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Effective management of high blood pressure in elderly and senile patients with arterial hypotension

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Abstract

Objective *of this study was to evaluate and compare the incidence of arterial hypotension and orthostatic hypotension in elderly and senile patients with hypertension and coronary artery disease (CAD) treated with a combination of angiotensin-converting enzyme inhibitors (ACEi) and calcium channel (CCB) or beta-blockers.*

Materials and methods. *The current study included 97 female and male participants from Krasnodar region with uncontrolled hypertension and CAD. Participants were randomized into two groups. In the first group, target blood pressure (BP) was achieved with ACEi with CCB, in the second — with ACEi and beta-blockers that were administered for 12 weeks. All patients completed questionaries, had BP checked in the office and undergone 24-hour blood pressure monitoring prior to starting treatment. We also assessed the risk factors for falls according to The Morse Fall Scale (MFS), orthostatic hypotension. After 12 weeks of treatment, office BP was re-checked and 24-hour BP monitoring with systolic and diastolic hypotension time index (HTI) calculations were performed.*

Results. *After 12 weeks of treatment, statistically significant reduction of office BP readings, heart rate (HR), main 12-hour BP monitoring parameters was noted in the patients from both groups. Target BP was achieved in 41 patients from the first group and 39 patients from the second group. Reduction in the main 12-hour BP monitoring parameters didn't depend on the administered anti-hypertensive drug combination. Fall risk according to MFS was significantly lower in patients treated with amlodipine plus perindopril compared with those who took bisoprolol and perindopril (20 points vs 27 points respectively, p<0.05). Patients treated with amlodipine and perindopril lost balance in the «standing with feet together» position in 19.1 % of cases, in the «tandem» or «semi-tandem» position — in 28.6 % of cases that is lower than in the bisoprolol and perindopril group (28.3 % and 39.1 % cases respectively, p<0.05). SHTI in amlodipine and perindopril group was lower than in the bisoprolol and perindopril group during the day (16 % vs 25 %, respectively, p<0.05) and night (18 % vs 28 %, respectively, p<0.05).*

Conclusion. *According to the results of this study, further research of high blood pressure treatment risks, the effects of different pharmacologic agents and their combinations on arterial hypotension seems reasonable and is needed for the development of optimal personalized treatment plans.*

Keywords: *arterial hypertension, arterial hypotension, orthostatic arterial hypotension, 24-hour blood pressure monitoring, antihypertensive therapy, personalized therapy.*

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Arterial hypertension is one of the leading risk factors of cerebro- and cardiovascular disease leading to disability and mortality [1]. Public health and social measures increase the number of elderly and senile patients and, therefore, the prevalence of hypertension and atherosclerosis including coronary artery disease (CAD) [2].

Current clinical guidelines recommend treating hypertension in patients with CAD with the renin-angiotensin system (RAS) inhibitors such as angiotensin-converting enzyme inhibitors (ACEi), beta-blockers and calcium-channel blockers (CCB). Lower blood pressure (BP) targets are recommended for most patients. Fixed combinations of antihypertensive medications are preferred as first-line therapy [3, 4].

Mortality risk remains high in patients with CAD even with well-controlled hypertension [2]. Pathophysiology of hypertension complications in elderly and senile patients, adverse events risk stratification and possible ways to improve prognosis are still of special interest for physicians and researchers.

Frequent and prolonged hypotension and inadequate hemodynamic reaction in orthostasis are important prognostic factors in patients with arterial hypertension. The prevalence of orthostatic hypotension in general population is 6–35 %, increases with older age and peaks in elderly and senile patients [6]. According to some authors, orthostatic hypotension increases the risk of ischemic cardiovascular complications and mortality in elderly and senile patients [8]. Orthostatic hypotension plays and increasingly important role in real clinical practice. Back in 2013 in Europe evaluation of orthostatic hypotension was recommended only for a specific group of patients. By 2018, it has been implemented as a necessary part of physical exam of all patients with CVD [3]. One of the most common symptoms of orthostatic hypotension is a drug-induced vertigo that causes additional limitations to a normal everyday life and increases the risk of falls and injury [7].

Chronic biological aspects of SBP changes in older patients with hypertension should also be considered. Recent studies have identified the association between excessive daytime SBP reduction with increased risk of dementia in the elderly [9]. Moreover, the large-scale Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) has shown the benefits of 24-hour BP monitoring over office BP in cardiovascular outcomes prediction [10].

Testing for orthostatic hypotension and 24-hour blood pressure monitoring in older patients with hypertension and atherosclerosis is still insufficiently used. There are no orthostatic reactions risk calculators that would include not only patient's medical history and orthostatic testing but also chronobiologic features of 24-hor BP profile and the effects of medications. Further research and developments are needed to create optimal patient-oriented approach and safe management approaches for older hypertensive individuals as today more intensive BP control is mostly preferred.

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Materials and methods

The current study included female and male patients aged 65–85 years with uncontrolled arterial hypertension stage 1–2 (BP>140/90 mmHg while on previous antihypertensive therapy) and stable atherosclerosis.

Or study was carried out in accordance with Good Clinical Practice standards and the Declaration of Helsinki. Study protocol was approved by the local Independent Ethics Committee. Prior to participation all patients signed informed consent.

Exclusion criteria were congenital heart defects, cardiomyopathy, history of arterial revascularization, acute stroke and/or myocardial infarction in the last 6 months, diabetes, autoimmune disease, chronic disability, malignancies, and infectious disease at the moment of enrollment and inability to follow the protocol.

All patients were randomized into two groups: 1st group (n=42) included patients treated with a 5–10/5–10 of amlodipine and perindopril (Prestance, Sevier, France) in the morning; 2nd group (n=45) included patients treated with 2.5–5/5–10 of bisoprolol and perindopril (Prestilol, Sevier, France) in the morning. Patients from both groups were also administered 10–20 mg of rosuvastatin per day and 100 mg of aspirin per day.

First, we collected medical history and asked the participants to complete questionaries, initiated antihypertensive treatment and determined regular follow-ups. We performed general physical and anthropometric exams (BP, height, weight, waist and hip circumference), laboratory tests, ECG, 12-hour BP monitoring with «Petr Telegin» (BPLabVasotens, Russia) device. The patients continued with their everyday activities with BP checked every 25 minutes during the day and every 50 minutes at night. Data analysis included night (n) and day (d) SBP and DBP values, elevated SBP and DBP time index, SBP and DBP variability index and the magnitude of the morning BP elevation.

According to the study design, drug dosages were elevated if antihypertensive treatment wasn't effective enough after 4 weeks.

Secondly, 12 weeks after, we evaluated office SBP and DBP, the frequency of target BP and performed 24-hour blood pressure monitoring. Mean dosage of medications after 12 weeks of treatment were: amlodipine and perindopril — 7.2/6.7, bisoprolol and perindopril — 4.2/8.9.

Lipid lowing therapy was corrected according to the current clinical guidelines, mean dose of rosuvastatin was 15.7 in the first group and 16.2 in the second group.

We assessed the risk factors for falling according to The Morse Fall Scale (MFS). Orthostatic test (BP check after 7 minutes supine and 1–3 minutes after standing up) was used as functional testing. The test was considered positive if SBP reduced for >20 mmHg and DBP > 10 mmHg. We also assessed the presence of balance problems with the 10-second balance test. The patient was asked to hold three positions «feet together», «semitandem» and «tandem» [5].

Repeat 24-hour blood pressure monitoring was performed to assess not only the magnitude but also hypotension time index (HTI). Hypotension was identified as SBP<130 mmHg and DBP<70 mmHg. There are no strict criteria for night-time hypotension for patients >65 years so we considered SBP < 105 mmHg and DBP < 55 mmHg as low.

Statistical analysis was carried out using Statistica 10.0, StatSoft. To assess the differences between groups we used Mann–Whitney U test for independent samples and The Wilcoxon signed-rank test for dependent variables. Two and more qualitative values were compared with Chi-squared test. P<0.05 was considered statistically significant.

Results

We examined 97 male and female participants from Krasnodar region.

Clinical characteristics are presented in Table 1.

Table 1. **Clinical characteristics patients included in the study**

Parameter	Value
Age, years	76 (64–85)
Duration of hypertension, years	19 (12–24)
Body mass index, k^2	25.1 (22.5–29.6)
Office SBP, mmHg	154 (141–162)
Office DBP, mmHg	89 (78–95)
HR, beats per minutes`	69 (62–84)

Note. DBP — diastolic blood pressure; HR — heart rate; SBP — systolic blood pressure.

BP significantly reduced after 12 weeks of treatment in both groups. Target BP levels were achieved in 41 patients from the 1st group and 39 patients from the 2nd group. HR reduced more in patients from the 2nd group (p<0.05) due to the effects of beta-blockers (Table 2).

Table 2. **Blood pressure and heart rate changes after treatment**

Parameter	At baseline		After 12 weeks of treatment	
	GROUP 1 (N=42)	GROUP 2 (N=45)	GROUP 1 (N=42)	GROUP 2 (N=45)
SBP, mmHg	155 (142–165)	157 (145–168)	132 (123–137)*	135 (122–142)*
DBP, mmHg	93 (85–101)	96 (89–105)	78 (67–81) *	80 (68–84) *
HR, beats per minutes`	81 (78–85)	83 (80–86)	78 (68–82)*	65 (60–72)*

Note. DBP — diastolic blood pressure; HR — heart rate; SBP — systolic blood pressure.

Table 3. **Changes of 24-hour BP parameters after 12 weeks of treatment with amlodipine and perindopril**

Parameter	Baseline (n=42)	After 12 weeks of treatment (n=42)	Δ %
SBP 24, mmHg	156 (149–165)	130 (122–141)	— 17.4*
DBP 24, mmHg	94 (85–98)	80 (75–83.5)	— 12.8*
SBPd 24, mmHg	157 (152–166)	132 (124–142)	— 16.1*
DBPn 24, mmHg	96 (82–99)	84 (75–88)	— 8.7*
SBP TId, %	92 (78–97)	22 (19–59)	— 62.9*
DBP TId, %	87 (75–95)	19 (5–29)	— 61.4*
SBPd variation, mmHg	21 (14–25)	12 (1–19)	— 21.5*
DBPd variation, mmHg	16 (10–19)	10 (6–12.5)	— 25.9*
SBPn, mmHg	154 (132–162)	127 (117–135)	— 14.9*
DBPn, mmHg	88 (75–91)	77 (68–80)	— 13.2*
SBP TIn, %	93 (80–95)	21 (6–30)	— 59.1*
DBP TIn %	78 (68–90)	18 (3–25)	— 58.9*
SBPn variation, mmHg	20 (13–25)	14 (6–18)	— 24.5*
DBPn variation, mmHg	19 (9–22)	10 (4–13)	— 25.5*

Note. SBP — systolic blood pressure; DBP — diastolic blood pressure; TI — time index; d — day; n — night; Δ % — parameter reduction in % after 12 weeks of treatment; * — p<0.05 considered statistically significant.

Table 4. **Changes of 24-hour BP parameters after 12 weeks of treatment with bisoprolol and perindopril**

Parameter	Baseline (n=45)	After 12 weeks of treatment (n=45)	Δ %
SBP 24, mmHg	157 (150–167)	132 (125–140)	— 16.5*
DBP 24, mmHg	92 (88–94)	80 (75–83.5)	— 13.2*
SBPd 24, mmHg	159 (152–169)	135 (122–140)	— 15.1*
DBPn 24, mmHg	93 (85–96)	85 (76–85)	— 8.3*
SBP TId, %	90 (79–96)	20 (19–59)	— 64.9*
DBP TId, %	85 (77–92)	15 (31–43)	— 62.4*
SBPd variation, mmHg	20 (15–26)	14 (12–17)	— 23.4*
DBPd variation, mmHg	16.5 (11.5–20)	11 (8–13.5)	— 29.2*
SBPn, mmHg	152 (136–160)	125 (115–132)	— 15.2*
DBPn, mmHg	86 (79–89)	78 (70–81)	— 12.3*
SBP TIn, %	91 (84–96)	19 (5–27)	— 62.8*
DBP TIn %	78 (68–90)	15 (3–23)	— 61.1*
SBPn variation, mmHg	19 (14–23)	13.5 (8–17.5)	— 23.7*
DBPn variation, mmHg	18.5 (11–20)	12.5 (6.5–10)	— 24.6*

Note. SBP — systolic blood pressure; DBP — diastolic blood pressure; TI — time index; d — day; n — night; Δ % — parameter reduction in % after 12 weeks of treatment; * — p<0.05 considered statistically significant.

After 12 weeks of treatment all other 24-hour BP monitoring parameters also decreased (p<0.05) (Table 3, 4). The magnitude of parameter changes didn't depend on the combination used (table 3, 4).

Patients in the amlodipine-perindopril group were at significantly lower risk of falling according to MFS compared with patients who took bisoprolol-perindopril (20 points vs 27 points, respectively, p<0.05) (Table 5).

Table 5. **Risk of falling according to The Morse Fall Scale**

Drug combinations	Points
amlodipine + perindopril (n=42)	20 (16–30)*
bisoprolol + perindopril (n=45)	27 (18–36)

Note. * – p<0.05 was considered statistically significant when comparing the frist and second groups.

Moreover, less patients in the amlodipine-perindopril group had balance defects: only 19.1 % of patients

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lost balance in «feet together» position and 28.6 % in «tandem» or «semitandem» positions compared with patients from bisoprolol-perindopril group (28.3 % and 39.1 %, respectively, p<0.05) (Table 6).

Table 6. **Prevalence of balance deficits in both groups**

Drug combinations	Balance deficits in "feet together" position, n %	Balance deficits in "tandem" and "semitandem" position, n %
amlodipine + perindopril (n=42)	8 (19.1)*	12 (28.6)*
bisoprolol + perindopril (n=45)	13 (28.3)	18 (39.1)

Note. * – p<0.05 was considered statistically significant when comparing the first and second groups.

In patients from the 2nd group BP decreased <130/70 mmHg during the daytime and < 105/55 mmHg at nighttime more compared with the 1st group. Time index of decreased SBP was significantly lower in the amlodipine-perindopril group compared with bisoprolol-amlodipine group during the day (16 % vs 25 %, respectively, p<0.05) and night (18 % vs 28 %, respectively, p<0.05). Time index of decreased DBP changes were similar (Table 7).

Discussion

Safety is one of the most important aspects of modern pharmacologic management of many diseases including hypertension. Personalized approach is usually needed to attain maximal safety. Frailty is elderly and senile patients requires careful selection of pharmacologic agents [11]. After target BP is achieved episodes of hypotension in older patients should be identified and eliminated. In frail patients with multiple comorbidities s long periods of low BP can lead to cognitive dysfunction [12] and increased risk of falling [13]. Individual features of 24-hour BP profile can't be identified during short office visits but are easily diagnosed with 24-hour BP monitoring.

According to modern clinical guidelines, a single agent, primarily, the renin-angiotensin-aldosterone system (RAAS) blockers such as ACEi and ARB, CCB and diuretics can be used in older adults for managing hypotension. However, these patients usually have multiple comorbidities such as various forms of CAD and require combination therapy.

Guidelines on hypertension present a lower BP cut-off that is significantly higher than in the definition of arterial hypotension (BP<100/60 mmHg). Therefore, some patients are in the «grey» zone between target BP according to clinical guidelines and arterial hypotension. As such, we compared the incidence of arterial hypotension (including orthostatic hypotension) and its signs: increased risk of falling according to MFS and balance deficits during functional tests in elderly and senile patients who've achieved target BP with ACEi and CCB or ACEi and beta-blockers.

After 4 weeks of antihypertensive treatment target office BP was achieved in both groups (in 95 % of patients in the first and in 93 % in the second group). The 24-hour BP monitoring showed reduction of all parameters in both groups. In the amlodipine and perindopril group patients were at a higher risk of falling according to MFS, higher incidence of balance deficits and lower prevalence of orthostatic hypotension compared with the bisoprolol and perindopril group.

These results may be possibly explained by some beneficial effects of perindopril and amlodipine in patients with chronic cerebral ischemia often seen in older patients with atherosclerosis and episodes of elevated BP. ACEi weren't associated with reduced cerebral, myocardial, or renal blood flow and their use didn't lead to reduced organ ischemia and increased collateral blood flow. Perindopril also reduces the level of angiotensin II, inhibits endothelial apoptosis, increases bradykinin and NO synthesis that have antiatherosclerotic effects [14]. CCB have anti-ischemic effects and their use isn't associated with arterial hypotension as they don't decrease normal BP. Dihydropyridine CCB don't have significant effects on carbohydrate and lipid metabolism have cerebroprotective and anti-atherosclerotic role [15].

According to our results, the prevalence of arterial hypotension and orthostatic hypotension is relatively high in older patients with hypertension and atherosclerosis. Various combinations of antihypertensive

Table 7. **Hypotension time index according to 24-hour BP monitoring**

Drug combinations	TId SBPd (%)	TId DBPd (%)	TId SBPn (%)	TId DBPn (%)
amlodipine + perindopril (n=42)	16 (5–23)*	19 (4–28)*	18 (6–25)*	24 (9–31)*
bisoprolol + perindopril (n=45)	25 (8–35)	22 (5–27)	28 (10–38)	26 (11–33)

Note. TId — time index of decreased blood pressure; SBP — systolic blood pressure; DBP — diastolic blood pressure; * – p<0.05 was considered statistically significant when comparing the frist and second groups.

agents have different effects on the development on these complications. Physicians should thoroughly choose antihypertensive treatment and use additional effectiveness control measures.

Conclusion

According to our results, high prevalence of hypotension and orthostatic hypotension in older patients with hypertension and atherosclerosis requires further research of drug-induced arterial hypotension. Not only direct antihypertensive mechanisms but also long-term effects should be considered when making any prognosis and developing personalized treatment plans.

Conflict of interest: none declared.

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