW with the frequency domain values and with some other parameters in women participants as the limitations of that study, the investigators showed that AKW was associated with heart rate variability parameters [16]. Because the main purpose of our study was to analyze the relationship between blood pressure patterns and AKW, variables of heart rate variability have not been investigated. However, the study by Sung et al. appears valuable by showing the relationship of AKW with the autonomic nervous system as well as the cardiovascular system.

Rayner et al. compared chest radiographs from 82 hypertensive and 77 normotensive patients. In their study, they not only found that AKW was larger in hypertensive patients compared to normotensive individuals but also demonstrated that AKW was correlated with age and systolic and diastolic blood pressure levels. In our study; the categorization of the patients as normotensive and hypertensive individuals revealed that AKW was significantly larger in hypertensive individuals compared to normotensive ones (36.4 ± 5.9 mm compared to 31.7 ± 5.1 mm, respectively; $p < 0.001$) [5].

Jeon et al. included 252 patients in a study investigating whether there was a relationship between the aortic pulse pressure (APP) and AKW. Besides finding larger AKW in patients with high APP, they also demonstrated a positive correlation between those two variables. Although the correlation they found in their study was weak ($r = 0.207$, $p < 0.001$); in the linear regression analysis, they showed a significant relationship between APP and AKW [17].

Sevencan et al. showed that when combined with renal resistive index, AKW could be a diagnostic and prognostic predictor of renal pathologies in individuals with essential hypertension [18].

In a study conducted by Gurbak et al. on 144 patients, the relationship between AKW and left ventricular hypertrophy was investigated in hypertensive patients. The investigators showed that an AKW of larger than 37 mm could predict left ventricular hypertrophy with high sensitivity and specificity [8]. In our study, AKW showed a significant correlation with the interventricular septum and aortic root diameter measured with transthoracic echocardiography.

Our study is a cross-sectional study; which included a population undergoing ABPM in a specific period. In our study, the diagnosis of hypertension was made or ruled out according to the ABPM results. The diameter of AKW in non-dipper individuals was found to be higher than that of dipper individuals and it was demonstrated that AKW values correlated with ABPM parameters in our study. The regression analysis is suggestive that AKW values of larger than 32.6 mm on the chest radiography would be associated with non-dipping blood pressures with 71.9% sensitivity and 75.7% specificity. To the best of our knowledge, our study is the first in associating AKW with blood pressure patterns.

In a large-scale study conducted in Korea, the relationship between AKW and MetS was investigated and it was shown that AKW was not only correlated with the MetS criteria but also increased as the number of metabolic syndrome components increased [10]. In our study; the rate of MS was significantly high in the group of individuals with a non-dipping blood pressure pattern, however, AKW was correlated only with the systolic blood pressure component of MetS. We think that the small number of individuals with MetS in our study population caused this result.

Conclusions

Being a simple and relatively inexpensive method AKW can modestly differentiate non-dipper individuals from dippers. AKW values above 32.6 mm warrants evaluation of the diurnal blood pressure profile.

Limitations of the study

Our study's major limitation is the small population size in the study groups. This study was a cross-sectional study and included patients meeting the inclusion criteria during a certain period. Even though the measurement of AKW is individual-based, a blinded researcher performed the measurements in our study in order to reduce both the error margin and the bias in the measured results.

Conflict of interest

The authors declare that they have no conflict of interest.

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Overweight/obesity as the dominant factors associated with hypertension in the elderly in Indonesia

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Abstract

Background: Increasing age causes a physiological decline, and the occurrence of diseases cannot be avoided. One of the most common comorbidity is hypertension, which increases the risk of cardiovascular disease, particularly in the elderly. This study aimed to determine the dominant factors associated with hypertension in the elderly in Indonesia.

Material and methods: The research design was a cross-sectional study using secondary data from the Indonesia Family Life Survey wave 5 in 2014. Hypertension category was determined based on the Joint National Committee 8 Hypertension Guidelines for individuals aged 60 years or older. Data of 1255 elderly individuals were analyzed using univariate analysis as well as bivariate analysis with chi-squared test and multivariate analysis with multiple logistic regression.

Results: Results showed that the proportion of hypertension in the elderly was 55% (3% and 52% controlled and uncontrolled hypertension, respectively). Bivariate analysis results showed that body mass index, physical activity, current smoking, employment, and marital status were the factors related to hypertension ($p < 0.05$). Multivariate analysis results showed that factors related to hypertension were body mass index ($OR_{adj} = 2.4$; 95% CI = 1.812–3.186), employment ($OR_{adj} = 1.6$; 95% CI = 1.248–2.047), marital status ($OR_{adj} = 1.3$; 95% CI = 1.035–1.710) and current smoking ($OR_{adj} = 0.7$; 95% CI = 0.599–0.998).

Conclusions: The dominant factor related to hypertension was BMI after controlling for employment, marital status, and current smoking.

Key words: current smoking; elderly; employment; hypertension; marital status; obesity

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Introduction

The physiological decline and incident diseases cannot be avoided with increasing age. One of the accompanying diseases is hypertension, a risk factor for cardiovascular morbidity and mortality, particularly in the elderly [1, 2].

Hypertension is defined as a systolic blood pressure (SBP) ≥ 140 mm Hg and/or diastolic blood pressure (DBP) ≥ 90 mm Hg. However optimal BP in adults is defined as SBP and DBP of 120 and 80 mmHg, respectively [3].

Based on the Joint National Committee (JNC) 8 Hypertension Guidelines for the general popu-

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lation aged ≥ 60 years, prescribed pharmacological therapy to reduce blood pressure starts if SBP or DBP is 150 or 90 mmHg, respectively (4–6). In elderly individuals without diabetes or chronic kidney disease (CKD), blood pressure level goal is SBP < 150 mm Hg and DBP < 90 mm Hg, and in elderly individuals with diabetes or CKD, the blood pressure level goal is SBP < 140 mm Hg and DBP < 90 mm Hg [7].

Hypertension is a preventable risk factor for several life-threatening conditions, including stroke. It is estimated that hypertension increases the risk of stroke 3–4 times compared with individuals without hypertension [8].

An estimated 1.56 billion adults will live with hypertension by 2025. Approximately 8 million people die worldwide annually because of hypertension, and approximately 1.5 million people die annually in the Southeast Asian region [9].

The incidence of hypertension increases with age. Hypertension affects approximately 10%, 40%, and > 65% of individuals aged 18–39 years, 40–59 years, and 60–79 years [2]. In Indonesia, based on data from the Basic Health Research in 2013, hypertension was the most common disease of elderly individuals (57.6%) [10]. Hypertension is the third leading cause of death after stroke and tuberculosis in Indonesia with a proportional mortality rate reaching 6.7% of deaths at all ages [8].

Some risk factors for hypertension are modifiable risk factors, including health conditions (overweight/obese, unhealthy diet, stress, sleep apnea, diabetes), lifestyle (sedentary lifestyle/lack of physical activity, tobacco usage, excessive alcohol usage), and risk factors that cannot be controlled are age, race, and family history [5]. This study aimed to determine the dominant factors associated with hypertension in the elderly in Indonesia.

Material and methods

Study design

This study used secondary data from the Indonesia Family Life Survey (IFLS). IFLS was a longitudinal survey of sustainable socio-economic factors and health. This was based on a sample of households representing approximately 83% of Indonesia's population living in 13 of 27 provinces in Indonesia in 1993: four provinces in Sumatra (North Sumatra, West Sumatra, South Sumatra, and Lampung), five provinces in Java (DKI Jakarta, West Java, Central Java, DI Yogyakarta, and East Java), and four provinces covering the remaining large islands (Bali, West Nusa Tenggara, South Kalimantan and South Sulawesi). IFLS has been conducted for five waves: IFLS1 in 1993, IFLS2 in 1997, IFLS3 in 2000, IFLS3 in 2007, and IFLS5 in 2014 [11]. In this study, data collected in IFLS5 were analyzed only. Thus, the research design was cross-sectional, where risk factors and outcomes were seen at the same time.

Population and subjects

The population in this study was all elderly (≥ 60 years) who were registered as samples in the IFLS5 and had complete measurement data for all variables. The IFLS5 included 3976 elderly individuals, in which 1255 elderly respondents had blood pressure measurements and complete data for all variables.

Measurements

Blood pressure was measured three times on both arms using a sphygmomanometer (Omron, HEM-7203), by regular trained interviewers on household members at home in a seated position. The mean blood pressure value from three measurements was included in the analysis [11, 12]. In this study, the mean blood pressure level was obtained and categorized using the JNC 8 Hypertension Guidelines standard. Hypertension category was defined as a history of hypertension or SBP ≥ 150 mm Hg and DBP ≥ 90 mm Hg without diabetes and CKD, or a history of diabetes or CKD with mean SBP ≥ 140 mm Hg and DBP ≥ 90 mm Hg. The normotension was defined as SBP < 150 mm Hg and DBP < 90 mm Hg without diabetes and CKD, or a history of diabetes or CKD with mean SBP < 140 mm Hg and DBP < 90 mm Hg. Hypertension was divided into controlled and uncontrolled hypertension. Controlled hypertension was defined as hypertensive patients with mean SBP < 150 mm Hg and DBP < 90 mm Hg without diabetes or CKD or mean SBP < 140 mm Hg and DBP < 90 mm Hg with diabetes or CKD. Uncontrolled hypertension was defined as hypertensive patients with mean SBP ≥ 150 mm Hg and DBP ≥ 90 mm Hg without diabetes or CKD or mean SBP ≥ 140 mmHg and DBP ≥ 90 mm Hg with diabetes or CKD.

Body weight was categorized depending on the body mass index (BMI) value, according to the WHO criteria for the Asian population: normal weight < 25 kg/m^2 and overweight/obesity ≥ 25 kg/m^2 [13, 14]. The BMI value was obtained by dividing weight by height square (weight/$height^2$). The weight was measured using the Camry scale, EB1003 model. Weight was measured to the nearest tenth of a kilogram. The plastic high-board Seca, 213 model was used to

measure height. Height was measured to the nearest millimeter [11].

Smoking behavior was determined by current smoking as "smoking" and "not smoking." If the respondent stated that he has stopped smoking less than 1 year, then the status of smoking was still categorized as "smoking"

In the global recommendations of physical activity for health, routine activities are moderate-to vigorous-intensity activity performed 3–5 days per week, 30–60 minutes per session or should be at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or equivalent combination of moderate- and vigorous-intensity activity [16]. In this study, the elderly was categorized to be "active" if doing at least 30 minutes of moderate activities 5 days per week or heavy activities 3 days per week or equivalent combination of moderate- and vigorous-intensity activity and was said to be "inactive" if the activity was less than that of "active" category.

Mental health was measured using Center for Epidemiologic Studies Depression (CES-D short) scale with 10 questions [11]. The categories were based on median values, namely the category "depression" and "healthy."

Employment status was defined as elderly individuals with current jobs or who were still getting income from their jobs. The employment category was "unemployed" or "employed."

Income was defined as the amount of annual income categorized in the percentile 1–5. Percentile 1–5 was categorized as "low income" and "high income" if annual income was ≤ percentile 3 and > percentile 3, respectively.

Marital status was categorized into "not married" if the respondent had never been married, separated from their partner, divorced, and "still married" if respondent still had a partner and lived together.

Elderly was defined as individuals aged ≥ 60 years [17, 18]. Age was categorized into "60–69 years" and "≥ 70 years" referred to as elderly and high-risk elderly, respectively [18].

Statistical analysis

Data analysis was performed by univariate analysis, bivariate analysis, with χ^2 test, as well as multivariate analysis with multiple regression logistic test. Significance was defined as $p < 0.05$. The results of the analysis were included in tables and figures. All statistical methods were applied using Stata IC 16.

Ethical clearance

The procedures of the IFLS survey have been reviewed and approved by the Institutional Review Boards in the United States (Rand Corporation, Santa Monica, California) and in Indonesia (Ethics Committee of Universitas Gadjah Mada in Yogyakarta for IFLS3-IFLS5, and Universitas Indonesia in Jakarta for IFLS1–IFLS2). Written informed consent was obtained from all the participants. Written informed consent was also obtained from the immediate family, caregiver, or guardian for children enrolled in the survey (https://www.rand.org). The study was conducted in accordance with the Declaration of Helsinki Ethical Principles and Good Clinical Practices.

Results

One thousand and fifty five elderly individuals were recruited to the study. The prevalence of hypertension was 691 (55%; 52% were uncontrolled and 3% controlled hypertension) (Figure 1).

Women comprised 52.8% of respondents. The age of the elderly in this study ranged from 60–101 years, which was categorized further into 60–69 years (elderly) and ≥ 70 years (high-risk elderly). Most of respondents were in the 60–69 years age group, which was at 67.7%. Of the total elderly individuals, 66.4% were married with living husband/wife.

The percentage of professionally active participants in the study was 63.3%, 68.7% had the lowest income. All variables included in the clinical characteristic of the study group are tabulated in Table 1.

Six of nine independent variables (BMI, current smoking, physical activity, mental health, employment, income, marital status, age, and sex) were sig-

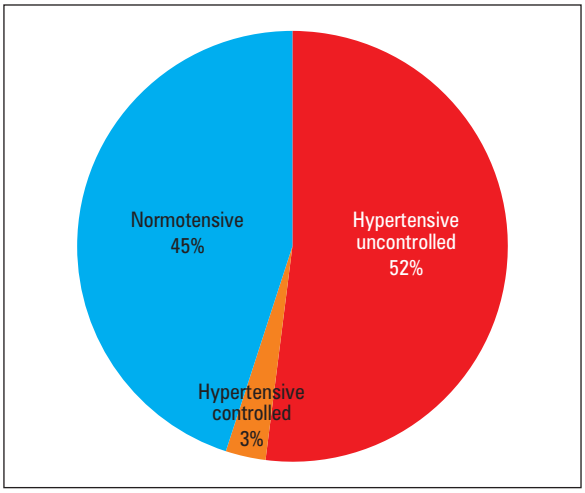

Figure 1. Blood pressure status in elderly people of Indonesia

Table 1. Factors associated with hypertension in the elderly

Variables	Hypertension (n = 691) (55%)	Normotension (n = 564) (45%)	Total (n = 1255)	p value	OR (95% CI)
Obesity					
Overweight/obese	233 (71.9%)	91 (28.1%)	324 (25.8%)	< 0.001	2.644
Non overweight/non-obese	458 (49.2%)	473 (50.8%)	931 (74.2%)		(2.010–3.479)
Current smoking					
Smoking	187 (45.6%)	223 (54.4%)	410 (32.7%)	< 0.001	0.567
Not smoking	504 (59.6%)	341 (40.4%)	845 (67.3%)		(0.447–0.720)
Physical activity:					
Not active	235 (59.3%)	161 (40.7%)	396 (31.6%)	0.038	1.290
Active	456 (53.1%)	403 (46.9%)	859 (68.4%)		(1.014–1.642)
Mental health					
Depressive symptoms	109 (51.9%)	101 (48.1%)	210 (16.7%)	0.314	0.859
Healthy	582 (55.7%)	463 (44.3%)	1045 (83.3%)		(0.463–1.813)
Employment					
Unemployed	297 (64.4%)	164 (35.6%)	461 (36.7%)	< 0.001	1.839
Employed	394 (49.6%)	400 (50.4%)	794 (63.3%)		(1.452–2.328)
Income					
Low income	489 (56.7%)	373 (43.3%)	862 (68.7%)	0.078	1.240
High income	202 (51.4%)	191 (48.6%)	393 (31.3%)		(0.976–1.575)
Marital status					
Not married	261 (61.8%)	161 (38.2%)	422 (33.6%)	0.001*	1.519
Still married	430 (51.6%)	403 (48.4%)	833 (66.4%)		(1.197–1.929)
Age:					
≥ 70 years old	236 (58.3%)	169 (41.7%)	405 (32.3%)	0.114	1.212
60–69	455 (53.5%)	395 (46.5%)	850 (67.7%)		(0.954–1.540)
Sex					
Female	403 (60.8%)	260 (39.2%)	663 (52.8%)	< 0.001*	1.636
Male	288 (48.6%)	304 (51.4%)	592 (47.2%)		(1.307–2.047)

*χ^2 test ($p < 0.05$); OR — odds ratio; CI — confidence interval

Table 2. The association of obesity, employment, marital status, and current smoking with hypertension

Variables	OR_{adj}	SE	p value*	95% CI
Obesity	2.403	0.346	< 0.001	1.812–3.186
Employment	1.599	0.202	< 0.001	1.248–2.047
Marital Status	1.330	0.170	0.026	1.035–1.710
Current smoking	0.773	0.101	0.048	0.599–0.998
Constant	0.830	0.089	0.083	0.673–1.024

*multiple regression logistic test ($p < 0.05$); OR_{adj} — adjusted odds ratio; SE — standard error; CI — confidence interval

nificantly associated with hypertension ($p < 0.05$), i.e., BMI, current smoking, physical activity, employment, marital status, and sex. Based on the multiple regression logistic analysis, eight variables entered as candidates: BMI, current smoking, physical activity, employment, income, marital status, age, and sex ($p < 0.25$). The final multivariate model is shown in Table 2.

The variables associated with presence of hypertension were BMI, employment and marital status, and current smoking ($p < 0.05$). The elderly with a BMI ≥ 25 kg/m^2 has a 2.4 times the risk of hypertension compared with the elderly with a BMI < 25 kg/m^2. The elderly people who were already retired had 1.6 times the risk of being diagnosed with hypertension compared with their professionally active counterparts. Noteworthy, elderly people who were active smokers had 0.7 times the risk of experiencing hypertension compared with the elderly individuals who are not smoking.

Discussion

This study outlines the cardiovascular risk profile of older patients with hypertension residing in Indonesia. Noteworthy, massive majority of hypertensive older patients were uncontrolled. The prevalence of hypertension in elderly women was higher (60.8%) compared with males (48.6%). Other studies in the elderly in Kolkata India also found that more (64%) of the elderly had hypertension, with 64.9% and 62.8% in the female and male elderly individuals, respectively [19]. The research in Pakistan also found that the incidence of hypertension was higher in the female elderly (78%) [20]. In the elderly people of Singapore, the prevalence of hypertension was comparable in both females and males which was 73.7% and 74.6%, respectively. But among them, the presence of uncontrolled hypertension was slightly higher in females (52.3%) compared to males (49.4%) [21]. From 15 million people with hypertension, barely 4% had controlled hypertension [8].

One of the most potent epidemiological risk factor for development of hypertension is overweight/obesity [22]. Both, increased BMI and advancing age were associated with higher blood pressure thus facilitating development of hypertension. Greater BMI has been also linked to higher cholesterol, heart disease, and stroke [23].

The elderly individuals with a BMI ≥ 25 kg/m^2 or elderly individuals with overweight/obesity in our study were in 25.8%. This is, however, lower than the prevalence of obesity in the elderly ≥ 60 years in the United States, where obesity is estimated at 37% [23]. Our study also showed the relationship between BMI and hypertension. A study in the Chinese elderly with relation to hypertension also documented a strong relationship between BMI and prevalent hypertension. However, the relationship between BMI and hypertension was attenuated when age was included as covariate in the analyses [24].

The elderly individuals with obesity had higher blood pressure as compared with the elderly individuals with normal BMI, which strongly points at the role of body mass control as an effective preventive measure [9]. This should be achieved by introduction of healthy diet, with high fiber consumption [25] along with increased physical activity, as recommended by expert documents [26].

The elderly individuals generally are less physically active; hence, they tend to spend less energy. Physical activity was the most tangible component of energy expenditure and the most controlled component. It is widely recommended that adults should engage in moderate physical activity for 30 min on most week days (a total of 150 min. over a week) [9, 16]. To increase physical activity, local communities and government agencies need to provide long-term health care programs designed specifically to prevent activity limitation in the elderly [27].

This study suggests that unemployment status confers risk for hypertension in elderly. Approximately two-thirds of the unemployed elder individuals were diagnosed with hypertension. Alternative studies from Pakistan confirm such relationship. Ishtiaq et al. documented that approximately 70% of those who were unemployed had poor control of hypertension [20]. Additionally, a study from Singapore showed that unemployment status was also related to uncontrolled hypertension. Unemployment status together with low income had a negative impact on the ability to buy anti-hypertensive drugs, which leads to non-adherence with treatment [21]. However such relationship is not evident, in part of European countries where no association between work status and hypertension was found [28].

Having a partner was a protective factor against high blood pressure. In our study, 62% of elderly people with hypertension were single. Several studies showed that individuals who were single (widowed, divorced etc.) were at higher risk of developing cardiovascular events [21, 22, 30]. People who always interact with their partners tend to control their partner's health through direct social control, such as encouraging, monitoring, reminding, and even threatening; hence, they adopt mutual healthy behaviors [21]. However, a study in Pakistan found that 78% of the population who were married or who had family had hypertension. Alternative explanation for this phenomenon was e.g., stress originated from household problems [20].

Cardiovascular disease is facilitated by smoking habits [3]. Smoking affects blood pressure, reduces exercise tolerance, promotes prothrombotic status, and endothelial dysfunction which altogether leads to chronic coronary syndromes or strokes cerebrovascular disease [9, 15]. Smokers have 2 to 4 times the risk of coronary heart disease as compared to their non-smoking counterparts [15, 31].

The results of this study showed that smoking was a common habit affecting one-third of elderly people. The prevalence of smoking in the elderly was higher than in Malaysia (15.2%), Lebanon (28.1%), and Europe (11.5%) [31]. The results of this study analysis showed that there was a relationship between current smoking status and prevalent hypertension is perplexed.

Smoking cessation is accompanied by substantial cardiovascular risk reduction, which underscores

necessity to broadly address this problem, also in elderly community of Indonesia where every third older person continues to smoke. This may translate to wide range of health benefit as one year after smoking cessation, the risk of heart attack is reduced by half which may be further decreased to the one observed in non-smokers after another 15 years. Additionally, the risk of lung cancer decreases by 50–60 percent after a decade without smoking which makes smoking cessation one of the most potent preventive measure [15].

Conclusion

Our study showed that large majority of elderly population of Indonesia is characterized by high blood pressure. Noteworthy, hypertension is accompanied by other potent cardiovascular risk factors such as overweight/obesity and surprisingly high percentage of current smoking. Our study identified most prevalent CV risk factors in elderly which should help to build an effective preventive strategies on a large scale.

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Cardiorespiratory effect of Swedish back massage in hypertensive patients: a randomized clinical trial

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Abstract

Background: Chronic stress is one of the main risk factors for incident hypertension. Behavioral methodologies, such as unwinding and rub, have a dramatic effect on controlling the individuals' reaction to stress, diminishing hypertension and heart rate, as well as changing temperature and respiration rate.

Material and methods: 90 patients with primary hypertension were enrolled to this open-label study. The patients have been haphazardly classified into an affect and an intervention cluster. In the two groups, systolic and diastolic blood pressure, heart rate, body temperature and respiratory rate) were measured and recorded two times a week before and after a ten-min Swedish back massage and relaxation for six weeks. The records have been accrued using a questionnaire which includes demographic records, a checklist of vital signs (systolic and diastolic blood pressure, heart rate, temperature, and respiratory) record, a fixed manometer and thermometer.

Results: Within the experimental group, systolic and diastolic blood pressure, heart rate, and respiratory levels reduced to 6.44 and 4.77 mm Hg, 2.9 bpm, 0.94 breaths per minute, respectively ($p < 0.001$) and temperature increased to 0.08°C after the back massage ($p = 0.004$).

Conclusion: The obtained results show the effectiveness of back massage in reducing blood pressure, heart rate, and respiratory as well as increased temperature in the study participants.

Key words: cardiorespiratory; back massage; hypertension

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Introduction

High blood pressure is one of the leading risk factors for cardiovascular disease. In 2018, nearly half a million deaths in the United States were could be either directly or indirectly ascribed to hypertension (HTN) [1, 2]. The prevalence of HTN in the USA is estimated at 108 million (45% of adult population) which translates to financial burden of approximately 131 billion USD yearly [3]. In Iran, the prevalence of HTN strikingly contrasts with the prevalence seen in westernized societies, and it is estimated at 20.1% [4].

Body massage result among others in stress relief, mental and physical refreshment which may in turn advantageously affect cardiovascular regulation [5, 6]. Both, acute and chronic stress promote rise in systolic and diastolic BP, respectively. As suggested, repetitive tactile incitement decreases diastolic BP

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over time [7]. Osborn et al. reported that complementary medicine could effectively decrease BP, which may be extremely important in country areas where patients have limited access to medications [8]. However, analysis using the Systematic Review Quality Assessment Tool showed that the studies assessing impact of massage on cardiovascular system were of poor quality [9]. Other limitations of these studies include intervention short time periods and non-standardized tools and protocols which make it difficult to compare the effects.

Taking into account all the shortcomings of previous reports, in our study we aimed to examine the effect of back massage on selected cardiovascular parameters in patients with primary hypertension.

Material and methods

We enrolled consecutive patients with hypertension who were referred to Imam Reza Clinic, Shiraz University of Medical Sciences, for high blood pressure evaluation from August to September 2013. Study protocol was approved by local Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC. 1392.S6603). Eligible participants were informed about the study objective and about the voluntary nature of their participation. Written informed consent form obtained from all participants. All data were anonymized and pseudonymized to comply with respective data management local regulations. Inclusion criteria were as followed: primary hypertension, age of 30–70 years old, absence of psychological diseases, no participation in other relaxation programs. Exclusion criteria included: skin and vertebral column disorders, ongoing treatment with anti-anxiety and sedative drugs, hypertension diagnosis of less than 6 months prior to enrollment, non-adherence to medication regimen during the study, history of hypotension, systolic blood pressure exceeding 170 mm Hg and/or diastolic BP exceeding 120 mm Hg, diabetes, chronic kidney disease, suprarenal tumors, and congenital heart defects, back pain because of backbone injuries, hernia or disk degeneration, recent lumbar region surgery.

The study sample size was determined based on the study by Hassanvand et al. entitled "The effect of back massage on BP and radial heart rate of patients with primary hypertension" [10] and using the following formula (d = 10, S = 8, $\alpha = 0.05$, $\beta = 0.2$).

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \times 2S^2}{d^2}$$

$$n = \frac{(1.96 + 0.84)22 \times 64}{100} \qquad n = 40$$

At first, the patients eligible for the study filled out the demographic information questionnaire and signed written informed consent. A total of 80 patients participated in the study and were randomly divided into an intervention and a control group, each containing 40 patients. Moreover, 5 patients were added to each group because of the attrition; thus, each group consisted of 45 patients.

To measure BP, heart rate and temperature in this study, a digital manometer and thermometer were used (digital manometer: Onyx model, the measurement accuracy of BP ± 3mm Hg, measurement accuracy of pulse ± 5%) which reliability and validity have been confirmed previously. Respiratory rate was assessed by medical inspection.

Operators were unaware of the fact whether the patient was allocated to intervention of control group.

Description of the procedure

Massage therapists were trained by a physical medicine expert. The expert supervised the performance of the therapists to assure about the uniformity of the procedure. Furthermore, two nurses assisted the patients with all the questionnaires to be filled after each procedure or both in experimental and control group. The massage that was applied in the present study is a part of Swedish massage which starts from neck to the back (from shoulders to lumber area) via compression or kneading and continues with pushing, tapotement, and ringing. The massage was performed twice a week between 8 A.M. and 13 P.M. for six weeks. A demographic questionnaire and BP, heart rate, temperature and respiratory rate records were filled for all the participants. In both groups, participants were asked to have a five-minute rest prior to BP, heart rate, temperature and respiratory rate were recorded. In the experimental arm, sesame oil was used for 10-minute massage. Immediately after the 10-min massage, BP, heart rate, temperature and respiratory were recorded again. In the control group, the patients rested for 10 min and BP, heart rate, temperature and respiratory were recorded.

Statistical calculations

Statistical analyses were performed using SPSS (Ver. 15). T test and chi square test were applied to analyze demographic data. Variables are presented as mean ± SD. Repeated measures ANOVA was used as appropriate. The significance level was set at p-value of < 0.05.

Results

Both the experimental and the control arms consisted of 45 patients (25, and 27 females respectively). Because four females did not continue their participation, 41 patients were considered in the control group. The mean age of the participants and other demographic variables for both groups are presented in Table 1.

The change in mean BP and pulse are presented in Table 2. In the experimental group, the mean systolic BP decreased by 6.4 mm Hg; the mean diastolic BP decreased by 4.8 mm Hg mean heart rate decreased by 2.9 bpm; the mean respiratory rate decreased by 0.9 breaths per minute; the mean temperature increased by 0.08°C. In the control group, the mean systolic BP decreased by 2.3 mm Hg, (p = NS); the mean diastolic BP decreased by 1.5 mm Hg, p = NS; the mean heart rate decreased by 1.0 bpm in the control group (p = NS); the mean respiratory rate decreased by 0.1 breaths per minute (p = NS); the mean temperature decreased by 0.03°C, p = NS).

The changes in systolic and diastolic BP, heart rate, temperature and respiratory rate were compared between the experimental and the control arm from sessions 1–12, and the results of repeated measures ANOVA indicated that the differences were statistically significant ($p < 0.001$, $p < 0.001$, $p = 0.008$, $p = 0.04$, $p = 0.04$). Furthermore, the

Table 1. The patients' demographic data

Variable		Experimental	Control	Total	Used test and p-value (intervention group *vs.* control group)
Age (mean ± SD)		56.8 ± 8.2	59.2 ± 8.5	58.0	t-test p = 0.18
Sex	Male	20	18	38	χ^2 p = 0.67
	Female	25	27	52	
Education level	Higher	7	3	10	χ^2 p = 0.48
	Secondary	13	11	24	
	Primary	20	24	44	
	Illiterate	5	7	12	
Occupation	Employee	3	1	4	χ^2 p = 0.76
	Self-employed	5	5	10	
	Retired	11	13	24	
	Housewife	26	26	52	
Marital status	Widowed	2	4	6	χ^2 p = 0.43
	Single	1	0	1	
	Married	42	41	83	

Table 2. The results on mean changes in variables. ANOVA with repeated measures

Variables	Group	F	p-value
Systolic BP	Experimental	11.39	< 0.001
	Control	2.29	0.05
Diastolic BP	Experimental	7.36	< 0.001
	Control	1.2	0.23
Heart rate	Experimental	5.35	< 0.001
	Control	5.69	< 0.001
Respiratory rate	Experimental	4.73	< 0.001
	Control	0.69	0.86
Temperature	Experimental	1.95	0.004
	Control	0.76	0.79

effects of time, group, and time*group on systolic BP, diastolic BP and heart rate in both groups were assessed using repeated-measures ANOVA (data not shown).

Discussion

Our study demonstrated potential utility of back massage in promoting BP and heart rate decreases. The size effect was modest, yet unanimous in almost all participants in the intervention group.

A study in Hong Kong showed that a 10-minute massage for 7 consecutive days by superficial stroke (alternative technique to the one studied here) was effective in decreasing high BP in elder patients with a history of stroke [11]. In a small comparative study which explored the impact of Swedish massage on BP, heart rate, and vital signs in females with hypertension authors reported similar results only after the four sessions [12]. Similarly, another study showed a decrease in BP and the heart rate after a 10-session back knead [10]. Contrasting with these findings, another study which evaluated body massage on cardiovascular control showed no significant changes in systolic and diastolic BP [13]. Nonetheless, the outcomes of several studies revealed that massage therapy reduced diastolic and systolic BP considerably [14–19].

Jahdi, Mehrabadi et al, showed that mother's vital signs during postpartum period decreased significantly after the massage compared to the control group [20]. The results of the studies show that massage therapy reduces systolic blood pressure, respiratory rate, and heart rate across different patients groups [21–26].

One of the limitations of the present study was that back massage was performed for 10 minutes only. Therefore, further studies are warranted to see whether longer duration or massage of alternative body areas with different techniques may exert comparable effects.

Conclusion

The results of the present study showed that a 12-session back massage decreased systolic and diastolic blood pressure, heart rate, and respiratory rate in hypertensive patients. Our findings warrants further studies on specific protocols of back massages as a non-pharmacological mean to improve BP control in hypertensive patients.

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Factors affecting blood pressure control in women aged 15–49

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Abstract

Background: While 25% of adult women in the world are hypertensive, the percentage of women who cannot achieve blood pressure control despite taking medication is 55.9 ± 1.5%. The aim of this study was to determine the prevalence and control rate of hypertension and to detect the factors affecting this situation in women in the 15–49 age group.

Material and methods: Seven hundred women in the 15–49 age group were selected and a questionnaire was applied. Height, weight, and blood pressure were measured and spot urines were collected on the same day. 24-hour sodium excretion and daily salt intake were calculated using the Kawasaki method.

Results: While 14.3% of the women were hypertensive, only 19% of them were able to achieve blood pressure control. Fifty-eight percent of the hypertensive women use more than 15 g/day of salt and the estimated 24-hour urinary sodium excretion of these women was 311.6 ± 39.5 mmol/L. Hypertensive women using less than 5 g/day of salt were 0.3%. Salty foods consumed by the hypertensive women were pickles (55.6%), cheese (92.6%), olives (88.8%), vine leaves (71.6%), sujuk and Turkish pastrami (47.6%), and tomato paste (100%).

Conclusions: In our study, participants were consuming large amounts of salt and there was a positive correlation between salt intake and blood pressure. Therefore, all efforts for sodium restriction are very important in the management of hypertension.

Key words: blood pressure control; risk factors; salt intake; women

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Introduction

According to reports by the World Health Organization, hypertension (HT) is the most preventable cause of death and is responsible for 62% of strokes and 49% of coronary heart diseases worldwide [1]. Throughout the world, 1.13 billion people are hypertensive and 1 in 5 is women. Fewer than 1 in 5 people with hypertension have the problem under control [2]. Hypertension is a very common problem in Turkey and 32.3% of women over the age of 18 are hypertensive.

Blood pressure (BP) of only 37.3% of hypertensive women who take medication is under control [3]. The prevalence of hypertension in adults aged > 30 years is 34.6% and of the individuals with hypertension, 28.9% are under control. [4]. Excessive salt intake in the diet is one of the main factors of hypertension [1, 5]. It is estimated that reducing salt intake in the diet to 6 g/day will reduce strokes

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by 24%, coronary heart disease by 18%, and will prevent 2.5 million deaths from stroke and coronary heart disease worldwide each year [6, 7].

A sedentary life, use of salt for long life food preservation, and the increase in consumption of processed food as a result of the development of industry in the last century have caused excessive salt consumption [8]. In addition, sodium-based food additives are among the most commonly consumed substances in the world. This is because sodium salts are not only food spoilage inhibitors but can also function as inexpensive flavor enhancers in a variety of foods. Only 5–10% of consumed salt is sourced from natural food [9]. Although the World Health Organization (WHO) recommends a daily consumption of 2 g of sodium (< 5 g/ day/salt) for adults [10], salt consumption per adult reaches 18 g/day per day in Turkey [11].

Salt is used extensively in the preparation and cooking of food in the Hacılar district of Kayseri. Traditionally, summer is the time when pickled foods are prepared in salty water at a rate varying from 6% to 20% to prevent food spoilage. Foods preserved in brine include pickles, cheese, olives, and vine leaves made with various vegetables and fruits. Tomato paste, which is obtained by crushing tomatoes and red peppers and by salting and thickening them in the sun in summer to be used in the winter, and sujuk and Turkish pastrami, which are prepared using salt, are foods frequently prepared and eaten in this region.

The salt intake of individuals can be assessed by either dietary surveys or the demonstration of 24-hour urinary salt excretion [9, 12]. However, as salt intake assessed by dietary questionnaires is prone to errors, its validity is low in general [12, 13]. The most reliable and accurate method of salt intake is to determine salt excretion in 24-hour urine [12, 14]. However, 24-hour urine collection is very difficult for both patients and multi-participant studies as it may cause incomplete collections, is time-intensive, and has high costs [12, 13]. Therefore, some methods have been developed to estimate 24-hour sodium excretion from spot urine samples [15–17].

The present study aimed to determine the prevalence and control rate of hypertension in women in the 15–49 age group in the Hacılar district of Kayseri and to determine the underlying factors.

Material and methods

Study design and participants

A cross-sectional field survey was conducted on women in the15–49 age group in the Hacılar District of Kayseri Province, from February 1 to May 1, 2016. Kayseri, one of the major industrial and commercial centers in Turkey, is located in the Central Anatolian Region between the northern latitude of 38° 18′ and the eastern longitude of 36° 58′. Its elevation is 1094 m and a continental climate is prevalent in the province.

In the district, with a population of 12,376, the number of women in the 15–49 age group is 2,722. The sample size of the study was calculated as a minimum of 683, taking a tolerance value of 0.03 and a confidence level of 0.95, and it was planned to include 700 women in the 15-49 age group. Women were selected from the list of 15–49 age group women in the Hacılar Family Health Center by the Simple Random Sampling method.

Data collection

The women included in the research study were visited at their homes, their consents were obtained, and they were informed of what to do for the processes of height, weight, blood pressure measurements, and urine intake.

Data collection and all measurements were carried out in the participants' homes. A questionnaire form consisting of 32 questions was filled by the researcher, using the face-to-face interview method to maintain the quality of the data. Demographic and social characteristics, brine food consumption habits, and salt consumption were investigated with the questionnaire. For the question "How often do you eat salty foods?" the possible answers were "almost every day", "about 3–5 times a week", "once a week", or "every fifteen days". Anthropometric and blood pressure measurements, and blood and urine sampling were performed for all participants.

Blood pressure measurement

Participants' blood pressures, after resting for 10 minutes, were measured twice with an adjustable cuffed sphygmomanometer, and the average of the two measurements was taken. The participants were not allowed to smoke, exercise, eat excessively, or consume caffeine before the blood pressure measurement. A health technician, who was informed by the researcher about the study, took the blood pressure measurements. Blood pressure assessments were made by taking into account the classification accepted by WHO. Hypertension was defined as a systolic BP of ≥ 140 mm Hg or a diastolic BP of ≥ 90 mm Hg [2]. Control of HT was defined as systolic BP < 140 mm Hg and diastolic BP < 90 mm Hg [19].

Body mass index determination

Body height and weight were measured to the nearest 0.1 cm and 100 g, respectively, while wearing light clothes without shoes. Body mass index (BMI) was calculated as weight (kg) divided by the square of body height (m), and classification was made according to WHO obesity criteria. According to this classification, those with BMI < 18.5 were considered as underweight, those with a BMI of 18.5–24.9 as normal, those with a BMI of 25–29.9 overweight, and those with a BMI of ≥ 30 and above as obese [18].

Urine sample collection

Urinary sodium and creatinine concentrations were measured using a spot sample. The second urine in the morning was collected by all participants at their home. All samples were self-collected mid-stream urines by each participant using a 10 mL sterilized container. The urine samples taken were placed in ice coolers and quickly transported to the Center Laboratory of the Medical Faculty of Erciyes University and stored at –20°C until analyzed. ISE (ion selective electrode) was used for the determination of sodium in urine, and Jaffe alkaline methods were used for the determination of creatinine. The 24-h urinary sodium excretion was estimated using the following equation, as presented by Kawasaki et al. [12, 15, 19].

24-h urine sodium excretion estimation

Estimated 24-hour urinary sodium excretion (mmol)/24 h = 16.3 × [spot urine Na (mmol/L)/ /spot urine Cr (mmol/L) × estimated 24-hour urinary Cr (mg)]0.5

This equation was used for predicted creatinine (Cr) excretion for 24 h (CrPr24h) estimated based on age, weight, and height.

CrPr24h (mg/24 h/women) = –12.63 × age + 15.12 × weight (kg) + 7.39 × height (cm) – 79.9

After determining CrPr24h, the urinary sodium excretion in 24 hours was measured (mmol/24 h can be calculated:

16.3 × [spot urine Na (mmol/L)/spot urine Cr (mmol/l) × estimated 24-hour urinary Cr (mg)].0.5

Lastly, daily salt intake (g/day) was converted from the 24-h urinary sodium excretion (mmol/day) multiplied by 0.0585.

Normal values of 24-h urinary sodium were accepted as 40–220 mmol/24 h [12, 15]. In this study, we classified the 24-h urinary Na value as normal if from 40–220 and as high value if ≥ 220.

We classified the estimated daily salt intake as < 5 g/day, 5–9 g/day, 10–14 g/day, and > 15 g/day, based on the WHO recommendation of 5 g/day [10].

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 22.0 for Windows. Whether the data obtained from the study followed normal distribution was tested by the Shapiro-Wilks and the Lilliefors tests. The Kruskal-Wallis test and the Mann-Whitney U test were used for variables that did not follow the normal pattern of distribution and one-way analysis of variance (ANOVA) tests were used for variables with normal distribution. The mean and standard deviation of variables such as BMI, blood pressure and urinary sodium excretion were calculated.

From the results obtained from the statistical tests applied, a p-value of less than 0.05 was considered statistically significant.

Results

The socio-demographic characteristics of the women participating in the study are shown in Table 1 and their anthropometric measurements, blood pressure, urine sodium, estimated salt intake, and creatinine levels are shown in Table 2.

The average age of the participants was 38.8 ± 9.4. It was found that 63.4% of the participants were illiterate or primary school graduates, 91% were housewives, 83.3% were married, 45.8% had 3 or more children, 85.7% did not smoke, 76.9% did not do regular physical activity, and 48.4% had a BMI of 30 and above. While 58% did not restrict salt, 14.3% were hypertensive, 25% had a family history of hypertension, and 54.9% had an estimated salt rate of over 15 grams per day.

Table 3 shows how often women consumed salty and pickled foods. Among the women participating in the study, 90.7% of made tomato paste, 96.8% pickles, 94.8% pickled vine leaves, and 73% made meat products themselves.

Out of 100 women previously diagnosed with hypertension, 81 were found to have high blood pressure, while only 19 were able to control their blood pressure. Thirty-five percent of hypertensive women had a diagnosis of hypertension for 2–3 years, 20% for about 20 years, and 85% of them use a single

Table 1. Distribution of women according to their socio-demographic characteristics

Variables	Number of patients (n = 700)	Percentage (%)
Age distribution		
15–19	32	4.6
20–29	94	13.4
30–39	202	28.9
40–49	372	53.1
Educational status		
Illiterate	126	18.0
Primary school	318	45.4
Secondary school	74	10.6
High school	113	16.1
University	69	9.9
Occupation		
Housewife	638	91.2
Officer	38	5.5
Worker	12	1.7
Self-employment	12	1.6
Social security		
Yes	647	92.4
No	53	7.6
Marital status		
Married	583	83.3
Single	56	8.0
Divorced/widowed	61	8.7
Number of children		
0	92	13.1
1	87	12.4
2	201	28.7
≥ 3	320	45.8
Place of residence		
Apartment	291	41.6
Single house	409	58.4
Economic status		
High	170	24.3
Middle	474	67.7
Low	56	8.0
Smoking status		
Non-smoker	100	14.3
Smoker	600	85.7
Regular physical activity		
Yes	162	23.1
No	538	76.9
Salt consumption in meals		
Salty	159	22.7
Little salt	481	68.7
Without salt	60	8.6
Salt restriction		
Yes	294	42.0
No	406	58.0
A history of hypertension		
Yes	100	14.3
No	600	85.7

Table 2. Distribution of the women according to their anthropometric characteristics

Variables	Number or mean ± SD	Percentage (%)
BMI [kg/m^2]		
BMI categories	29.4 ± 5.9	
Normal weight (18.5–24.9)		
Overweight (25.0–29.9)	150	21.5
Obese (≥ 30)	211	30.1
Body weight [kg]	339	48.4
Body height [cm]	74.8 ± 14.5	
BP categories	158 ± 0.1	
Normotensive		
Hypertensive	619	88.4
BP [mm Hg]		
Systolic BP	81	11.6
Diastolic BP	115.6 ± 16.4	
Spot urinary	73.3 ± 10.3	
Na [mmol/L]		
Creatinine [mg/dL]	154.0 ± 64.3	
Estimated 24-hour urinary sodium excretion [mmol/L]	114.0 ± 62.4	
Normotensive	267.8 ± 60.2	
Hypertensive	266.9 ± 59.1	
Estimated daily 24 h urinary sodium categories [mmol/L]	274.2 ± 68.8	
40–220	170	24.3
≥ 220	530	75.7
Estimated daily salt intake [g]	15.7 ± 3.5	
Salt intake categories [g/day]		
< 5	2	0.3
5–9	26	3.7
10–14	288	41.1
> 15	384	54.9

BMI — body mass index; BP — blood pressure

drug. As much as 96% of these women reported that they take their medication regularly.

The factors associated with blood pressure in the study population are presented in Table 4.

Among the hypertensive women, 92.6% were in the 40–49 age group ($p < 0.001$), 91.3% did not attend school or graduate from primary school ($p < 0.001$), 63% had 3 or more children ($p < 0.011$), 80.2% were married ($p < 0.05$), 67.9 % had a BMI ≥ 30 and above ($p < 0.001$), 54.3% used conscious salt restriction ($p < 0.05$), 58% used salt above 15 g/day ($p < 0.005$), 55.6% consumed pickles ($p < 0.005$), 92.6% consumed pickled cheese ($p < 0.05$), and 57.8% consumed sausage-salami ($p < 0.005$) (Tab. 4).

91.4% of the women who do regular physical activity are walking for physical activity. 58.5% of women with conscious salt restriction are in their 40s ($p < 0.05$), 51.9% are exercising ($p < 0.005$),

Table 3. Relationship between women's pickled food consumption and blood pressure

Pickled foods	Blood pressure		p
	Normotensive n (%)	Hypertensive n (%)	
Pickles			
Never	169 (27.3)	36 (44.4)	
Everyday	76 (12.3)	10 (12.3)	
3–5 times a week	35 (5.7)	2 (2.5)	0.012
1–3 times a week	218 (35.2)	17 (21.0)	
1 time in 15 days	121 (19.5)	16 (19.8)	
Cheese			
Never	94 (15.2)	6 (7.4)	
Everyday	475 (76.6)	72 (88.9)	
3–5 times a week	23 (3.7)	1 (2.5)	
1–3 times a week	27 (4.5)	2 (1.2)	0.051
1 time in 15 days	–	–	
Olives			
Never	41 (6.6)	9 (11.2)	
Everyday	510 (82.4)	62 (76.5)	0.699
3–5 times a week	21 (3.4)	3 (3.7)	
1–3 times a week	41 (6.6)	6 (7.4)	
1 time in 15 days	6 (1.0)	1 (1.2)	
Vine leaves			
Never	152 (24.6)	23 (28.4)	
Everyday	6 (1.0)	–	
3–5 times a week	3 (0.5)	1 (1.2)	0.492
1–3 times a week	13 (2.1)	3 (3.7)	
1 time in 15 days	445 (89.2)	54 (66.7)	
Soudjouk pastrami			
Never	270 (43.6)	42 (51.9)	
Everyday	8 (1.3)	1 (1.2)	0.097
3–5 times a week	11 (1.8)	–	
1–3 times a week	128 (20.7)	18 (22.2)	
1 time in 15 days	202 (32.6)	20 (24.7)	
Tomato paste			
Never	–	–	
Everyday	610 (98.5)	79 (97.5)	0.071
3–5 times a week	7 (1.0)	–	
1–3 times a week	2 (0.3)	2 (2.5)	
1 time in 15 days	–	–	

Table 4. Parameters associated with the blood pressure of the women

Variables	Blood pressure		p
	Normotensive n (%)	Hypertensive n (%)	
Age distribution			
15–19	32 (5.2)	–	
20–29	93 (15.0)	1 (1.2)	0.000
30–39	197 (31.8)	5 (6.2)	
40–49	297 (48.0)	75 (92.6)	
Educational status			
Illiterate	79 (12.8)	47 (58.0)	
Primary school	291 (47.0)	27 (33.3)	0.000
Secondary school	73 (11.8)	1 (1.2)	
High school	112 (18.1)	1 (1.2)	
University	64 (10.3)	5 (6.3)	
Number of children			
0	85 (13.7)	7 (8.6)	
1	79 (12.8)	9 (11.1)	0.011
2	187 (30.2)	14 (17.3)	
≥ 3	268 (43.3)	51 (63.0)	
Marital status			
Married	518 (83.7)	65 (80.2)	0.026
Single	54 (8.7)	2 (2.5)	
Divorced /widowed	47 (7.6)	14 (17.3)	
Family history of hypertension			0.047
Yes	148 (23.9)	27 (33.3)	
No	471 (76.1)	54 (66.7)	
BMI categories			
≤ 24.9	147 (23.7)	3 (3.7)	0.000
≥ 25– ≤ 29.9	188 (30.4)	23 (28.4)	
≥ 30	284 (45.9)	55 (67.9)	
Conscious salt restriction			
Yes	250 (40.4)	44 (54.3)	0.012
No	369 (59.6)	37 (45.7)	
Salt intake [g/day]			
< 5	–	2 (2.5)	
5–9	23 (3.7)	3 (3.7)	0.001
10–14	259 (41.8)	29 (35.8)	
> 15	337 (54.4)	47 (58.0)	

BMI — body mass index

and 50.9% have a hypertensive person in their family ($p < 0.005$).

The parameters associated with the urinary sodium excretion levels of the participants are presented in Table 5.

Overall, the 24-h urinary sodium excretion was 267.8 ± 60.2 mmol/day and daily salt intake was 15.7 ± 3.5 g/day. Twenty-four-hour urinary sodium excretion values of only 24.3% of the participants were normal. As seen in this table, there is statistical parallelism between the salt intake and the urine sodium excreted ($p < 0.001$). It was statistically observed that the estimated 24-hour urine sodium excretion of women increased more in older ($p < 0.05$), higher BMI ($p < 0.001$), married ($p < 0.001$), uneducated or primary school graduates ($p < 0.05$), and consuming salty food ($p < 0.05$) (Tab. 5). We see the same features in hypertensive women.

The factors affecting the inability to control hypertension are given in Table 6. These factors are: being in the 40–49 age group (OR: 3.50, 95% CI: 1.57–7.77), having a low level of education (OR: 0.58, 95% CI: 0.46–0.74), and not making a conscious salt restriction (OR: 0.57, 95% CI: 0.34–0.959).

Table 5. Parameters associated with the urinary sodium excretion levels of the women

Variables	Sodium excretion levels		p
	n (%)	Mean ± SD	
Age distribution			
15–19	32 (4.6)	239.7 ± 43.5	0.006
20–29	94 (13.4)	270.0 ± 55.4	
30–39	202 (28.9)	261.3 ± 59.5	
40–49	372 (53.1)	273.1 ± 62.3	
Marital status			
Married	583 (83.3)	272.1 ± 60.5	0.000
Single	56 (8.0)	248.7 ± 53.2	
Divorced/Widowed	61(8.7)	243.8 ± 56.4	
Educational status			
Illiterate	126 (18.0)	266.3 ± 68.3	0.045
Primary school	318 (45.4)	274.9 ± 59.2	
Secondary school	74 (10.6)	256.7 ± 59.1	
High school	113 (16.1)	262.5 ± 57.1	
University	69 (9.9)	258.1 ± 52.9	
BMI categories			
≤ 24.9	150 (21.4)	252.1 ± 51.9	0.000
≥ 25– ≤ 29.9	211 (30.1)	267.1 ± 55.3	
≥ 30	339 (48.4)	275.2 ± 65.3	
Pickle consumption			
Yes	495 (70.7)	271.6 ± 61.1	0.020
No	205 (29.3)	259.6 ± 57.5	
Vine leaves consumption			
Yes	525 (75.0)	270.8 ± 60.0	0.020
No	175 (25.0)	258.6 ± 60.3	
Conscious salt restriction			
Yes	294 (42.0)	261.0 ± 59.3	0.012
No	406 (58.0)	272.7 ± 60.6	
Salt intake [g/day]			
< 5	2 (0.3)	99.13 ± 0.5	0.000
5–9	26 (3.7)	153.3 ± 14.9	
10–14	288 (41.1)	220.8 ± 24.0	
> 15	384 (54.9)	311.6 ± 39.5	

BMI — body mass index; SD — standard deviation

Table 6. Factors associated with the lack of control of hypertension

	Odds ratio	95% CI Lower–Upper	p
Age (older age, 40–49)	3,503	1.577–7.779	0.002
Educational status (lower level of education)	0.587	0.463–0.745	0.000
Conscious salt restriction (failure to apply salt restriction)	0.570	0.341–0.954	0.032

CI — confidence interval

Discussion

This study investigated the incidence of HT, control rate, and related factors in women living in the Hacılar region of Kayseri, Turkey. This study is a very comprehensive assessment for this region.

One of the main findings in this study is that 14.3% of the population between the ages of 15–49 in this region is hypertensive and another main finding is that blood pressure control is found at a low rate of 19%. Studies have shown that women are better at treating hypertension than men are, but worse in controlling it, and the rate of control decreases as age increases [20, 21].

The reason why the percentage of hypertensive women in our sample was lower as compared to the whole country is that we recruited people under 18 years of age. When looking at the common characteristics of hypertensive women living in this region, it is seen that 92.6% were 40–49 years old, 91.3% did not go to school or graduated from primary school, 80.2% were married, 67.9% of them had a BMI of 30 and above, 63% had 3 or more children, and 33.3% had a family history of hypertension. In addition, 55.6% of them consumed pickles, 92.6% consumed homemade pickled cheese, and 58% consumed more than 15 g/day salt per day. In studies conducted in Turkey, the rate of hypertension in women was 32.3% and these women were older, obese, generally primary school graduates, did less physical activity, and did not restrict salt. It was also seen that 37.3% of these women could control their hypertension [3].

According to a study conducted in Iran, the frequency of hypertension in women was found to be 32.5% and their BMI 28.4% [22]. In Indians, it was observed that 10.9 % of women between the ages of 15–49 were hypertensive, and these hypertensives were older, obese, married individuals, and had low education levels [23].

There are several objective and reliable methods for assessing salt intake, such as 24-h urinary sodium excretion measurement, food consumed record, and weighing method. The most valuable method is to look for sodium in the 24-h urine, but we preferred to look for sodium in the spot urine due to misconceptions that may occur in studies carried out on large groups. In this study, the estimated salt intake of women was calculated using the methods that have been developed to estimate 24-h sodium excretion.

The estimated salt intake in the Hacilar region in Kayseri, Turkey is approximately 15 g/day. This is well above the mean value of < 5 g/day recommended by WHO. Accordingly, sodium excretion is approximately 267.8 ± 60.2 mmol/day. As a result of these calculations, those with the highest sodium excretion in the urine are the 40–49 age group (273.1 ± 62.3 mmol/day), married (272.1 ± 60.5

mmol/day), no school (266.3 ± 68.3 mmol/day), being a primary school graduate (274.9 ± 59.2 mmol/day), obese (275.2 ± 65.3 mmol/day), those who consume pickles (271.6 ± 61.1 mmol/day) and vine leaves (270.8 ± 60.0 mmol/day) as pickled food, those who do not consciously restrict salt (272.7 ± 60.6 mmol/day), and those who consume more than 15 g/day of salt per day (311.6 ± 39.5 mmol/day). In a study conducted in Turkey, 24-hour urinary sodium excretion of women 274.3 ± 135.1 mmol/day and the daily salt intake 18.1 g/day were observed. It was reported that these women were obese, of a lower educational status, and older [11]. In a study in Japan, sodium excretion in 24-hour urine samples was found to be 174 mmol/day [24]. In two separate studies conducted in Brazil, the daily salt intake of women living in Brazil was 9.08 g/day [25] while the salt intake of African women living in Brazil was 4.5 g/day and sodium excretion was 203.1 ± 84.9 mmol/day [14]. These hypertensive people were older, with low education levels, obesity, and the prevalence of hypertension was 21.3% [14]. In China, more than half of the population (53.4%) was overweight or obese and 22.9% had hypertension. In the population, the mean 24-hour urinary sodium excretion was 235.7 (mmol) [26]. In the 24-hour urine samples, 134.7 mmol/day sodium excretion and 8.8 g/day salt intake were observed in Chinese women, who migrated to Italy. In this study, the rate of hypertension in women was reported to be 38%, and only 19% could control their blood pressure with medication [27]. In Norway, sodium excretion of 3.53 g/day and salt intake of 7.55 g/day in 24-hour urine samples were observed in women [13]. 24-hour sodium excretion in Australia was observed as 2.718 mg/24 hr, and salt intake as 6.41 g/day [28]. In general, salt intake in the world is seen well above the WHO recommended value of < 5 g/day.

In our study, 81 of 100 women was still hypertensive, even if drug therapy was administered. It can be assumed that advanced age, high BMI, low education level and excessive salt consumption could cause this situation. Frequent consumption of pickled and high-salt foods in these regions indicates that the control of hypertension will be very difficult. Changes in eating habits and lifestyle are necessary to control blood pressure.

The observation that high blood pressure is seen more frequently in people with low education levels may be attributed primarily to the fact that people with low education are in the advanced age group. In addition, we have the opinion that a low education level is an important factor in gaining healthy eating habits and creating awareness of protecting one's own health.

One of the most important implications of the study is the mistakes made by hypertensive patients, which make blood pressure control difficult. Believing that herbs such as garlic, parsley, and lemon will lower their blood pressure instead of antihypertensive drugs and not accepting that the treatment will last a lifetime, use of antihypertensive drugs belonging to neighbors and relatives, not having information about the drug used, or changing medication without consulting a doctor are some of the most common mistakes.

The limitation of this study was that the gold standard for measuring sodium excretion was not used. Instead, we tried to estimate the 24-hour condition with the formula of sodium value obtained with spot urine.

Conclusion

Since obesity and salt intake are two reversible causes of high blood pressure, weight control and salt restriction are required for good blood pressure control. Advanced age is also an important risk factor for hypertension. There is no chance to stop aging, but we think that salt restriction, weight control, and an active life that start at a very early age may delay or prevent negative effects of aging.

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Ethical approval

The study was approved by the Erciyes University Faculty of Medicine Ethics Committee on 15/08/2014 with approval number 2014/495. In addition, the Turkish Public Health Agency of Family Medicine Training and Development Department of the Presidency gave approval (02/11/2014 2014.5729.2090 / research permit No. 229).

Consent

After explaining the study to the participants, their consent was obtained.

Conflicts of interest

The authors declare that they have no conflicts of interest. We confirm that this work is original and it has not been published elsewhere. All authors contributed to this study and we declare that all authors agree with the content of the article.

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Assessment of atherogenic indices and lipid ratios in the apparently healthy women aged 30–55 years

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Abstract

Background: Cardiovascular disease (CVD) is the main cause of death worldwide and atherogenic dyslipidemia is an established risk factor for CVD. This cross-sectional study aimed to assess the atherogenic indices and lipid ratios, including atherogenic coefficient (AC), atherogenic index of plasma (AIP), cholindex (CI), Castelli risk index-1 (CRI-1), CRI-2, and non-HDL-C, in women living in the Tabriz, Iran during April–May 2017.

Material and methods: Anthropometric measurements, fasting serum lipids, and blood pressure of 150 women aged 30–55 years in Tabriz, Iran was evaluated. The atherogenic indices were calculated by the established formulas.

Results: The prevalence of high AIP, AC, CI, CRI-1, CRI-2 and non-HDL-C ratios were 64.5%, 36.2%, 20.4%, 77%, 7.2% and 44.7%, respectively. In the multiple-adjusted quantile regression analysis, significant relationships were found between CI ratio and diastolic blood pressure (DBP) (B = 3.76, p = 0.035) and between CRI-2 ratio and DBP (B = 0.005, p = 0.042) and age (B = 0.005, p = 0.031).

Conclusions: This study indicated that the majority of studied women had a high risk of CVD based on atherogenic indices. Further public health efforts are required to enhance awareness of women and healthcare providers about preventing and controlling CVD risk.

Key words: atherogenic indices; lipid ratios; dyslipidemia; cardiovascular risk factors; women

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Introduction

Cardiovascular disease (CVD) is the most important cause of death worldwide. The incidence of CVD is increasing all over the world, particularly in developing countries [1]. There are 17.5 million deaths annually due to CVD in the world. It has been estimated that 50% of all deaths per year are attributed to CVD in Iran [2], and these figures will increase because of growing CVD's risk factors [3]. In the past, the risk of heart disease in women has been underestimated due to the misperception that females are protected against CVD. In fact, CVD is the primary cause of mortality in women [4, 5].

Dyslipidemia is an established risk factor for CVD in the general population [6]. It was defined

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as elevated triglycerides (TG), high low density lipoprotein cholesterol (LDL-C) and low high density lipoprotein cholesterol (HDL-C) levels [6]. Many clinical studies make effort to introduce better markers of atherogenic dyslipidemia that can predict the risk of CVD more precisely than classical biochemical indicators [7, 3]. These markers include new lipid ratios that are associated with an increased atherogenic potential [8].

Atherogenic index of plasma (AIP) [(logTG)/HDL-C] is a strong predictor of infarction, acute coronary events, atherosclerosis and CVD morbidity and its complications [9, 10]. In situations where all atherogenic parameters are normal, AIP may be the alternative screening tool [3]. Noumegni et al. reported that the 10-year risk of cardiovascular events among HIV-infected adults in Yaoundé, Cameroon, was significantly correlated with the AIP [8]. Results of a study by Ni et al. on patients undergoing coronary angiography, demonstrated that AIP was a significant independent predictor of all-cause mortality and cardiovascular events in women without prior myocardial infarction or coronary revascularization [11].

The atherogenic coefficient (AC), the ratio of non-HDL-C to HDL-C, is another ratio that relies on the significance of HDL-C in predicting the risk of CAD [12]. Cholindex (CI), the net effect of atherogenicity, is calculated by subtracting HDL-C from LDL-C. It is considered as the most independent predictor and relative risk value of coronary artery disease [13].

The Castelli risk indexes 1 (TC/HDL-C) and 2 (LDL-C/HDL-C) ratios are independent risk factors for CAD, which have a good predictive value for future cardiovascular events. Several studies reported that higher serum AC, CRI-1 and non-HDL-C were associated with increased risk of stroke independent of other potential confounding factors [14, 15].

In addition to dyslipidemia, other modifiable cardiovascular risk factors are hypertension, obesity, less physical activity, smoking, diabetes mellitus, low social economic status, and nutrition [16]. To our best knowledge, no published data are available about risk factors of CVD in women living in Tabriz, Iran. Hence, the present study aimed to evaluate atherogenic indices and lipid ratios and their association with other CVD risk factors in women living in Tabriz, Iran.

Material and methods

Study participants

The present cross-sectional study was carried out on 150 women aged 30–55 years who attended health centers in Tabriz and met the inclusion criteria of the study during April–May 2017. Our participants were selected by the convenience sampling method. The study protocol was approved by the ethical committee of Tabriz University of Medical Sciences (Ethical code: IR. TBZMED.REC.1396.8). The sample size was calculated based on the correlation between AIP and waist circumference (WC) (r = 0.23) [3], and considering 95% confidence level and 80% power in two-tailed tests with STATA14 software to be 150 subjects. Of the 1182 target population, firstly160 women were selected and invited to study, then 10 subjects excluded due to uncompleted cooperation in the study. The final sample included 150 women. All participants signed written informed consent after being informed of the study procedure. Exclusion criteria were: athlete or having strenuous physical labor, being pregnant or lactating, smoking, and women with a history of the disease (such as kidney and nerve disease, heart disease, diabetes, hepatic, cancer and etc.) or with use of nutritional supplements or medication.

Anthropometric measurements

Body weight was measured using a calibrated beam scale while subjects wearing light clothing and barefoot and recorded to the nearest 0.5 kg. Height was measured using mounting tape with the participants' arms hanging freely at their sides and recorded to the nearest 0.5 cm. Body mass index (BMI) was obtained by dividing the weight in kilograms by the square of height in meters. Measurements of WC and hip circumference (HC) were taken with a tape measure in centimeters and rounded to 0.5 cm. WC was determined at the midpoint between the lowest rib and the iliac crest while the participant was standing and after expiration. Waist-hip ratio (WHR) was calculated by dividing the size of the waist by the HC [17, 18].

Blood pressure measurements

Blood pressure (BP) was measured twice in the morning by using a mercury sphygmomanometer together with an adult cuff, on the upper right arm, with the arm horizontally on a table, and subsequently 5 min rest in the sitting position. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured as the first detectable sound and the disappearance of Korotkoff sounds, respectively [17]. The mean of the two readings was calculated for analysis.

Biochemical assays

Venous blood samples (5 mL) were drawn from all participants after a 12 hours fasting. The serum

samples were separated from the whole blood by centrifugation and stored frozen immediately at –70°C until assay. Serum concentrations of TC, TG and HDL-C were evaluated by using the commercial kits (ParsAzmoon kits, Tehran, Iran) with using the autoanalyzer (Alcyon 300 Automated Biochemistry Analyzer; Abbott Laboratories, Abbott Park, IL, USA). When internal quality control reached the acceptable criteria all samples were analyzed. TC and TG were assayed with enzymatic methods using cholesterol esterase, cholesterol oxidase, and glycerol phosphate oxidase. HDL-C was measured after precipitation of the apolipoprotein B-containing lipoproteins [19]. LDL-C was calculated by the Friedewald formula: *LDL-C = TC – (HDL-C + TG/5)* [20].

The atherogenic indices were calculated using the following established formulas [15, 21, 22]:

$$AIP = log\ (TG/HDL\text{-}C)$$

$$AC = (TC–HDL\text{-}C)/HDL\text{-}C$$

$$CI = LDL\text{-}C – HDL\text{-}C\ (TG < 400\ mg/dL) =$$
$$= LDL\text{-}C – HDL\text{-}C + 1/5\ TG\ (TG > 400\ mg/dL)$$

The CI ratio in categorical form is as mmol/L.

$$CRI\text{-}1 = TC/HDL\text{-}C$$

$$CRI\text{-}2 = LDL\text{-}C/HDL\text{-}C$$

$$Non\text{-}HDL\text{-}C = TC – HDL\text{-}C$$

AIP values of < 0.11, 0.11 to 0.21, and > 0.21 are associated with low, medium, and high cardiovascular risk, respectively [3]. The following are the abnormal values for cardiovascular risk: AC > 3.0, CI > 2.07, CRI-1 >3.0, and CRI-2 > 3.3 [18]. Non-HDL-C < 130 mg/dL is considered as desirable [15].

Statistical analyses

Statistical analyses were performed by STATA software [ver.13] (Stata Corp, College Station, Texas 77845 USA). Normality of the numeric variables was checked by Kolmogorov-Smirnov test. Data were presented using mean (SD), and frequency (percent) for the normal and categorical variables, respectively. To assess the relationship between serum atherogenic indices with other variables, univariate and multivariate quantile regression modelling was used due to non-normal distribution of the dependent variables. In the multivariate model, the effect of confounders was adjusted and the simultaneous relationship of the predictors was assessed. The criterion to include the variables in the univariate analyses was using the significant variables. The R2 was used as a model fit measure. No interaction was examined. In all analyses, p values less than 0.05 were considered as significant and 95% confidence intervals of the regression coefficients were presented. Since this was a cross-sectional study, this choice preserves the power in the analyses, especially in the multivariate analysis.

Results

The mean age of women was 40.21 years. According to the AIP category, 70.4% of subjects were at high risk of CVD (Tab. 1). Abnormal AC, CI, CRI-1,

Table 1. Clinical and biochemical parameters of the studied women (n = 150)

Variables	Mean or n	SD or %
Age [years]	40.21	5.88
Blood pressure [mm Hg]		
SBP	113.30	9.27
DBP	71.41	8.08
Traditional lipid profiles [mg/dL]		
TG	124.55	69.47
TC	177.73	32.67
HDL-C	50.52	14.54
LDL-C	102.29	28.96
Nontraditional lipid profiles		
AIP (%)	0.35	0.26
< 0.11	23	15.1
0.11–0.21	22	14.5
> 0.21	107	70.4
AC (%)	2.72	1.03
≤ 0.3	95	63.8
> 0.3	55	36.2
CI (%)	51.77	3.42
≤ 2.07	119	79.6
> 2.07	31	20.4
CRI-1 (%)	3.72	1.03
≤ 3.0	33	23
> 3.0	117	77
CRI-2 (%)	2.17	0.82
≤ 3.3	139	92.8
> 3.3	11	7.2
Non-HDL-C [mg/dL] (%)	127.75	31.26
≤ 130	84	55.3
>130	66	44.7

AIP — atherogenic index of plasma; AC — atherogenic coefficient; CRI-1 — Castelli risk index-1; CRI-2 — Castelli risk index-2; CI — cholindex; DBP — diastolic blood pressure; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; Non-HDL-C — non- high-density lipoprotein cholesterol; SBP — systolic blood pressure; TG — triglyceride; TC — total cholesterol

CRI-2, and non-HDL-C ratios were identified in 36.2%, 20.4%, 77%, 7.2% and 44.7% of participants, respectively (Tab. 1).

In the multiple-adjusted quantile regression analysis that the simultaneous relationship of AIP, AC, CI, CRI-1, and CRI-2 indices with age, BMI, WHR, WC, SBP, and DBP were assessed, significant positive relationships were found between CI ratio and DBP and between CRI-2 ratio with age and DBP (Tab. 2).

Discussion

This research is the first study to examine the status of the atherogenic indices and lipid ratios in women living in Tabriz, Iran. The previous observations suggested that lipid ratios could be used for detecting subjects at higher risk of CVD and atherosclerosis when all values of lipoproteins seem normal and/or TG concentrations are elevated [12].

AIP ratio is shown to be associated with hypertension, diabetes, metabolic syndrome, insulin resistance, and the increased risk of cardiovascular events. Moreover, it may possess a better prognostic value than TC, LDL-C, and HDL-C concentrations. The background of this theory is that AIP is a surrogate for the concentration of atherogenic small dense LDL particles. Accordingly, such particles are more prone to the oxidation process and can subsequently induce the expressions of adhesion molecules on endothelial cells, which promote endothelial dysfunction [10]. In addition, AC ratio reflects the atherogenic potential of the entire spectrum of lipoprotein fractions [23]. CI ratio can also be used for the evaluation of all lipids risks for coronary artery disease in only one parameter [13].

In the present study, based on AIP category, 70.4% of subjects were indicated to be at a high risk of CVD. Based on our findings, high-risk AC and CI were also detected in 36.2% and 20.4% of the participants, respectively. Moreover, the prevalence rates of abnormal AC and CI ratios were higher in our subjects compared to the results of the study conducted by Olamoyegun et al. on semi-urban adults who were at least 18 years old [21].

According to the results, the most prevalent form of atherogenic indices was high CRI-1 (77%). It was shown that CRI-1 reflects coronary plaques formation as well as the thickness of intima-media in the carotid arteries of young adults [21]. Besides, an abnormal CRI-2 ratio was detected in 7.2% of the participants. CRI-2 ratio may provide a better risk assessment of coronary artery disease, since it con-

Table 2. Multiple-adjusted quantile regression analysis between some atherogenic indices and other risk factors in women

	AIP		AC		CI		CRI-1		CRI-2	
	B (95% CI)	p-value	B (95% CI)†	p-value*	B (95% CI)	p-value	B (95% CI)	p-value	B (95% CI)	p-value
Age	−0.000 (−0.00– 0.00)	0.588	−0.006 (−0.01–0.00)	0.122	1.10 (−2.26–4.47)	0.587	−0.006 (−0.01–0.00)	0.122	0.005 (−0.01– −0.00)	0.031*
BMI	0.000 (−0.00–0.00)	0.388	0.004 (−0.01–0.02)	0.715	4.74 (−4.3–1.3)	0.389	0.004 (−0.01–0.02)	0.715	0.006 (−0.00–0.02)	0.433
WHR	0.001 (−0.011–0.014)	0.833	0.278 (−0.76–1.3)	0.658	−7.73 (−5.8–4.2)	0.801	0.278 (−0.76–1.3)	0.658	0.301 (−0.50–1.1)	0.539
WC	−0.000 (−0.00–0.00)	0.410	−0.003 (−0.01–0.00)	0.643	−1.38 (−6.7–3.9)	0.670	−0.003 (−0.01–0.00)	0.643	−0.003 (−0.01–0.00)	0.446
SBP	0.000 (−0.00–0.00)	0.709	0.002 (−0.00–0.00)	0.543	−1.09 (−4.16–1.98)	0.557	0.002 (−0.00 –0.00)	0.543	0.001 (−0.00–0.00)	0.578
DBP	−0.000 (−0.00–0.00)	0.200	−0.007 (−0.01–0.00)	0.107	3.76 (2.87–7.24)	0.035*	−0.007 (−0.01–0.00)	0.107	0.005 (−0.01– −0.00)	0.042*

AIP — atherogenic index of plasma; AC — atherogenic coefficient; BMI — body mass index; CRI-1 — Castelli risk index-1; CRI-2 — Castelli risk index-2, CI — cholindex; DBP — diastolic blood pressure; SBP — systolic blood pressure; WC — waist circumference; WHR — waist-hip ratio; p-value based on univariate and multivariate quantile regression; *p < 0.05 is significant; †confidence interval

tains both atherogenic and protective lipid fractions [13]. In line with our results, in the study performed by Olamoyegun et al. on adults, abnormal CRI-1 and CRI-2 were identified in 55.2% and 16.8% of the population, respectively [21].

Non-HDL-C may be used to evaluate the atherogenic effects of LDL-C, TG, and VLDL-C in serum, which also reflects the contents of all atherogenic apolipoprotein-B-containing lipoproteins [13]. There is also a clear evidence that non-HDL-C is a strong predictor of cardiovascular risk and morbidity, and its predictive value even exceeds that of LDL [10]. Thus, it is recommended that non-HDL-C should be included in the routine lipid assessment of patients. According to the findings of this study, 44.7% of the included participants had high serum non-HDL-C. Similarly, Kumpatla et al. reported that 43% of type 2 diabetic patients had elevated non-HDL-C despite having an optimal LDL-C level. Thus, it was recommended that non-HDL-C should be included in the routine lipid assessment of patients [24].

Based on the results, the increased CI and CRI-2 ratios both were correlated with a higher DBP. In a study by Singh et al. on 50 women with pre-eclampsia, significant relationships were reported between some atherogenic indices and blood pressure [25]. Accordingly, it was suggested that lipids can cause hypertension through oxidative stress. It is noteworthy that oxidative stress promotes vascular smooth muscle cell proliferation, hypertrophy, and collagen deposition, which finally lead to the thickening of the vascular media and narrowing of the vascular lumen. Furthermore, lipid peroxides stimulate thromboxane synthesis and inhibit endothelial-derived relaxing factors resulting in vasoconstriction [25].

According to our results, the elevated CRI-2 ratio was associated with age. In this regard, the results of a study conducted by Kazemi et al. on 5207 individuals aged between 15 and 70 years old demonstrated that the atherogenic index increased with aging. It was also indicated that the catabolism of LDL-C decreases with increasing age [26]. Notably, a reduction in the activity of the LDL-C receptors in the liver is likely to be responsible for this age-related impairment of LDL-C catabolism and subsequently the increased LDL-C levels [4].

Based on our results, means of TG, TC, HDL-C, and LDL-C in the studied women were in the normal range partially. However, the obtained results on new generation lipid ratios indicated that, the studied women were at a high risk of CVD. These findings confirm that the lipoprotein-related indices are better tools in the assessment of cardiovascular risks compared to the conventional lipid profiles.

This study also had some limitations such as cross-sectional design and lack of a control group. Therefore, it is not possible to engage any cause-effective relationship between variables. Moreover, other risk factors of CVD such as individual's food habits and alcohol consumption were not examined in this study. The precise causes of the high prevalence of risk factors of CVD in our participants warrant longitudinal studies. The result of the current study may help policymakers in the implementation of a population-based strategy to screen, prevent, monitor, and control CVD in women.

Conclusions

This study indicated that the majority of studied participants had a high risk of CVD based on atherogenic indices, especially CRI-1 and AIP. Elevated DBP was associated with higher CI and CRI-2. Increased CRI-2 was also related to age. Further public health efforts are required to enhance awareness of women and healthcare providers about preventing and controlling CVD risk.

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Authorship

The whole project was designed and conducted by M.R., as a supervisor; and R.M.G. contributed to data gathering and on-site study management. Sampling methodology and statistical analysis were performed under the direction of M.A.J. All authors contributed to manuscript preparation and approved the final manuscript.

Conflict of interests

The authors declare no conflicts of interest, both financial and non-financial, for this study.

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Informacja o leku Bisocard, 2,5 mg, Bisocard 5 mg, Bisocard 10 mg, tabletki powlekane. **Skład jakościowy i ilościowy**: **Bisocard, 2,5 mg** jedna tabletka powlekana zawiera 2,5 mg bisoprololu fumaranu (Bisoprololi fumaras). Substancja pomocnicza o znanym działaniu: laktoza jednowodna w ilości 122,5 mg. Wykaz substancji pomocniczych: Skrobia kukurydziana, Krzemionka koloidalna bezwodna, Sodu laurylosiarczan, Talk, Magnezu stearynian; Otoczka: Hypromeloza, Makrogol 400, Tytanu dwutlenek (E 171). **Bisocard, 5 mg, tabletki powlekane:** Jedna tabletka powlekana zawiera 5 mg bisoprololu fumaranu (Bisoprololi fumaras). Substancja pomocnicza o znanym działaniu: laktoza jednowodna w ilości 115 mg. Wykaz substancji pomocniczych: Laktoza jednowodna, Skrobia kukurydziana, Krzemionka koloidalna bezwodna, Sodu laurylosiarczan, Talk, Magnezu stearynian; Otoczka tabletki powlekanej 5 mg: Hypromeloza, Makrogol 400, Tytanu dwutlenek (E 171), Żelaza tlenek żółty (E 172); Otoczka tabletki powlekanej 10 mg: Hypromeloza, Makrogol 400, Tytanu dwutlenek (E 171), Żelaza tlenek czerwony (E 172). **Postać farmaceutyczna**: tabletki powlekane. Bisocard 2,5 mg tabletki powlekane – białe lub prawie białe, podłużne, obustronnie wypukłe tabletki z wytłoczoną linią podziału. Bisocard 5 mg tabletka powlekana: Jasnożółte, okrągłe, obustronnie wypukłe tabletki z wytłoczoną linią podziału po jednej stronie oraz znakiem „5" po drugiej stronie. Bisocard 10 mg tabletki powlekane: Jasnoróżowe, okrągłe, obustronnie wypukłe tabletki z wytłoczoną linią podziału po jednej stronie oraz znakiem „10" po drugiej stronie. Tabletkę powlekaną można podzielić na dwie równe dawki. **Wskazania do stosowania**: Bisocard 2,5 mg: Stabilna, umiarkowana do ciężkiej, przewlekła niewydolność serca z zaburzoną czynnością skurczową lewej komory (frakcja wyrzutowa ≤35% w ocenie echokardiograficznej), w skojarzeniu z inhibitorami ACE, lekami moczopędnymi oraz, w razie konieczności, z glikozydami naparstnicy. Bisocard 5 mg, Bisocard 10 mg: Nadciśnienie tętnicze. Dławica piersiowa. Stabilna, umiarkowana do ciężkiej, przewlekła niewydolność serca z zaburzoną czynnością skurczową lewej komory (frakcja wyrzutowa ≤ 35% w ocenie echokardiograficznej), w skojarzeniu z inhibitorami ACE, lekami moczopędnymi oraz, w razie konieczności, z glikozydami naparstnicy. **Dawkowanie i sposób podawania. Bisocard 2,5 mg** w standardowym leczeniu przewlekłej niewydolności serca stosuje się inhibitor ACE (lub antagonistę receptora angiotensyny II, jeśli pacjent nie toleruje inhibitorów ACE), lek beta-adrenolityczny, leki moczopędne i w uzasadnionych przypadkach, glikozydy naparstnicy. Leczenie bisoprololem należy rozpoczynać u pacjentów w stabilnym stanie klinicznym (bez ostrej niewydolności serca). Leczenie przewlekłej niewydolności serca powinien prowadzić lekarz z doświadczeniem w tej dziedzinie. Faza dostosowania dawki: leczenie bisoprololem stabilnej, przewlekłej niewydolności serca wymaga etapu dostosowania dawki. Leczenie bisoprololem należy rozpoczął od stopniowego zwiększania dawki, zgodnie z poniższym schematem: 1,25 mg raz na dobę przez pierwszy tydzień. Jeśli dawka jest dobrze tolerowana, należy ją zwiększyć do: 2,5 mg raz na dobę przez następny tydzień. Jeśli dawka jest dobrze tolerowana, należy ją zwiększyć do: 3,75 mg raz na dobę przez kolejny tydzień. Jeśli dawka jest dobrze tolerowana, należy ją zwiększyć do: 5 mg raz na dobę przez 4 kolejne tygodnie. Jeśli dawka jest dobrze tolerowana, należy ją zwiększyć do: 7,5 mg raz na dobę przez 4 kolejne tygodnie. Jeśli dawka jest dobrze tolerowana, należy ją zwiększyć do: 10 mg raz na dobę w leczeniu podtrzymującym. Maksymalna zalecana dawka wynosi 10 mg raz na dobę. W trakcie i po okresie ustalania dawki może wystąpić przejściowe nasilenie niewydolności serca, niedociśnienie tętnicze lub bradykardia. W trakcie ustalania dawki zaleca się uważne monitorowanie parametrów życiowych pacjenta (ciśnienie tętnicze, tętno) oraz objawów nasilenia niewydolności serca. Objawy te mogą wystąpić już w pierwszym dniu leczenia. Modyfikacja leczenia: leczenie bisoprololem stabilnej, przewlekłej niewydolności serca jest z reguły długotrwałe. Jeśli maksymalna zalecana dawka nie jest dobrze tolerowana, można rozważyć jej stopniowe zmniejszanie. W przypadku przemijającego nasilenia niewydolności serca, niedociśnienia tętniczego lub bradykardii należy ponownie rozważyć dawkę jednocześnie podawanych leków. Może być również konieczne czasowe zmniejszenie dawki bisoprololu lub rozważenie jego odstawienia. Należy zawsze rozważyć wznowienie podawania i (lub) zwiększenie dawki bisoprololu, gdy uzyska się stabilizację stanu pacjenta. Jeśli rozważane jest zakończenie leczenia, zaleca się stopniowe zmniejszanie dawki, ponieważ nagłe odstawienie leku może prowadzić do ostrego pogorszenia stanu pacjenta. Zaburzenia czynności nerek lub wątroby: brak danych dotyczących farmakokinetyki bisoprololu u pacjentów z przewlekłą niewydolnością serca i zaburzeniami czynności nerek lub wątroby. Zwiększanie dawki u tych pacjentów wymaga szczególnej ostrożności. Pacjenci w podeszłym wieku: nie ma konieczności dostosowania dawki. Dzieci i młodzież: brak doświadczenia dotyczącego stosowania bisoprololu u dzieci, dlatego nie zaleca się jego podawania w tej grupie pacjentów. Sposób podawania: podanie doustne. Tabletki należy przyjmować rano. Można je przyjmować zarówno w trakcie posiłku, jak i przed jedzeniem. Tabletki należy połykać bez rozgryzania, popijając płynem. **Bisocard 5 mg, Bisocard 10 mg**: Nadciśnienie tętnicze i dławica piersiowa – dawkowanie należy dostosować indywidualnie, biorąc pod uwagę częstość tętna pacjenta i skuteczność leczenia. Zalecana dawka początkowa to 5 mg raz na dobę. W razie konieczności dawkę dobową można zwiększyć do 10 mg raz na dobę. Maksymalna zalecana dawka wynosi 20 mg raz na dobę. W niektórych, łagodniejszych, przypadkach nadciśnienia tętniczego może być wystarczające podawanie dawki 2,5 mg raz na dobę. Zaburzenia czynności nerek lub wątroby: u pacjentów z ciężkimi zaburzeniami czynności nerek (klirens kreatyniny < 20 ml/min) i u pacjentów z ciężkimi zaburzeniami czynności wątroby dawka nie może być większa niż 10 mg na dobę. Doświadczenie dotyczące stosowania bisoprololu u pacjentów poddawanych dializie jest ograniczone, ale nie dowiedziono, aby zmiana dawkowania była u nich konieczna. Przerwanie leczenia: nie zaleca się nagłego przerywania leczenia. Zmniejszanie dawki powinno odbywać się stopniowo, co tydzień o połowę, zwłaszcza u pacjentów z chorobą niedokrwienną serca. Stabilna przewlekła niewydolność serca: w standardowym leczeniu przewlekłej niewydolności serca stosuje się inhibitor ACE (lub antagonistę receptora angiotensyny II, jeśli pacjent nie toleruje inhibitorów ACE), lek beta-adrenolityczny, leki moczopędne i w uzasadnionych przypadkach, glikozydy naparstnicy. 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Jeśli dawka jest dobrze tolerowana, należy ją zwiększyć do: 10 mg raz na dobę w leczeniu podtrzymującym. Maksymalna zalecana dawka wynosi 10 mg raz na dobę. W trakcie i po okresie ustalania dawki może wystąpić przejściowe nasilenie niewydolności serca, niedociśnienie tętnicze lub bradykardia. W trakcie ustalania dawki zaleca się uważne monitorowanie parametrów życiowych pacjenta (ciśnienie tętnicze, tętno) oraz objawów nasilenia niewydolności serca. Objawy te mogą wystąpić już w pierwszym dniu leczenia. Modyfikacja leczenia: leczenie bisoprololem stabilnej, przewlekłej niewydolności serca jest z reguły długotrwałe. Jeśli maksymalna zalecana dawka nie jest dobrze tolerowana, można rozważyć jej stopniowe zmniejszanie. W przypadku przemijającego nasilenia niewydolności serca, niedociśnienia tętniczego lub bradykardii należy ponownie rozważyć dawkę jednocześnie podawanych leków. Może być również konieczne czasowe zmniejszenie dawki bisoprololu lub rozważenie jego odstawienia. 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Tabletki należy połykać bez rozgryzania, popijając płynem. **Przeciwwskazania**: Bisoprolol jest przeciwwskazany w przypadku: nadwrażliwości na bisoprolol lub na którąkolwiek substancję pomocniczą, ostrej niewydolności serca lub podczas okresów niewyrównania niewydolności serca wymagających dożylnego stosowania leków o działaniu inotropowym dodatnim, wstrząsu kardiogennego, bloku przedsionkowo-komorowego II lub III stopnia (bez stymulatora serca), zespołu chorego węzła zatokowego, bloku zatokowo-przedsionkowego, objawowej bradykardii, objawowego niedociśnienia tętniczego, ciężkiej astmy oskrzelowej lub ciężkiej przewlekłej obturacyjnej choroby płuc, ciężkich postaci zarostowej choroby tętnic obwodowych lub ciężkich postaci zespołu Raynauda, nieleczonego guza chromochłonnego, kwasicy metabolicznej. **Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania**: leczenie bisoprololem stabilnej, przewlekłej niewydolności serca należy rozpoczął od fazy dostosowania dawki. Podczas rozpoczynania i kończenia leczenia stabilnej, przewlekłej niewydolności serca konieczne jest ścisłe kontrolowanie stanu pacjenta. Brak doświadczenia klinicznego ze stosowaniem bisoprololu u pacjentów z niewydolnością serca, u których występują jednocześnie następujące choroby i stany: cukrzyca insulinozależna (typu I); ciężkie zaburzenia czynności nerek; ciężkie zaburzenia czynności wątroby; kardiomiopatia restrykcyjna; wrodzona wada serca; organiczne wady zastawek powodujące znaczne zaburzenia hemodynamiki; zawał mięśnia sercowego w ciągu ostatnich 3 miesięcy; wiek powyżej 80 lat. Leczenia bisoprololem nie wolno przerywać w sposób nagły bez zdecydowanej konieczności (zwłaszcza u pacjentów z chorobą niedokrwienną serca), gdyż może to prowadzić do przemijającego nasilenia choroby serca. Bisoprolol należy stosować ostrożnie u pacjentów: ze skłonnością do skurczu oskrzeli, np. z astmą oskrzelową lub obturacyjną chorobą dróg oddechowych (należy jednocześnie podawać leki rozszerzające oskrzela, a w przypadku zwiększenia się oporu w drogach oddechowych, które może okresowo występować u pacjentów z astmą, należy rozważyć zwiększenie dawki beta2-adrenomimetyków); z cukrzycą, ze znacznymi wahaniami stężenia glukozy we krwi. (bisoprolol może maskować objawy hipoglikemii); stosujących ścisłą dietę; z blokiem przedsionkowo-komorowym I stopnia; z dławicą piersiową typu Prinzmetala; z chorobą zarostową tętnic obwodowych (możliwe nasilenie dolegliwości, zwłaszcza na początku leczenia); z alergią w wywiadzie (bisoprolol, podobnie jak inne leki beta-adrenolityczne może zwiększać wrażliwość na alergeny i nasilenie reakcji alergicznych); z nadczynnością tarczycy (leczenie bisoprololem może maskować objawy tyreotoksykozy); z guzem chromochłonnym nadnerczy (bisoprolol można stosować dopiero po podaniu leków alfa-adrenolitycznych); z łuszczycą lub z łuszczycą w wywiadzie (bisoprolol można zastosować jedynie po dokładnym rozważeniu stosunku korzyści do ryzyka); podczas leczenia odczulającego; poddawanych znieczuleniu ogólnemu (zablokowanie receptorów beta-adrenergicznych zmniejsza częstość występowania zaburzeń rytmu i niedokrwienia mięśnia sercowego podczas wprowadzenia do znieczulenia i intubacji oraz w okresie pooperacyjnym. Obecnie zaleca się kontynuowanie blokady receptora beta-adrenergicznego w okresie okołooperacyjnym. Anestezjolog musi być poinformowany o stosowaniu beta-adrenolityku ze względu na możliwość interakcji z innymi lekami, prowadzących do bradyarytmii, osłabienia odruchowej tachykardii i zmniejszenia zdolności do kompensacji utraty krwi. Jeśli przed zabiegiem, konieczne jest przerwanie leczenia beta-adrenolitykiem, produkt leczniczy należy odstawiać stopniowo tak, aby proces odstawiania zakończył się na około 48 godzin przed zniecznieniem). Produkt Bisocard zawiera laktozę. Nie należy go stosować u pacjentów z rzadko występującą dziedziczną nietolerancją galaktozy, brakiem laktazy lub zespołem złego wchłaniania glukozy-galaktozy. Produkt Bisocard zawiera mniej niż 1 mmol (23 mg) sodu na jedną tabletkę, to znaczy produkt uznaje się za „wolny od sodu". **Działania niepożądane**: częstość występowania działań niepożądanych określono w następujący sposób: bardzo często (≥1/10), często (≥1/100 do <1/10), niezbyt często (≥1/1000 do <1/100), rzadko (≥1/10 000 do <1/1000), bardzo rzadko (<1/10 000), częstość nieznana (nie może być określona na podstawie dostępnych danych). Rzadko: zwiększone stężenie triglicerydów, zwiększona aktywność enzymów wątrobowych (AlAT, AspAT). Zaburzenia serca. Bardzo często: Bradykardia (u pacjentów z przewlekłą niewydolnością serca) Często: Nasilenie niewydolności serca (u pacjentów z przewlekłą niewydolnością serca)Niezbyt często: Zaburzenia przewodzenia przedsionkowo-komorowego, nasilenie niewydolności serca (u pacjentów z nadciśnieniem tętniczym lub dławicą piersiową), bradykardia (u pacjentów z nadciśnieniem tętniczym lub dławicą piersiową). Zaburzenia układu nerwowego. Często: Zawroty głowy*, ból głowy*. Rzadko: Omdlenie. Zaburzenia oka. Rzadko: Zmniejszone wydzielanie łez. Bardzo rzadko: Zapalenie spojówek. Zaburzenia ucha i błędnika Rzadko: Zaburzenia słuchu. Zaburzenia układu oddechowego, klatki piersiowej i śródpiersia. Niezbyt często: Skurcz oskrzeli u pacjentów z astmą oskrzelową lub chorobą obturacyjną dróg oddechowych w wywiadzie. Rzadko: Alergiczne zapalenie błony śluzowej nosa. Zaburzenia żołądka i jelit. Często: Zaburzenia żołądkowo-jelitowe, takie jak nudności, wymioty, biegunka, zaparcie. Zaburzenia skóry i tkanki podskórnej. Rzadko: Reakcje nadwrażliwości, takie jak świąd, nagłe zaczerwienie skóry, wysypka. Bardzo rzadko: Leki beta-adrenolityczne mogą wywoływać lub nasilać objawy łuszczycy lub wywoływać wysypkę łuszczyco-podobną; łysienie. Zaburzenia mięśniowo-szkieletowe i tkanki łącznej Niezbyt często: Osłabienie mięśni, kurcze mięśni. Zaburzenia naczyniowe. Często: Uczucie ziębnięcia lub drętwienia kończyn, niedociśnienie tętnicze zwłaszcza u pacjentów z niewydolnością serca. Zaburzenia ogólne. Często: Uczucie zmęczenia*, astenia (u pacjentów z przewlekłą niewydolnością serca). Niezbyt często: Astenia (u pacjentów z nadciśnieniem tętniczym lub dławicą piersiową). Zaburzenia wątroby i dróg żółciowych. Rzadko: Zapalenie wątroby. Zaburzenia układu rozrodczego i piersi. Rzadko: Zaburzenia potencji. Zaburzenia psychiczne Niezbyt często: Zaburzenia snu, depresja. Rzadko: Koszmary senne, omamy. Dotyczy tylko pacjentów z nadciśnieniem tętniczym lub dławicą piersiową: * Objawy te występują zwłaszcza na początku leczenia. Mają na ogół łagodny przebieg i ustępują zwykle w ciągu 1 do 2 tygodni (dotyczy Bisocard 5 mg, 10 mg tabl. powlekane). **Podmiot odpowiedzialny posiadający pozwolenie na dopuszczenie do obrotu:** PharmaSwiss Česká republika s.r.o., Jankovcova 1569/2c, 170 00 Praga 7, Republika Czeska. **Numery pozwolenia na dopuszczenie do obrotu:** Bisocard 2,5 mg tabletki powlekane: Pozwolenie URPLWMiPB nr 14983. Bisocard 5 mg tabletki powlekane: Pozwolenie URPLWMiPB nr 8045, Bisocard 10 mg tabletki powlekane: Pozwolenie URPLWMiPB nr 8044. **Kategoria dostępności:** Produkt leczniczy wydawany z przepisu lekarza (Rp.). Informacji udziela: Bausch Health Poland sp. z o.o., Budynek New City, ul. Marynarska 15, 02-674 Warszawa, tel. 22 627 28 88. Data aktualizacji: 01.2020 r.

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Informacja o leku Nebispes 5 mg tabletki. Skład jakościowy i ilościowy: każda tabletka zawiera 5 mg nebiwololu, co odpowiada 5,45 mg nebiwololu chlorowodorku. Substancje pomocnicze o znanym działaniu: 85,96 mg laktozy jednowodnej w 1 tabletce; krospowidon typ A, poloksamer 188, Powidon K-30, celuloza mikrokrystaliczna, magnezu stearynian. **Postać farmaceutyczna:** tabletka. Białe, okrągłe, dwuwypukłe tabletki, ze skrzyżowanymi rowkami dzielącymi po jednej stronie, o średnicy około 9 mm. Tabletkę leku Nebispes można podzielić na cztery równe dawki. **Wskazania do stosowania:** leczenie nadciśnienia samoistnego. Leczenie łagodnej i umiarkowanej stabilnej przewlekłej niewydolności serca jako leczenie uzupełniające standardową terapię u pacjentów w podeszłym wieku (70 lat lub więcej). **Dawkowanie i sposób podawania:** Nadciśnienie tętnicze. Dorośli – jedna tabletka 5 mg na dobę, najlepiej przyjmowana o stałej porze każdego dnia. Działanie obniżające ciśnienie tętnicze występuje po l-2 tygodniach leczenia. W razdkich przypadkach optymalne działanie leku może wystąpić dopiero po 4 tygodniach. Leczenie skojarzone z innymi lekami przeciwnadciśnieniowymi. Leki blokujące receptory beta-adrenergiczne mogą być stosowane w monoterapii lub w skojarzeniu z innymi lekami przeciwnadciśnieniowymi. Jak dotąd, addycyjne działanie przeciwnadciśnieniowe obserwowano jedynie podczas jednoczesnego stosowania leku Nebispes z hydrochlorotiazydem w dawce 12,5-25 mg. Pacjenci z niewydolnością nerek: zalecana dawka początkowa dla pacjentów z niewydolnością nerek wynosi 2,5 mg na dobę. W razie konieczności dawkę dobową można zwiększyć do 5 mg. Pacjenci z niewydolnością wątroby: dane dotyczące pacjentów z niewydolnością wątroby lub zaburzeniami czynności wątroby są ograniczone. Dlatego stosowanie leku Nebispes u tych pacjentów jest przeciwwskazane. Pacjenci w podeszłym wieku: u pacjentów w wieku powyżej 65 lat zalecana dawka początkowa wynosi 2,5 mg na dobę. W razie potrzeby dawkę dobową można zwiększyć do 5 mg. Jednocześnie, ze względu na ograniczone doświadczenie kliniczne u pacjentów w wieku powyżej 75 lat, należy zachować ostrożność i ściśle obserwować pacjentów. Dzieci i młodzież: z uwagi na brak danych na temat bezpieczeństwa i skuteczności, nie zaleca się stosowania produktu Nebispes u dzieci i młodzieży w wieku poniżej 18 lat. Przewlekła niewydolność serca. Leczenie stabilnej przewlekłej niewydolności serca należy rozpocząć poprzez stopniowe zwiększanie dawki, aż do uzyskania optymalnej dawki podtrzymującej określonej dla każdego pacjenta. Pacjenci powinni mieć stabilną przewlekłą niewydolność serca bez ostrej niewydolności przez ostatnie sześć tygodni. U pacjentów otrzymujących leki działające na układ sercowo-naczyniowy, w tym leki moczopędne i (lub) digoksynę i (lub) inhibitory ACE i (lub) antagonistów receptora angiotensyny II, dawkowanie tych leków powinno być ustabilizowane podczas ostatnich dwóch tygodni przed rozpoczęciem leczenia lekiem Nebispes. Dawkę początkową należy zwiększać co 1-2 tygodnie, w zależności od tolerancji leku przez pacjenta: 1,25 mg nebiwololu, zwiększyć do 2,5 mg nebiwololu raz na dobę, następnie do 5 mg raz na dobę i następnie do 10 mg raz na dobę. Maksymalna zalecana dawka wynosi 10 mg nebiwololu raz na dobę. Podczas stopniowego zwiększania dawki, w przypadku nasilenia niewydolności serca lub nietolerancji leku, najpierw zalecane jest zmniejszenie dawki nebiwololu lub, w razie konieczności, natychmiastowe przerwanie leczenia (w przypadku ciężkiego niedociśnienia tętniczego, nasilenia niewydolności serca z ostrym obrzękiem płuc, wstrząsu kardiogennego, bradykardii objawowej lub bloku przedsionkowo-komorowego). Pacjenci z niewydolnością nerek: nie jest wymagane dostosowanie dawki w przypadku łagodnej do umiarkowanej niewydolności nerek, gdyż dawkę zwiększa się stopniowo do dawki maksymalnej tolerowanej przez pacjenta. Brak doświadczeń u pacjentów z ciężką niewydolnością nerek (stężenie kreatyniny w surowicy ≥ 250 µmol/l). Dlatego stosowanie nebiwololu u tych pacjentów nie jest zalecane. Pacjenci z niewydolnością wątroby: dane dotyczące pacjentów z niewydolnością wątroby są ograniczone. Dlatego stosowanie leku Nebispes u tych pacjentów jest przeciwwskazane. Pacjenci w podeszłym wieku: nie jest wymagane dostosowanie dawki, gdyż dawkę zwiększa się stopniowo, do dawki maksymalnej tolerowanej przez pacjenta. Dzieci i młodzież: z uwagi na brak danych na temat bezpieczeństwa i skuteczności, nie zaleca się stosowania produktu Nebispes u dzieci i młodzieży w wieku poniżej 18 lat. **Przeciwwskazania:** nadwrażliwość na substancję czynną lub na którąkolwiek substancję pomocniczą, niewydolność wątroby lub zaburzenia czynności wątroby, ostra niewydolność serca, wstrząs kardiogenny lub epizody niewyrównanej niewydolności serca, wymagające dożylnego podawania leków o działaniu inotropowym dodatnim. W zespole chorego węzła zatokowego, w tym bloku zatokowo-przedsionkowym, bloku serca drugiego i trzeciego stopnia (bez rozrusznika), skurczu oskrzeli lub astma oskrzelowa w wywiadzie, ciężka przewlekła choroba obturacyjna płuc, nieleczony guz chromochłonny, kwasica metaboliczna, bradykardia, niedociśnienie tętnicze, ciężkie zaburzenia krążenia obwodowego. **Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania:** znieczulenie ogólne: utrzymująca się blokada receptorów beta-adrenergicznych zmniejsza ryzyko arytmii w czasie wprowadzenia do znieczulenia oraz intubacji. Jeśli blokada receptorów beta-adrenergicznych jest przerwana w celu przygotowania pacjenta do zabiegu chirurgicznego, należy przerwać podawanie beta-adrenolityków co najmniej na 24 godziny przed zabiegiem. Należy zachować ostrożność podczas stosowania niektórych środków znieczulających, wpływających depresyjnie na mięsień sercowy. Można zapobiec wystąpieniu reakcji ze strony nerwu błędnego poprzez dożylne podanie atropiny. układ sercowo-naczyniowy: nie należy stosować leków beta-adrenolitycznych u pacjentów z nielecznq zastoinową niewydolnością serca, aż do ustabilizowania się ich stanu. Leki blokujące receptory beta-adrenergiczne mogą wywoływać bradykardię: jeśli częstość tętna wynosi poniżej 50-55 uderzeń na minutę i (lub) pacjent odczuwa objawy wskazujące na bradykardię, dawkę należy zmniejszyć. Należy zachować ostrożność w przypadku stosowania leków beta-adrenolitycznych: u pacjentów z zaburzeniami krążenia obwodowego (choroba lub objaw Raynauda, chromanie przestankowe), ponieważ może wystąpić zaostrzenie tych zaburzeń; u pacjentów z blokiem serca pierwszego stopnia, z powodu wydłużenia przez beta-adrenolityki czasu przewodzenia; u pacjentów z dławicą piersiową typu Prinzmetala, z powodu ryzyka niehamowanego skurczu tętnic wieńcowych za pośrednictwem receptorów alfa: leki blokujące receptory beta-adrenergiczne mogą zwiększać liczbę i czas trwania napadów dławicowych. Zwykle nie zaleca się jednoczesnego podawania nebiwololu z antagonistami wapnia typu werapamil i diltiazem, z lekami przeciwarytmicznymi klasy I oraz z lekami przeciwnadciśnieniowymi działającymi ośrodkowo. Metabolizm i układ endokrynologiczny: produkt Nebispes nie wpływa na stężenie glukozy u pacjentów z cukrzycą. Mimo to należy zachować ostrożność u tych pacjentów, ponieważ nebiwolol może maskować niektóre objawy hipoglikemii (tachykardia, kołatanie serca). Leki blokujące receptory beta-adrenergiczne mogą maskować objawy tachykardii w nadczynności tarczycy. Nagłe odstawienie produktu może nasilić objawy. Układ oddechowy: u pacjentów z przewlekłymi obturacyjnymi chorobami płuc leki blokujące receptory beta-adrenergiczne należy stosować ostrożnie, ponieważ leki te mogą nasilać zwężenie dróg oddechowych. Inne: pacjenci z łuszczycą w wywiadzie powinni przyjmować beta-adrenolityki jedynie po dokładnym rozważeniu. Rozpoczęcie leczenia przewlekłej niewydolności serca nebiwololem wymaga regularnej obserwacji. Nie należy nagle przerywać leczenia, chyba, że jest to wyraźnie zalecone. Produkt leczniczy zawiera laktozę. Lek nie powinien być stosowany u pacjentów z rzadko występującą dziedziczną nietolerancją galaktozy, brakiem laktazy lub zespołem złego wchłaniania glukozy-galaktozy. Leki blokujące receptory beta-adrenergiczne mogą zwiększać wrażliwość na alergeny oraz ciężkość reakcji anafilaktycznych. Beta-adrenolityki mogą powodować zmniejszenie wydzielania łez. **Działania niepożądane:** częstość działań niepożądanych określono w następujący sposób: często ≥ 1/100 do < 1/10, niezbyt często ≥ 1/1000 do ≤ 1/100, bardzo rzadko ≤ 1/10 000, nieznane (nie może być określona na podstawie dostępnych danych). Nadciśnienie tętnicze: Zaburzenia układu immunologicznego – Częstość nieznana: obrzęk naczynioruchowy, nadwrażliwość; Zaburzenia psychiczne – niezbyt często: koszmary senne, depresja; Zaburzenia układu nerwowego – często: ból głowy, zawroty głowy, parestezje; Bardzo rzadko: omdlenia; Zaburzenia oka – niezbyt często: zaburzenia widzenia; Zaburzenia serca – niezbyt często: bradykardia, niewydolność serca, spowolnienie przewodzenia przedsionkowo-komorowego/blok przedsionkowo-komorowy; Zaburzenia naczyniowe – niezbyt często: niedociśnienie tętnicze, chromanie przestankowe (lub jego nasilenie); Zaburzenia układu oddechowego, klatki piersiowej i śródpiersia – często: duszność; niezbyt często: skurcz oskrzeli; Zaburzenia żołądka i jelit – często: zaparcia, nudności, biegunka; niezbyt często: niestrawność, wzdęcia, wymioty; Zaburzenia skóry i tkanki podskórnej – niezbyt często: świąd, wysypka rumieniowa; bardzo rzadko nasilenie łuszczycy; częstość nieznana: pokrzywka; Zaburzenia układu rozrodczego i piersi – niezbyt często: impotencja; Zaburzenia ogólne i stany w miejscu podania – często: zmęczenie, obrzęk. Podczas stosowania niektórych leków blokujących receptory beta-adrenergiczne obserwowano także następujące działania niepożądane: omamy, psychozy, splątanie, oziębienie/zasinienie kończyn, objaw Raynauda, suchość oczu i zespół oczno-śluzówkowo-skórny typowy dla praktololu. Beta-adrenolityki mogą powodować zmniejszenie wydzielania łez. Przewlekła niewydolność serca: dostępne są dane dotyczące działań niepożądanych występujących u pacjentów z przewlekłą niewydolnością serca, pochodzące z jednego kontrolowanego placebo badania klinicznego z udziałem 1067 pacjentów otrzymujących nebiwolol i 1061 pacjentów otrzymujących placebo. W badaniu tym działania niepożądane, których związek z leczeniem oceniano jako możliwy, zostały zgłoszone łącznie przez 449 pacjentów otrzymujących nebiwolol (42,1%), w porównaniu do 334 pacjentów otrzymujących placebo (31,5%). Najczęściej zgłaszanymi działaniami niepożądanymi u pacjentów otrzymujących nebiwolol były bradykardia i zawroty głowy, oba występujący u około 11% pacjentów. Częstość występowania wśród pacjentów otrzymujących placebo wynosiła odpowiednio około 2% i 7%. Stwierdzono następujące częstości występowania działań niepożądanych (których związek z lekiem oceniano jako możliwy), które uznano za istotne w przypadku leczenia przewlekłej niewydolności serca: nasilenie niewydolności serca wystąpiło u 5,8% pacjentów otrzymujących nebiwolol, w porównaniu do 5,2% pacjentów otrzymujących placebo. Ortostatyczne niedociśnienie tętnicze odnotowano u 2,1% pacjentów otrzymujących nebiwolol, w porównaniu do 1,0% pacjentów otrzymujących placebo. Nietolerancja leku wystąpiła u 1,6% pacjentów otrzymujących nebiwolol, w porównaniu do 0,8% pacjentów otrzymujących placebo. Blok przedsionkowo-komorowy pierwszego stopnia wystąpił u 1,4% pacjentów otrzymujących nebiwolol, w porównaniu do 0,9% pacjentów otrzymujących placebo. Obrzęki kończyn dolnych odnotowano u 1,0% pacjentów otrzymujących nebiwolol, w porównaniu do 0,2% pacjentów otrzymujących placebo. **Podmiot odpowiedzialny posiadający pozwolenie na dopuszczenie do obrotu:** Bausch Health Ireland Limited, 3013 Lake Drive, Citywest Business Campus; Dublin 24, D24PPT3, Irlandia. **Numer pozwolenia na dopuszczenie do obrotu:** Pozwolenie URPLWMiPB nr 14354. **Kategoria dostępności:** Produkt leczniczy wydawany z przepisu lekarza (Rx). Urzędowa cena detaliczna* Nebispes 5 mg x 28 tabl. wynosi 14,43 zł. Wysokość dopłaty świadczeniobiorcy* Nebispes 5 mg x 28 tabl. wynosi 6,53 zł. Informacji udziela: Bausch Health Poland Sp. z o.o., Budynek New City, ul. Marynarska 15, 02-674 Warszawa, tel. 22 627 28 88. Data aktualizacji: 06.2021 r.

* Obwieszczenie Ministra Zdrowia z dnia 20 sierpnia 2021 r. w sprawie wykazu refundowanych leków, środków spożywczych specjalnego przeznaczenia żywieniowego oraz wyrobów medycznych na 1 września 2021 r.

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* Zarejestrowane wskazanie dla leku Bisocard 5 mg tabletki powlekane i 10 mg tabletki powlekane zgodnie z ChPL – Dławica piersiowa.

† Zarejestrowane wskazanie dla leku Nebispes 5 mg tabletki zgodnie z ChPL – Leczenie łagodnej i umiarkowanej, stabilnej, przewlekłej niewydolności serca jako leczenie uzupełniające standardową terapię u pacjentów w podeszłym wieku (70 lat lub więcej).

** Zarejestrowane wskazanie dla leku Bisocard 2,5 mg tabletki powlekane, Bisocard 5 mg tabletki powlekane i Bisocard 10 mg tabletki powlekane zgodnie z ChPL – Stabilna, umiarkowana do ciężkiej, przewlekła niewydolność serca z zaburzoną czynnością skurczową lewej komory (frakcja wyrzutowa ≤ 35% w ocenie echokardiograficznej), w skojarzeniu z inhibitorami ACE, lekami moczopędnymi oraz, w razie konieczności, z glikozydami naparstnicy.

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