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PILL THERAPY IN OUTPATIENTS WITH COMPLICATED COMORBID HYPERTENSIVE DISEASE: COMPARISON OF FIXED COMBINED VERSUS ISOLATED MODES

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Abstract: Hypertensive disease is a chronic systemic entity characterized by constant blood pressure level elevation above 130/80 mm Hg induced on genetic background by complex of etiological factors causing disorders of vascular tonus and/or cardiovascular system regulation. We compared the treatment effect of the fixed combination pill (lisinopril, amlodipine, rosuvastatin) with the isolated pill therapy that contained ACE inhibitor (ramipril, lisinopril, perindopril), diuretic (thiazide or loop), statins, calcium channel blocker from minimum to maximally titrated doses — from 5 + 10 + 10 and 2.5 + 12.5 to 10 + 20 + 20 and 5 + 25 in the treatment of the main diseases — hypertensive disease, ischemic heart disease, dyslipidemias, diabetes mellitus type 2, and in postoperative patients (aortocoronary shunts, angioplasty). **Methods.** Randomized clinical trial with 104 outpatients both male and female older than 40 years. Patients of control group (with diagnosis of hypertensive disease and cholesterol level above 6,0) were recommended the following medicines: ACE inhibitors, thiazide diuretics once daily in the morning, rosuvastatin 10 mg or atorvastatin 20 mg once daily in the evening. Additionally, in cases of poorly controlled hypertension — calcium channel blockers: nifedipine 20 mg in the evenings, and for those with implanted stents and angioplasty — aspirin 75 mg in the evening. Patients of the main group were offered fixed combination pill (lisinopril, amlodipine, rosuvastatin) 5 + 10 + 10 or 10 + 20 + 20 once daily in the evening and aspirin 75 mg in the evening or glucose lowering medication. **Results**. There was statistically significant difference of pre- and post-treatment values found of systolic blood pressure registered in both groups ($p < 0.001$) and diastolic blood pressure for control group ($p < 0.001$). There was statistically significant difference between control and main groups in total cholesterol level. Cholesterol levels were statistically significantly reduced in patients with fixed combined therapy compared to isolated therapy mode ($p < 0.01$). Fixed combined therapy combination treatment was noticed to be more beneficial both in regards to arterial hypertension and concurrent diseases such as diabetes mellitus type 2, congestive heart diseases, and metabolic syndrome as well as in postoperative patients with aorto-coronary shunts, angioplasty, stent placement, strokes and myocardial infarctions episodes.

Key words: arterial hypertension, dyslipidemia, diabetes mellitus, statins, combined pill therapy, isolated pill therapy, body mass index, cholesterol, creatinine, triglycerides, angiotensin converting enzyme inhibitors

СРАВНЕНИЕ ЭФФЕКТИВНОСТИ ПОЛИКЛИНИЧЕСКОГО ЛЕЧЕНИЯ КОМБИНИРОВАННЫМИ И ИЗОЛИРОВАННЫМИ ТАБЛЕТИРОВАННЫМИ ПРЕПАРАТАМИ У КОМОРБИДНЫХ ПАЦИЕНТОВ С ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНЬЮ

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Резюме: Гипертоническая болезнь — хроническое системное заболевание, характеризующееся стойким повышением цифр АД более 130/80 мм рт ст, вызванное нарушением регуляции тонуса сосудов и работы сердечно-сосудистой системы. Мы сравнили эффект терапии комбинированным препаратом (амлодипин, лизиноприл, розувастатин) с изолированными препаратами группы ингибиторов ангиотензин-конвертазы (рамиприл, лизиноприл, периндоприл), диуретиками (тиазидными и петлевыми), статинами, блокаторами кальциевых каналов — от минимально до максимально титруемых доз — от 5 + 10 + 10 и 2.5 + 12.5 до 10 + 20 + 20 и 5 + 25 мг в ходе терапии основных нозологических форм (гипертоническая болезнь 2-й стадии и степени тяжести, ишемическая болезнь сердца, дислипидемия, сахарный диабет 2-го типа, состояние после аорто-коронарного шунтирования или стентирования). **Методы**. Рандомизированное клиническое исследование, в котором приняли участие 104 пациента мужского и женского пола возрастной группы старше 40 лет. Пациентам контрольной группы с диагнозом гипертоническая болезнь 2-й стадии и степени тяжести и уровнем холестерина выше 6,0 мМ/л назначались: ингибитор ангиотензин-превращающего фермента + тиазидные диуретики один раз в день утром, розувастатин 10 мг вечером либо аторвастатин 20 мг вечером. Также дополнительно пациентам назначались блокаторы кальциевых каналов нифедипин 20 мг вечером и при установленных аортокоронарных стентах — кардиомагнил 75 мг на ночь. Пациентам основной группы назначался комбинированный препарат, содержащий в одной таблетированной форме лизиноприл, амлодипин и розувастатан в дозировке 5 + 10 + 10 либо 10 + 20 + 20 один раз в день вечером. **Результаты**. Были выявлены статистически значимые различия до и после лечения в систолических показателях артериального кровяного давления в обеих группах ($p < 0.001$) и диастолического его уровня в контрольной группе ($p < 0.001$). Между контрольной и основной группами статистически значимые различия были выявлены в значениях общего холестерина — уровень общего холестерина был статистически значимо ниже у пациентов основной группы ($p < 0.01$). Комбинированная терапия оказывает более быстрый эффект в достижении целевых уровней как холестерина, так и цифр артериального кровяного давления. Эффективность комбинированной терапии отмечается как у пациентов без сопутствующих заболеваний, так и у пациентов с рядом сопутствующих заболеваний, таких, как инфаркт миокарда или инсульт в анамнезе, сахарный диабет 2-го типа, метаболический синдром.

Ключевые слова: артериальная гипертензия, дизлипеидемия, сахарный диабет, статины, комбинированная таблеточная терапия, изолированная таблеточная терапия, индекс массы тела, уровень холестерин, креатинин, триглицериды, ингибиторы ангиотензин-превращающего фермента

INTRODUCTION

Hypertensive disease is a chronic systemic entity characterized by constant blood pressure level elevation above 130/80 mm Hg induced on genetic background by complex of etiological factors causing disorders of vascular tonus and/or cardiovascular system regulation. It starts as essential arterial hypertension and, in its progress, involves and joins secondary arterial hypertension mechanisms of various kinds [1]. Cardiovascular diseases accompanied by arterial hypertension and their fatal complications such as stroke and myocardial infarction are the leading causes of morbidity and mortality worldwide [11]. Hypertensive disease has a negative impact on both cardiovascular and renal systems. Even in high-income countries population still suffers from poorly controlled hypertension disease. Main strategies that are implemented nowadays to control hypertension involve initiating treatment on time, modification of the way of living (high level of aerobic physical activity, DASH [Dietary Approaches to Stop Hypertension] diet, and exposure to fresh air), as well as possible shift from monotherapy to combined therapy and usage of fix-dosed combinations in one pill. Benefits of proper controlling of arterial hypertension are evident. Sometimes combining therapy can become a useful way out to reach the most adequate prolonged hypertension control. [11]

There are several studies that indicate that in practice at least two anti-hypertensive drugs are necessary to reach a successful control of the disease. The main classes of medicines recommended include: ACE inhibitors, calcium channel blockers, diuretics and beta-adrenoblockers. All medications can be recommended separately or in one fixed combined pill [24]. Currently there is a tendency to abandon the combination of beta-adrenoblockers and diuretics due to their adverse effects. The preferred method is a combination of renin-angiotensin system inhibitor/ACE inhibitor or a sartan with a calcium channel blocker or a diuretic [20].

The classic of Russian literature Nikolay Alekseevich Dobrolyubov (1836–1861), although he was not a medical doctor, nevertheless wisely noticed, that among all living beings, the Homo gets sick and recovers in the most complicated way [2]. Quite in the spirit of his thought, it should be noted that the efficient therapy of hypertensive disease is possible with proper adherence to treatment regimen only, as well as with regular education of the patients about the risks and benefits of hypertension control. It is especially essential for effective achievements of outpatient care purposes.

We decided to implement the fixed therapy — consisting of angiotensin converting enzyme (ACE) inhibitor, calcium channel blocker and a sartan (lisinopril, amlodipine, or rosuvastatin) in a one combined pill and compare the effectiveness of this mode of treatment to an isolated mode of therapy that included the same classes of medications, but given in the separate pills, in order to see how combined fixed pill therapy can affect blood pressure targeted levels, total cholesterol level, patient's adherence to the recommended treatment, and several other blood biochemical parameters, including blood levels of alanin-aminotransferase (ALT), aspartate-aminotransferase (AST), creatinine, potassium, sodium and triglycerides. We decided to evaluate dynamics of Quetelet's body mass index (BMI) as well. Subsequently we tried to evaluate how adherence to treatment can influence complication risks such as stroke and myocardial infarction, improve quality of life and prolong survival in patients with hypertensive disease and usual concurrent comorbidities, such as diabetes mellitus type 2 and dyslipidemia [4].

THE AIM OF THE STUDY

was to determine if there are any statistically significant differences between blood pressure control numbers, total cholesterol values, blood biochemical profile, blood electrolytes and BMI in two groups of complicated comorbid arterial hypertension outpatients, *using either fixed or isolated antihypertensive pills' combinations.*

MATERIAL AND METHODS

The study was a prospective randomized clinical trial with 104 outpatients involved, both males and females, aged older than 40 years. We studied them in Moscow, at the Consultative and Diagnostical Outpatient Clinic # 121.

The main treatment efficiency criteria were: 1) Targeted blood pressure levels achieved less than 130/80 mm Hg; 2) Total cholesterol level achieved less than 5 mM/l; 3) the best adherence possible; 4) BMI stable; 5) blood electrolytes (potassium, magnesium, sodium), and blood levels of creatinine, uric acid, phosphokinase — tending to normal.

Additionally, in order to determine adherence to the recommended treatment, patients were asked to fill out the questionnaire. Most questions included factors that could form proper adherence to the recommended therapy and that could also determine lack of adherence as one of the possible factors of poor treatment efficacy.

The study continued during 4 months.

The patients were randomly assigned to either control or main (experimental) group. Both groups contained male and female patients older than 40 years old with the following diagnosis in both groups: ischemic heart disease, hypertensive disease stage 2, congestive heart failure, metabolic syndrome, diabetes mellitus type 2, atherosclerosis, chronic kidney disease, arrythmia, and dyslipidemias. Some patients underwent angioplasty, aortocoronary shunts and had episodes of stenocardia, strokes and heart attacks in anamnesis.

There were 63 patients in the control group and 41 patients in the main group.

The major patient complaints included headache, uncontrolled blood pressure values, uncontrolled glucose levels, fatigue, malaise, excessive weight, loss of energy, as well as complaints of postoperative patients who underwent aortocoronary shunt and angioplasty interventions.

Patients' age in control group 62.2 (12.1) and experimental group 61.2 (9.2) were statistically equal ($p = 0.64$). Gender distributions in control group 43f (68.3%) / 20m (31.7%) and experimental group 30f (73.2%) / 11m(26.8%) are also differed non-significantly ($p = 0.59$).

Patients of control group with hypertensive disease and cholesterol levels more than 6,0 mM/l were recommended the following groups of medicines: ACE inhibitors, thiazide diuretics (Ramipril and hydrochlorothiazide 5 + 25 mg) once daily in the morning, rosuvastatin 10 mg or atorvastatin 20 mg once daily in the evening. Additionally, in case of poorly controlled arterial hypertension we applied calcium channel blockers nifedipine 20 mg in the evenings, and for those cases with implemented stents and angioplasty — aspirin 75 mg in the evening. In case of concurrent comorbidities of diabetes mellitus type 2 — metformin 1000 mg daily, or diabeton 3,5 mg daily was used.

Patients of the main (experimental) group were offered fixed combination pill (lisinopril, amlodipine, rosuvastatin in one tablet) 5 + 10 + 10 or 10 + 20 + 20 once daily in the evening and aspirin 75 mg in the evening or glucose lowering medication.

We compared the effectiveness of the fixed combination pill (lisinopril, amlodipine, rosuvastatin) therapy with the isolated pill therapy that included in separate tablets an ACE inhibitor (ramipril, lisinopril, perindopril), a diuretic (thiazide or loop diuretic), statins, calcium channel blocker from minimum to maximal titrated doses (from 5 + 10 + 10 and 2.5 + 12.5 to 10 + 20 + 20 and 5 + 25 in the treatment of the main diseases.

Descriptive statistics for quantitative data consisted of mean value and standard deviation for normally distributed samples and median with first and third quadrilles for other samples. Statistical significance of effect for paired samples were studied by paired t-test for normal samples and Wilcoxon test for other ones. For independent samples t-test was applied when data displayed normal pattern of distribution, and Mann-Whitney test if not. Normality was studied using Kolmogorov-Smirnov test.

Nominal data were described with frequencies and percentages of the total for each attribute's value. Significance of difference between groups was studied by χ-squared test.

For all tests P-values less then 0.05 were considered as an indication of statistical significance.

RESULTS

Table 1 shows if any differences in main studied parameters measured before and after treatment were found and if they were statistically significant comparing two groups of patients. There was statistically significant difference of pre- and post-treatment values found of systolic blood pressure registered in both groups ($p < 0.001$) and diastolic blood pressure for control group ($p < 0.001$). But there was no statistically significant difference as regards to these parameters between main and control groups. There was statistically significant difference between combined pill treatment and separate pills treatment groups in cholesterol levels achieved. Cholesterol levels were statistically significantly reduced in patients with fixed-mode therapy compared to those on separate-mode one ($p < 0.05$). There were no statistically significant changes between two groups of patients concerning BMI, as well as in blood levels of glucose, creatinine, ALT, AST, triglycerides, potassium, magnesium, and sodium, as well as in their pulse rates, that is why the above-mentioned values are absent in the table.

Table 1

Statistically significant changes in main parameters studied (N stands for number of patients)

Attribute	Main group, N = 63			Control group, N = 41		
	Mean(SD) Me (Q1;Q3)	Mean (SD) Me (Q1;Q3)	P value	Mean(SD) Me (Q1;Q3	Mean(SD) Me (Q1;Q3	P value
Systolic Blood Pressure (mm Hg)	159 (19)	128(37)	< 0.001	160 (21)	127 (19)	< 0.001
Diastolic Blood Pressure (mm Hg)	95 (90;100)	83 (80;90)	0.09	100 (90;100)	80 (73;87)	< 0.001
Total Cholesterol (mM/l)	5.77(1.60)	4.77 (1.40)	0.015	5.18 (1.19)	4.73 (1.23)	0.12

Total cholesterol level (TC) in blood was reduced after treatment by 0,45 mM/l in the control group that was, however, not statistically significant, but its reduction by 0,99 mM/l in the main group was statistically significant (Fig. 1).

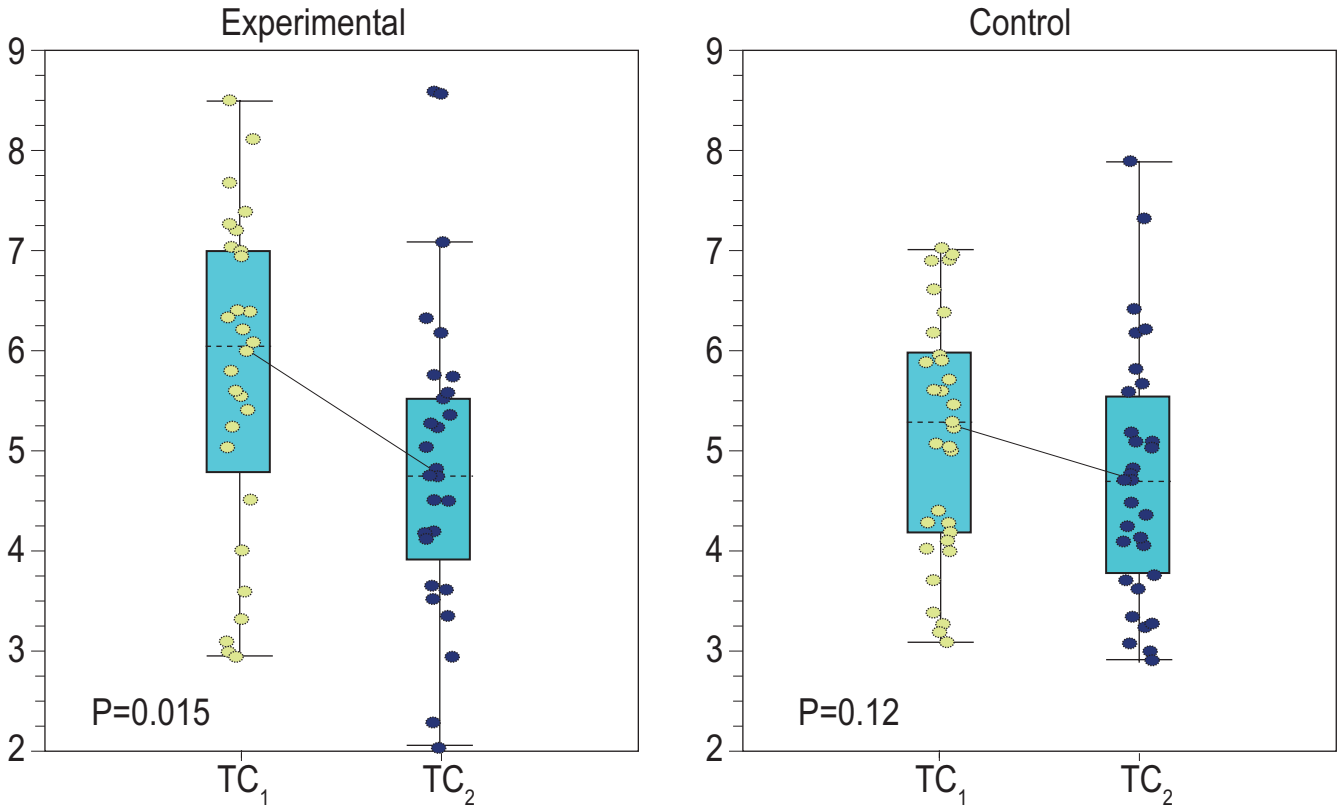

Fig. 1. Total blood cholesterol (TC) levels in combined pill treatment group (left) and isolated pill treatment group (right) groups before (1) and after (2) treatment

DISCUSSION

Fixed combination therapy was noticed to be more beneficial in both patients with essential hypertension only and patients with concurrent comorbidities such as diabetes mellitus type 2, congestive heart failure, metabolic syndrome and postoperative patients with aortocoronary shunts operations and stent placement, as well as with strokes and myocardial infarctions episodes in the anamnesis. Similar effects were noticed in the research made by J. Redon et al. [19]. There was also a tendency noticed in the patients to abstain from sartan use due to possible side effects and rare liver damage side effects described in mass media. Having sartans in the combination pill therapy resulted not only in statistically significant cholesterol level reduction, according to present study, but also in significant decrease in such hemodynamic and echocardiographic parameters as diastolic and systolic blood pressure level, myocardial mass and heart rate, according to O.M. Bochar et al. [6].

We concluded that fixed therapy is more efficient in both blood pressure and dyslipidemias control. Fewer side effects were noticed after fixed combination therapy and lower dose of the titration, compared to isolated treatment [8].

Primary care physicians and general practitioners are specialists responsible for the effective management of hypertensive disease and lifestyle modifications associated with better blood pressure and hyperlipidemia control. We conducted our study on the base of the primary healthcare system institution — an outpatient consultative and diagnostic polyclinic.

Both social and biological factors have great impact on individual efficacy of chronic arterial hypertension control in treatment of outpatients, and the matter is studied extensively.

Studies of the primary healthcare system conducted in China showed that BMI, age and living in urban areas compared to rural areas have been considered negative factors in achieving blood pressure targeted numbers. Positive factors turned out to be better education and lower baseline systolic blood pressure [24]. Negative consequences of uncontrolled high blood pressure included not only high risk of stroke and myocardial infarction, but also elevated blood levels of both asymmetric dimethylarginine (ADMA) and creatinine [17].

Studies conducted by M.E. Statsenko and M.V. Derevyachenko that included 30 patients with diabetes mellitus type 2 and arterial hypertension showed that the combination of an ACE inhibitor and a diuretic can be effective not only in achieving blood pressure goals but also safe for recovering endothelial function in patients with arterial hypertension and diabetes mellitus type 2. The results of occlusion tests were used as the method to determine the concentration of NO metabolites and endothelin-1 in urine and serum [23].

C.A.C. da-Silva et al., 2019 in their studies tried to establish the correlation between certain occupation (police officers), metabolic syndrome, overweight/obesity, hyperlipidemia and hypertension. They have figured out that there is a tendency to develop certain diseases with certain occupational skills and time frame of working [7].

L.C. Baptista et al. conducted a study where the implemented exercise for both group — control and experimental — was used. They divided patients age 60 or more into two treatment groups — first group got only ACE inhibitors, second got ACE inhibitor and combined therapy. The results showed that the functional status improved significantly in both groups. Monotherapy with ACE inhibitor significantly reduced both blood pressure and body mass index, and combined therapy reduced hip-to-waist ratio and blood pressure. ACE inhibitors and exercise can both be implemented successfully to achieve targeted blood pressure results and improve health-related quality of life [4].

There are also studies showing that fixed combination of calcium channel blockers, diuretic and ACE inhibitors showed high rate of achievement of target blood pressure levels [15]. One should keep in mind though that vigorous early hypertension treatment can worsen renal outcome by reducing renal perfusion — there are recent studies conducted by R. Greite et al., that proved this concept. Adding calcium channel blocker to the scheme of ACE inhibitor + diuretic showed significantly better results of achieving target blood pressure levels in the study conducted by T.M. Solomennchuk et al. (which allowed to achieve target levels of blood pressure in 79% — 86% of cases). Combined treatment was characterized by good endurance and high adherence to treatment scheme [22].

There have been several studies conducted on molecular level: Recently S. Zhang et al. showed a positive correlation between lengthening of leukocyte telomere size and decreased systolic blood pressure and pulse pressure. They concluded that arterial hypertension is associated with telomere length [24]. M. He et al. studied a transmembrane serine protease named corin that activates atrial natriuretic peptide and tried to associate the corin structure with the underline mechanism of hypertension [13].

The relationship between adherence to antihypertensive drugs and the risk of death has been assessed in the study by S.H. Rea et al., 2020. The adherence was measured as the risk of death in frail and non-frail elderly individuals. Adherence was measured by the proportions of the follow-ups covered by prescriptions. High-adherence patients exhibited statistically significant lower risk of all-cause mortality as well as cardiovascular mortality compared to low-adherence [18].

There is also possible positive effect on the patient's cognitive function with better hyperlipidemia and hypertension control, that helps to prevent dementia and retard the progressing of Alzheimer disease. An additional antihypertensive drug guanfacine was proved to be effective in the treatment of arterial hypertension due to its favorable antihypertensive action, few side-effects, and the possibility of administration in daily single doses [10]. In patients with heart failure with preserved ejection fraction, several months of pulmonary arterial hypertension-specific treatment proved to increase both right ventricular and left ventricular stroke volumes [14].

We measured adherence and compliance according to the questionnaires. Patients compliant with the medication who have not forgotten to take the prescribed combined or monotherapy,

had shown better results according biochemical values and blood pressure control numbers achieved.

There has been a trend towards poor hypertension disease control worldwide. Different studies concluded that there is an association between various biological and psycho-social factors and failure of treatment. At the same time patient education and treatment compliance significantly contribute towards better control of elevated blood pressure [3]. Most common factors that can contribute to the increased blood pressure include ethnicity/race and country of origin (for example, it was demonstrated that population of Hispanic origin is less susceptible to hypertension compared to US-born people). The lifestyle and risk behaviors such as alcohol consumption and tobacco smoking are of strong significance also [25–27].

There have been numerous clinical trials showing patients with arterial hypertension require at least two or more antihypertensive drugs to reach adequate blood pressure control. Current European guidelines for the arterial hypertension treatment recommend combined therapy once monotherapy failed. In certain situations, such as markedly elevated blood pressure values, very high cardiovascular risks and lower than 130/80 targets are required — combined therapy can be used as a first line. Among the most common advantages of combined therapy: Earlier and more efficient therapeutic effect, fewer side effects and lower titration doses used [9]. Our study shows better adherence with fixes combined therapy pill, statistically significant systolic and diastolic blood pressure control and statistically significant total cholesterol level reduction compared to isolated mode of therapy. Several other works provided similar data. There is proved evidence that combined therapy reduces cardiovascular morbidity and mortality rate. Combined therapies with an angiotensin-converting enzyme inhibitor (ACEI) and a calcium channel blocker (CCB) is one of the combinations recommended by the European Society of Hypertension. There were identified 122 potentially relevant studies. 38 included combined therapies in one or both treatment schemes. A total of 12 publications were retrieved and provided data on the effects of the combined therapy with an ACEI and a CCB on cardiovascular mortality/morbidity in patients with HT [19]. The study of M.J. Schuemie et al., 2020 demonstrated the application of the Large-scale Evidence Generation and Evaluation across a Network of Databases (LEGEND) principles to hypertension treatments [21]. Patients who took fixed combined pill had reached statistically significant cholesterol level reduction and blood pressure control levels. Their adherence to the recommended therapy turned out to be better [16]. The advantage of combined fixed therapy included fast and more significant effect, better patient adherence to the recommended therapy, fewer side effects compared to isolated therapy and lower titration doses compared to isolated therapy [5, 9]. Efficacy of the fixed combined therapy was proved in patients without comorbid conditions and with comorbidities and concurrent diseases such as stroke/infarction, chronic heart disease, ischemic heart disease, diabetes mellitus type 2, metabolic syndrome. The effectiveness of the blood pressure and cholesterol levels' control in the outpatient settings can be evaluated and subsequently modified based on the results of our study — fixed pill combinations can be successfully used to achieve targeted cholesterol values, target blood pressure numbers, improve heart rate, and help prevent cardiovascular complications.

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