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Pooled analysis of the three trials of the TRIUMF series: efficacy of a triple fixed combination of antihypertensive drugs in the practice of physicians of different specialties in Ukraine

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The aim – to compare the data obtained in the TRIUMF (antihyperTensive theRapy in UkraIne – BP optiMization in Focus) trials, in particular, TRIUMF-1, TRIUMF-2, TRIUMF-3, to determine possible patterns and significant factors affecting BP control in patients taking 2 or more antihypertensive drugs and switching to the original single pill combination (SPC) of perindopril arginine/indapamide/amlodipine.

Materials and methods. For the pooled analysis, data on 5960 patients obtained from the three trials of the TRIUMF series were selected. All the studies were multicenter prospective trials conducted at different times in Ukraine with the involvement of general practitioners (TR-1), cardiologists (TR-2), and family practitioners (TR-3). According to the inclusion criteria, patients over 18 years of age with hypertension and a history of taking 2 or 3 antihypertensive drugs for at least 1 month whose BP remained above 140/90 mm Hg could be included in the study. The drug of choice for further therapy was Triplixam (Servier, France) – a single pill combination (SPC) of perindopril arginine, amlodipine and indapamide. Each patient was observed for 3 months. Patients visited physicians in 1–2 weeks, 2 months after the start of the study and the corresponding therapy adjustment. The adherence rate was assessed before and after 2 months. The use of beta-blockers (BBs) in the treatment of the cohort of patients with hypertension was analyzed separately. The final analysis included a comparison of the data obtained in the TRIUMF trial series.

Results and discussion. The use of a SPC of perindopril arginine/indapamide/amlodipine allowed to achieve the target BP levels (140/90 or less) after 2 months of therapy in 84 % of patients with a history of taking a combination therapy (2 drugs – 65 %, 3 drugs – 35 %). One of the important criteria for choosing the dose of a triple SPC is the baseline BP values. The higher the degree of hypertension, the higher the dose prescribed by physicians. The minimum dose of the SPC of perindopril arginine, indapamide and amlodipine (5/1.25/5 mg) was prescribed for stage 1 hypertension in 62 %, stage 2 hypertension in 38 %, and stage 3 hypertension in 15 % of patients; the maximum dose (10/2.5/10 mg) was prescribed for stage 1 hypertension in 9 %, stage 2 hypertension in 15 %, and stage 3 hypertension in 43 % of patients included in the study ($p<0.05$). Therapy with the triple SPC of perindopril arginine, indapamide and amlodipine was well tolerated: adverse events were observed in 0.63 % (TR-1), 1 % (TR-3) and 1.86 % (TR-2) of cases, which was largely due to the previous use of two (65 %) or three (35 %) antihypertensive drugs comprising the SPC by the study patients. Beta-blockers (n=2012) were prescribed due to the presence of a comorbidity (coronary heart disease, angina pectoris – 33.5 %, heart failure – 28.3 %) rather than due to lowered BP. The combination of perindopril arginine/indapamide/amlodipine with BB was well tolerated and 83.9 % of patients achieved BP ≤ 140/90 mm Hg, while 9.36 % achieved ≤ 130/80 mm Hg after 2 months of treatment. There was a significant improvement in the adherence to treatment (TR-2,

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TR-3) in the majority of patients (75 and 70 %), due to high antihypertensive efficacy, convenience of pill's administration (one pill instead of three) and good tolerability of the original SPC.

Conclusions. Regular medical supervision (cardiologists, family practitioners, general practitioners), high antihypertensive efficacy of the SPC (84 % of patients reached the target BP levels after 2 months of therapy), convenience of pill's administration (one pill instead of three), high adherence to treatment confirmed in TR-2 and TR-3 in most patients, and good tolerability of the original SPC of perindopril arginine, indapamide and amlodipine led to a significant improvement in the effectiveness of treatment of patients with hypertension.

Key words: arterial hypertension, antihypertensive therapy, fixed combination, adherence to treatment.

Today, cardiovascular diseases (CVD) are the major cause of premature death among residents of industrialized countries worldwide. In addition, their high medical and social impact is related to a significant reduction or loss of ability to work. In recent years, CVDs have shown a trend to affect younger population. A special role in the occurrence and progression of cardiovascular events is played by the presence of hypertension, which is one of the main risk factors for cardiovascular (CV) complications. Timely diagnosis and adequate pharmacotherapy not only impact its effective management but also the patient's quality of life and prognosis [1–3].

According to the official statistics of the Ministry of Health, hypertension accounts for up to half of all cases of blood circulatory system diseases in Ukraine [4]. It should be noted that the actual figures, especially under martial law, may be higher, as not all patients are aware of their disease due to various objective reasons, including the lack of regular medical examinations and timely diagnosis. In addition to hypertension, more than 2/3 of these patients have coronary heart disease and/or atherosclerosis of other localization (cerebrovascular disease, peripheral atherosclerosis) and are at very high risk for CV complications, including death [5–6]. In such cases, the need for optimal medical therapy becomes especially urgent due to a significantly more unfavorable prognosis for the patient.

There is no doubt that timely initiated therapy is one of the key factors determining the effectiveness of hypertension control, deceleration of its progression and development of complications. Analysis of data from national epidemiological studies shows that most patients (more than 80 %) have uncontrolled hypertension [7–9]. This is usually due to suboptimal drug selection, inadequate dosage, late prescription of therapy, including single-pill combinations (SPCs), inadequate treatment monitoring, and low patient adherence.

Considering that blood pressure (BP) regulation as a complex, multicomponent physiological process, its disruption requires correction of various links in the pathogenesis, which, accordingly, requires the use of combinations of antihypertensive drugs that can provide proper hypertension control. Data from clinical and epidemiological studies indicate that antihypertensive drugs from different groups can provide effective correction of certain disease components and prevent various types of complications: angiotensin-converting enzyme (ACE) inhibitors (ACEi) – coronary complications, calcium channel blockers (CCBs), diuretics – strokes [9–13]. Moreover, the combined use of drugs from different groups, in addition to the prevention of major CV complications, allows to provide a nephroprotective effect (CCBs cause vasodilation of afferent arterioles, while ACEi reduce the resistance of afferent arterioles, which provides a synergistic effect for the prevention of renal dysfunction in patients with hypertension) [9–10]. Therefore, the combination of CCBs and ACEi is currently considered to be one of the most effective in the correction of hypertension, as it not only provides a therapeutic effect on various links of BP dysregulation but also effectively prevents typical complications in this category of patients. Current guidelines state that the use of thiazide-like diuretics, or so-called saluretics (indapamide), rather than classical (loop or thiazide) diuretics, is highly effective, as they not only provide better BP control but also significantly improve the quality of life and provide a better prognosis (they have no metabolic risk and no pronounced diuretic effect). In addition, the synergistic effect of the components in fixed combinations of antihypertensive drugs is important for achieving target BP values [9–13].

Patient adherence to treatment is known to be a principal factor for the effective treatment of chronic diseases, such as hypertension. The use of triple therapy as an SPC provides effective control of hypertension, while the use of three separate drugs may create problems with patient adherence to treatment. High adherence to treatment is one of the key reasons for the use of SPCs of antihypertensive drugs, given their simple and convenient administration [12–14].

The aim of our work was to compare the data obtained in the TRIUMF (antihyperTensive theRapy in UkraIne – blood pressure optiMization in Focus) trial

series, in particular, TRIUMF-1, TRIUMF-2, TRIUMF-3, using a pooled analysis to determine possible patterns and significant factors affecting BP control in patients taking 2 or more antihypertensive drugs and switching to the original single pill combination (SPC) of perindopril arginine/indapamide/amlodipine («Triplixam», Servier).

MATERIALS AND METHODS

All the TRIUMF trials were multicenter and prospective and were conducted at different times in Ukraine:

- TRIUMF-1 was conducted from 14/12/2015 to 02/04/2016. The study involved 50 general practitioners from 41 centers in Ukraine, with a total of 3953 patients.
- TRIUMF-2 was conducted from 01/11/2016 to 02/04/2017. The study was conducted by cardiologists from 17 regional centers, with a total of 3556 patients participating in the study.
- TRIUMF-3 was conducted from 11/04/2018 to 20/09/2018 by 218 family practitioners with the involvement of 4113 patients.

According to the inclusion criteria, patients over 18 years of age with hypertension and a history of taking 2 or 3 antihypertensive drugs for at least 1 month whose BP remained above 140/90 mm Hg could be involved in the study. The protocol required that each patient signed a participant declaration, an informed consent to participate in the study.

Exclusion criteria were orthostatic hypotension; history of cerebrovascular events within the last 3 months (ischemic stroke, cerebral hemorrhage, transient ischemic attack); history of heart disease within the last 6 months: cardiogenic shock, myocardial infarction, hemodynamic instability after acute myocardial infarction, untreated decompensated heart failure, coronary revascularization, congestive heart failure or history of congestive heart failure with NYHA functional class II, III or IV, severe aortic or mitral valve stenosis or hypertrophic cardiomyopathy, unstable angina (except for Prinzmetal angina); history of ventricular arrhythmias; known renal dysfunction: creatinine clearance values classified as moderate or severe renal insufficiency, or bilateral renal artery stenosis, or stenosis of a single kidney, or history of gout; any history of serious illness (including cancer) that may interfere with the study, or history of mental or psychological disorder; chronic obstructive pulmonary disease in the acute stage; type 2 diabetes mellitus in the stage of decompensation (HbA1c > 7.5 %); pregnancy and lactation; alcohol or drug dependence; severe hepatic insufficiency (more than three times elevated ALT, AST).

The BP dynamic pattern in all trials was assessed after 2 weeks (or 1 week for inpatients) and 2 months from the start of treatment.

The pooled analysis of the three trials included data suitable for analysis (excluding incomplete and duplicate records) for a total of 5960 patients.

The main objectives of the pooled analysis of the three TRIUMF trials were:

1. To evaluate factors that justified the physician's choice of the dose of the original SPC of perindopril arginine/indapamide/amlodipine for the patient's therapy;
2. To analyze the dependence of BP dynamics on the baseline BP level and the prescribed dose of the original SPC of perindopril arginine/indapamide/amlodipine;
3. To determine the place and role of beta-blockers (BBs) in pooled analisys cohort in the context of use of the original SPC of perindopril arginine/indapamide/amlodipine, taking into account objective indicators of the hypertensive patient's condition;
4. To draw general conclusions based on the results of the pooled analysis.

The description of statistical methods was published earlier [9–10].

Medication adherence was evaluated by X. Girerd et al. Questionnaire (Girerd X, Radauceanu A, Achard JM, et al. Evaluation of patient compliance among hypertensive patients treated by specialists. Arch Mal Coeur Vaiss. 2001 Aug;94(8):839-42. [In French]).

RESULTS AND DISCUSSION

For the pooled analysis, data for 5960 patients from three trials of the TRIUMF series (TRIUMF-1, TRIUMF-2, and TRIUMF-3) that were fully suitable for processing and met the analysis objectives were selected.

Patient general characteristics (profile)

All patients included in the pooled analysis (n=5960) had elevated BP at the time of enrollment in the study despite treatment with antihypertensive drugs: the mean values were 171.9/98.7 mm Hg, which significantly exceeds the target values for the treatment of hypertension. It should be noted that the study included patients with hypertension of varying degrees,

but, as expected, the vast majority had stage 2 and 3 hypertension – 49.5 % and 41.1 %, respectively. The smallest number of participants had stage 1 hypertension (9.4 %). The degrees of hypertension were assessed by the BP level, which was measured at the inclusion visit against the background of current antihypertensive therapy at that time. The majority of those included in the study were women – 61.7 % (mean age – 64.85 years). Men were of a younger age (mean age – 60.73 years), which is consistent with epidemiological studies on the later development of cardiovascular diseases, including hypertension, in women.

The average duration of the disease was 11.65 years. Quite expectedly, this indicator directly depended on the severity of hypertension – patients with more severe disease had a longer average duration of the disease.

The interim assessment revealed a clear correlation between the severity of hypertension and the presence of risk factors such as hyperglycemia, hypercholesterolemia, renal dysfunction, obesity, and a burdened family history. Most study participants (79.3 %) had hypercholesterolemia, and this indicator directly correlated with the severity of hypertension. A similar trend was observed for hyperglycemia (fasting glucose level over 7 mmol/L) – 12 % of the subjects, with the highest number of cases among patients with stage 3 hypertension. The percentage of patients with functional renal impairment (assessed by creatinine level) also increased with the severity of hypertension. The degree of these disorders also clearly correlated with the degree of hypertension. A family history of CV mortality was found in 24 % of patients with stage 1 hypertension (approximately one in four), while in patients with stage 3 hypertension – 31 % (i.e., one in three!); on average, in 28.7 % of the subjects. A similar trend was observed in the case of obesity (body mass index (BMI) ≥ 30 kg/m2) – in about one in three patients with stage 1 hypertension (28 %) and almost one in two (45 %) patients with stage 3 hypertension (on average, in 41.9 % of cases).

Thus, the higher the degree of hypertension, the more CV risk factors the patient had.

The comorbidities in the patients enrolled in the study included stable angina in 33.5 % of the subjects, diabetes mellitus (DM) in 20.1 %, left ventricular hypertrophy (LVH) in 77 % (assessed by ECG or EchoCG), atrial fibrillation (AF) in 6.2 %, heart failure (HF) in 28.3 %, and kidney disease in 8.3 % of patients. In all cases, there is a clear trend toward an increase in the number of concomitant diseases together with the stage of hypertension.

Thus, in all three trials of the TRIUMF series, the analysis of patient profiles shows a clear trend toward an increase in the risk for patients with more severe hypertension: in particular, but not exclusively, due to the formation and progression of comorbidities. This determines the earliest possible prescription of appropriate pharmacotherapy (it should be considered that at the time of enrollment in the study, all patients were receiving antihypertensive therapy, which, unfortunately, did not allow them to achieve the target levels of BP and, accordingly, did not stop the progression of hypertension). The data are summarized in *Table 1*.

All patients enrolled in the TRIUMF trial series were receiving combination antihypertensive therapy at the time of enrollment *(Table 2)*: more than half of the patients (53 %) were receiving a combination of individual drugs (2 or 3 pills), while 47 % were receiving a SPC of active ingredients.

Patients mostly received a combination of ACEi+diuretic (33 %), ACEi+CCB (28 %), angiotensin II receptor blocker (ARB)+diuretic (15 %) as baseline therapy; in the case of triple therapy, the most commonly used combinations were ACEi+CCB+diuretic (28 %) and BB+ACEi+diuretic (26 %). Data are presented in *Table 3*.

During the screening [17], a survey of investigators revealed that the main criteria for choosing a triple SPC were the lack of efficacy of previous antihypertensive therapy (86 %), high efficacy of SPC in long-term treatment (90 %), convenience of pill's administration (88 %), and the optimal composition of the components of the antihypertensive combination (ACE inhibitor, diuretic, and CCB).

In accordance with the terms of the TRIUMF trial series, the investigators independently decided on the dose of the original SPC of perindopril arginine/indapamide/amlodipine to be prescribed to patients in each specific clinical situation. One of the significant advantages of the drug is a wide range of doses (perindopril arginine/indapamide/amlodipine: 5/1.25/5; 5/1.25/10; 10/2.5/5; 10/2.5/10 mg, respectively), which allows for a personalized approach to therapy. In addition, we have already noted that in the treatment of chronic diseases, patient adherence becomes one of the most important criteria, and taking one pill a day is quite convenient and reduces the likelihood of missing a dose (as can happen when one needs to take several pills). The pharmacokinetic profile of the active substances of the original SPC of perindopril arginine/indapamide/amlodipine provides 24 hours BP control, which also contributes to patient adherence to therapy [9–10, 14–15, 17].

Table 1
Baseline characteristics of patients of the pooled analisys of three trials of the TRIUMF series

Criterion	Total population (n=5960)		Stage 1 hypertension (n=560; 9.4 %)		Stage 2 hypertension (n=2941; 49.5 %)		Stage 3 hypertension (n=2446; 41.1 %)	
	n/value	%	n/value	%	n/value	%	n/value	%
Male	2281	38.3	188	34	1144	39	943	39
Female	3677	61.7	372	66	1797	61	1501	61
Av. age, years Male	60.73		59.64		60.62		61.11	
Female	64.85		62.93		64.54		65.69	
Av. dur. of hypertension, years	11.65		9.63		10.82		13.11	
Av. SBP, mm Hg	171.92		149.73		164.08		186.58	
Av. DBP, mm Hg	98.73		89.22		95.35		105.07	
Stage 1 hypertension		9.4						
Stage 2 hypertension		49.5						
Stage 3 hypertension		41.1						
Risk factors								
Smoking		22		22		22		23
CV mortality in family history		28.71		24		29		31
Obesity BMI ≥ 30 kg/m^2		41.9		28		37		45
Laboratory examinations								
Cholesterol > 5.0 mmol/L	3754	79.3	322	75.4	1844	77.8	1577	82
Glucose 7.0 mmol/L and >	611	12	36	7.7	244	9.6	330	15.8
Creatinine, mkmol/L	n=2993/v.88.9							
below 115 mkmol/L men or 107 mkmol/L women	2524	84.3	240	90.9	1227	84.3	1046	82.9
155–133 mkmol/L men or 107–124 mkmol/L women	370	12.4	20	7.5	189	13	161	12.8
↑133 mkmol/L men or 124 mkmol/L women	99	3.3	4	1.5	40	2.7	55	4.4
Comorbidities								
DM	1195	20.1		14.8		18		23.8
Angina pectoris	1996	33.5		24		31.9		37.6
Myocardial infarction (MI)	635	10.7		7.7		11		10.7
Lesions of peripheral vessels	854	14.3		15		13		15.7
LVH	4591	77		70.7		77		78.7
AF	370	6.2		3.8		5.3		7.9
HF	1686	28.3		24.5		25.2		32.9
Stroke	604	10.1		8		9		11.8
Kidney disease	497	8.3		8		7.2		9.7

Table 2
Characteristics of baseline antihypertensive therapy (at the time of inclusion in the study)

Criterion	Total population (n=5960)		Stage 1 hypertension (n=560; 9.4 %)		Stage 2 hypertension (n=2941; 49.5 %)		Stage 3 hypertension (n=2446; 41.1 %)	
	n/value	%	n/value	%	n/value	%	n/value	%
Treatment								
SPC	2498	47						
Combination of individual tablets	2834	53						
Number of AH drugs 2 3	3159 1682	65 35	330 146		1716 756		1277 778	

Table 3
Distribution of patients based on the baseline antihypertensive therapy

Criterion	Total population		Stage 1 hypertension (n=560; 9.4 %)		Stage 2 hypertension (n=2941; 49.5 %)		Stage 3 hypertension (n=2446; 41.1 %)	
	n/value	%*	n/value	%	n/value	%	n/value	%
2 drugs								
ACEi + diuretic	1031	33	115	35	522	30	389	31
ACEi + CCB	891	28	101	31	475	28	311	24
ARB + diuretic	473	15	29	9	253	15	189	15
ARB + CCB	285	9	21	6	145	8	116	9
CCB + diuretic	48	2	7	2	23	1	18	1
BB + diuretic	53	2	6	2	24	1	23	2
ACEi + BB	378	12	36	11	185	11	155	12
Other	171	5	14	4	87	5	70	6
	* 3159 = 100 %							
3 drugs								
ACEi + CCB + diuretic	471	28	43	29	224	30	204	26
ARB + CCB + diuretic	198	12	13	9	76	10	109	14
BB + ACEi + diuretic	441	26	43	29	193	26	204	26
BB + ARB + diuretic	136	8	14	10	61	8	61	8
BB + CCB + diuretic	34	2	7	5	8	1	19	2
Other	402	24	26	18	194	26	181	23
	* 1682 = 100 %							

It should be noted that we have identified some trends in the choice of drug dose by the investigators. In particular, the most frequently prescribed dose was 10/2.5/5 mg (36.5 %), and the lowest dose was 5/1.25/5 mg (30.7 %). In our opinion, these patterns can be explained by the fact that the minimum dose is most often chosen by clinicians right after switching from another combination therapy, and the 10/2.5/5 mg dose contains increased doses of perindopril arginine and indapamide with the same dose of amlodipine, which allows to improve further antihypertensive efficacy with a lower risk of adverse effects.

Table 4

Distribution of patients based on the administration of different doses of the original SPC of perindopril arginine/indapamide/amlodipine*

Criterion	Total population (n=5960)		Stage 1 hypertension (n=560; 9.4 %)		Stage 2 hypertension (n=2941; 49.5 %)		Stage 3 hypertension (n=2446; 41.1 %)	
	n/value	%	n/value	%	n/value	%	n/value	%
Dosing of the original SPC of perindopril arginine/ indapamide/amlodipine								
5/1.25/5	1828	30.7	347	62%	1104	38%	367	15%
5/1.25/10	389	6.5	35	6 %	234	8 %	119	5 %
10/2.5/5	2184	36.6	129	23%	1151	39%	902	37%
10/2.5/10	1559	26.2	49	9 %	452	15%	1058	43%

* The difference between indicators is statistically significant compared to those for different doses of the original SPC of perindopril arginine, indapamide and amlodipine, respectively ($p<0.05$).

It is notable that cardiologists used the maximum dose of the drug almost twice as often as family practitioners, which led to more effective BP control (≤ 130/80 mm Hg) in a larger group of patients (69.7 % vs. 59.1 % with family practitioners – TRIUMF-3 data).

Data on the prescription of Triplixam are summarized in *Table 4* and *Appendix 1*.

One of the key criteria for choosing the dose of the original SPC of perindopril arginine/indapamide/amlodipine was the BP values at baseline – quite a logical pattern can be observed: the more pronounced the degree of hypertension, the higher the dose of the drug prescribed by physicians. At the same time, it is obvious that this was one of the main, but not the only, selection criteria, as the presence of comorbidities and baseline therapy played a significant role. It is noteworthy that higher doses of the original SPC of perindopril arginine/ indapamide/amlodipine were prescribed more frequently to patients who had been using a combination of three drugs before enrollment in the study *(see Appendix 1)*.

In our opinion, one of the most urgent problems in the management of hypertension is the widespread practice of delaying the prescription of a triple combination of antihypertensive drugs in the early stages of hypertension. The main reason is the fear of physicians about the «extra power» of this combination, which, in their opinion, can cause a significant decrease in BP below the patient's physiologically normal values [9–10, 17]. That is why, in clinical practice, the triple combination is often prescribed mainly to patients with stage 3 hypertension, when other combination therapy no longer allows achieving target BP values [9–10, 14–15, 17]. At the same time, at this stage, the patient already has comorbidities and a high risk of cardiovascular complications due to the late initiation of adequate therapy [11]. The consequences are, at minimum, the need for higher doses of the triple combination or the need to prescribe an additional, fourth drug.

In the analysis of the three trials of the TRIUMF series, we noted an important thing from a practical point of view: the administration of the original SPC of perindopril arginine/indapamide/amlodipine to patients with stage 1 hypertension and lower baseline BP values was accompanied by a decrease (normalization) of BP by fewer units than in the case of higher BP values (more severe hypertension). This trend can be clearly seen in *Figure 1*.

This is due to physiologically inherent mechanisms of BP counterregulation in the human body. Maintaining pressure in the aorta is the only mechanism that contributes to the body's survival. In fact, with the use of antihypertensive drugs, one of the pharmacological effects will be a decrease in this parameter, which will result in the activation of neurohumoral regulation (sympathoadrenal system) to compensate for the decrease in aortic pressure. That is why use of SPC for low-grade hypertension will not results in excessive BP reduction due to the inclusion of mechanisms of BP counterregulation. The existence of this mechanism is proved by studies in which the placement of a rigid stent in the baroreceptor zone of the carotid arteries was accompanied by the development of collaptoid states in patients [16].

In all patients with varying stages of hypertension, a gradual and steady decrease in BP was observed starting with the first control visit one (for inpatients) or two weeks after the therapy initiation. It is important to

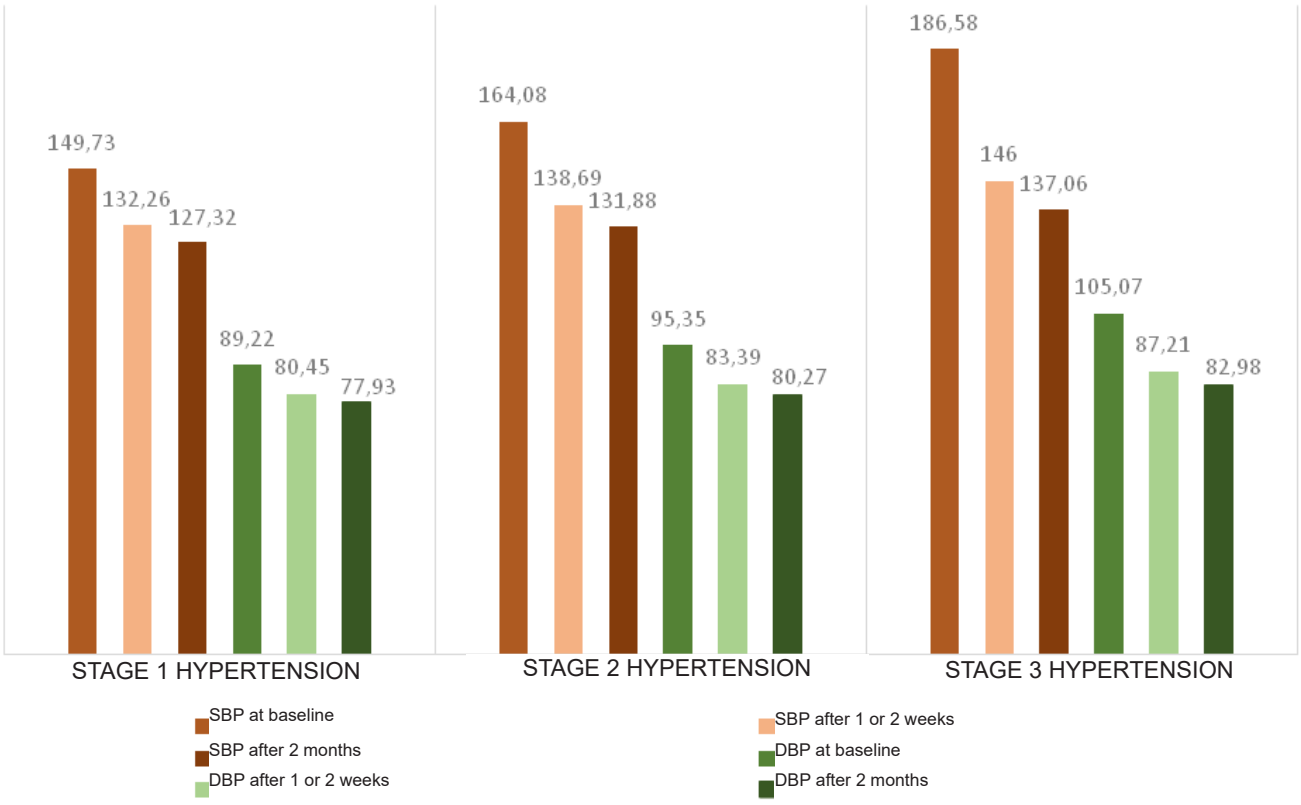

Figure 1. **Dynamics of SBP/DBP changes in patients with different stages of hypertension (n=5960, * difference between indicators is statistically significant compared to those before treatment with the original SPC of perindopril arginine/indapamide/amlodipine (p<0.001)).**

note that the decrease in BP during the first week was not rapid due to the gradual development of the pharmacological effect of the drug components, which has a very positive effect on the tolerability of therapy by patients, as they do not experience sharp fluctuations in BP and associated changes in their health. It should also be noted that the intensity of the pressure reduction depended solely on the baseline BP (it was more moderate in stage 1 hypertension and increased with severity of the disease) and did not depend on the baseline therapy, as described in more detail in previous publications.

The antihypertensive effect increased steadily throughout the observation period. BP decreased by an average of 38.67 mm Hg (SBP) and 17.96 mm Hg (DBP), which was statistically significant in the general patient population. Most modern clinical guidelines and recommendations for the treatment of hypertension are known to be unanimous regarding the target BP, which should be below 140/90 mm Hg. However, good tolerance to the therapy does not preclude the possibility of maintaining BP at 130/80 mm Hg or lower, as this is associated with a lower risk of developing CV complications.

After 2 months of therapy, the vast majority of treated patients (84 %) achieved BP values below or equal to 140/90 mm Hg. However, there were certain differences depending on the administered dose of the original SPC of perindopril arginine/indapamide/amlodipine *(Figure 2)*.

We should also comment on the correlation between the dose of the original SPC of perindopril arginine/indapamide/amlodipine and the pattern of BP reduction in patients with hypertension of varying severity *(Table 5)*.

The first pattern that draws attention is the prescription of higher doses of SPC to patients with higher BP values, but as we noted above, this was not the only criterion for dose selection (important factors influencing the investigator's choice of the dose of the original triple SPC of perindopril arginine/indapamide/amlodipine were the presence of comorbidities and previous antihypertensive therapy). In addition, when analyzing the dynamic pattern of BP reduction, there was actually a comparable (percentage) decrease in BP:

- at the first visit (week 1 or 2): the use of D1 led to a decrease in SBP by 16.65 %; D2 – by 15.65 %; D3 – by 17.6 %; D4 – by 20.74 %.

Table 5

BP reduction pattern in patients with hypertension of varying severity depending on the dose of the original SPC of perindopril arginine/indapamide/amlodipine

Criterion	Total population		D1 (n=1828; 30.7 %)		D2 (n=389; 6.5 %)		D3 (n=2184; 36.6 %)		D4 (n=1559; 26.2 %)	
	n	value	n	value	n	value	n	value	n	value
Entire population										
Average SBP										
Initial	5182	172.25	1557	164.13	342	168.28	1862	172.69	1281	182.29
in 1 week or 2 weeks	5182	141.15	1557	136.81	342	141.93	1862	142.27	1281	144.48
in 2 months	5117	133.58	1553	130.2	341	134.52	1858	134.4	1280	136.23
Mean DBP										
Initial	5182	98.85	1557	95.67	342	97.12	1862	99	1281	102.75
in 1 week or 2 weeks	5182	84.71	1557	82.62	342	84.50	1862	85.36	1281	86.30
in 2 months	5117	80.89	1553	79.18	341	80.94	1858	81.24	1280	82.48

D1 refers to the dose of the active substances perindopril arginine/indapamide/amlodipine, respectively (5/1.25/5 mg); D2 (5/1.25/10 mg); D3 (10/2.5/5 mg); D4 (10/2.5/10 mg).

- the same values in 2 months: D1 – by 20.67 %; D2 – by 20.06 %; D3 – by 22.17 %; D4 – by 25.27 %.
- with DBP, the percentage of decrease was as follows: D1 – 13.64 %; D2 – 12.99 %; D3 – 13.8 %; D4 – 16.01 % during the first week of therapy.
- decrease in DBP after 2 months from the start of therapy was as follows: D1 – 17.24 %; D2 – 16.66 %; D3 – 17.94 %; D4 – 19.73 %.

Thus, the BP reduction was gradual, but stable and proportional to the baseline values. The antihypertensive effect of the SPC is known to begin from the first days of therapy, but its development (increase) occurs gradually: the main part of the antihypertensive effect is developed during the first week, while the final stabilization and, in most cases, the achievement of target BP values occurs by the second month of therapy. A proportional decrease in SBP and DBP in patients (the percentage is comparable) should also be noted, which indicates an effective correction of all components of the pathogenesis.

Tolerability of therapy was assessed in each trial of the TRIUMF series [9–10, 17]. Thus, about 1.0 % of patients in the TRIUMF-1 trial discontinued the study SPC of perindopril arginine/indapamide/amlodipine due to the development of adverse effects: hypotension (6 (0.5 %)), lower leg edema (4 (0.3 %)), dry cough (2 (0.16 %)). During the study period, 66 (1.86 %) patients

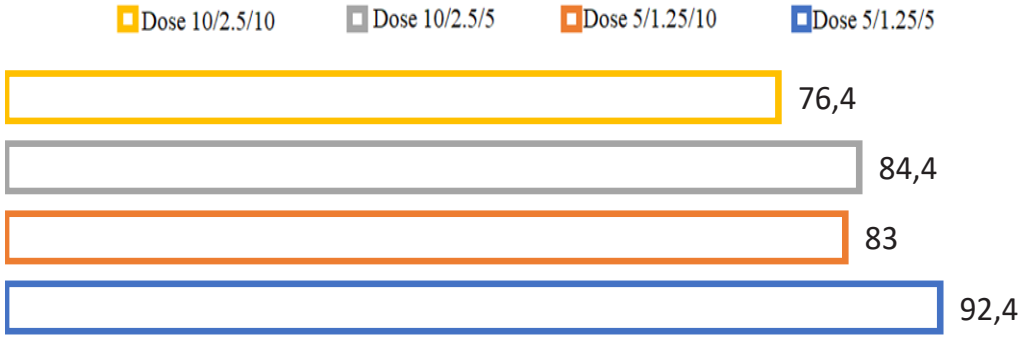

Figure 2. **Achieving a BP level of 140/90 mm Hg or lower after 2 months of therapy, depending on the dose of the original SPC of perindopril arginine/indapamide/amlodipine.**

in TRIUMF-2 trial had adverse reactions. Peripheral edema (n=19; 0.5 %) and dry cough (n=15; 0.4 %) were most common, but in less than 1 % of patients. In TRIUMF-3 trial, only 26 (0.63 %) patients had adverse reactions. The most commonly observed symptoms were cough (n=7), lower extremity edema (n=8), and hypotension (n=9). SPC was well tolerated – adverse events were observed rarely, which can be explained by the previous administration of two (65 %) or three (35 %) antihypertensive drugs comprising the SPC to the patients.

Adherence to treatment was determined in TRIUMF-2 and TRIUMF-3 trials before and after 2 months of therapy with the original triple SPC of perindopril arginine/indapamide/amlodipine. The use of 1 pill instead of three with each individual active ingredient simplifies the drug regimen, makes it more convenient for the patient, and therefore helps to increase adherence and, as a result, the effectiveness of treatment, including in the long term.

It should be noted that the initial adherence to treatment for the majority of participants in TRIUMF-2 and TRIUMF-3 was low (51.4 % and 63.0 %, respectively), 38.2 % and 27.5 % had moderate adherence, and only 10.3 % and 9.5 % had high adherence. After 2 months of therapy, the situation changed significantly: a significant improvement in the adherence to treatment was observed in most patients (75 % in TRIUMF-2 and 70 % in TRIUMF-3). The number of patients with low adherence decreased to 2.7 % and 7.7 %, and with high adherence increased to 54.1 % and 48.3 %, respectively.

Separately, we analyzed the use of BB in the treatment of the study cohort of patients with hypertension. Some patients were treated with BB prior to enrollment in the study (n=1925): BB was part of a 2-drug combination therapy (31 %), a 3-drug combination therapy (51 %), a 4-drug combination therapy (12 %), or was taken as monotherapy (6 %).

After patients were enrolled in the study and switched to the original triple SPC of perindopril arginine/indapamide/amlodipine, an additional prescription of BB was made at the first visit in 122 patients (2.04 % of the total population). In total, 2012 patients (33.7 %) received complex therapy with the original triple SPC of perindopril arginine/indapamide/amlodipine and BB.) Description of the study group is provided in *Annex 2*.

It is noteworthy that the inclusion of BB in the treatment led to slight differences in the distribution of patients receiving different doses of the SPC: in particular, the percentage of patients receiving the maximum dose of the original triple SPC of perindopril arginine/indapamide/amlodipine in combination with BB increased (the number of patients receiving other SPC dosing options slightly decreased). This pattern is quite reasonable, since the vast majority of patients (56 %) who received the original triple SPC of perindopril arginine/indapamide/amlodipine and BB had stage 3 hypertension and comorbidities that acquired additional use of BB, such as angina pectoris (33.5 %) and HF (28.3 % of subjects) (the percentage is higher than in less severe hypertension).

It is important to note that 83.89 % of patients treated with the combination of the original triple SPC of perindopril arginine/indapamide/amlodipine + BB achieved the target BP (140/90 mm Hg or lower) after 2 months of therapy; another 9.36 % achieved BP of 130/80 mm Hg or lower *(Figure 3)*.

The analysis of dose changes of the original triple SPC of perindopril arginine/indapamide/amlodipine when used concomitantly with BB is also an important indicator, as these data allow us to assess not only the efficacy of the combination therapy but also its tolerability. In the vast majority of patients, no dose adjustment was performed (87 %), and the percentage of patients who received a reduced dose of the SPC was even higher (7 %) than the number of patients who received an increased dose (5 %). These data indicate the effectiveness of the combined use of drugs, as well as significant prospects for further study of the efficacy and tolerability of this combination, and assessment of the feasibility of their combined use, especially in terms of reducing cardiovascular risks in the long term.

CONCLUSIONS

1. In the TRIUMF trials (polled analisys includes 5960 patients), according to a survey of investigators, the main criterion for choosing the original single pill combination (SPC) of perindopril arginine/indapamide/amlodipine should be considered insufficient efficacy of previous antihypertensive therapy (86 %), optimal composition of the components of the antihypertensive combination (ACE inhibitor, diuretic, CCB), high efficacy of the combination in long-term treatment (90 %), and convenience of pill's administration (88 %).

2. Initially investigators most often prescribed a SPC with the lowest dose of amlodipine – 5 mg (67.3 % of patients), given the possible development of hypotension and the occurrence of adverse effects (lower extremity edema). However, during the study, SPC was

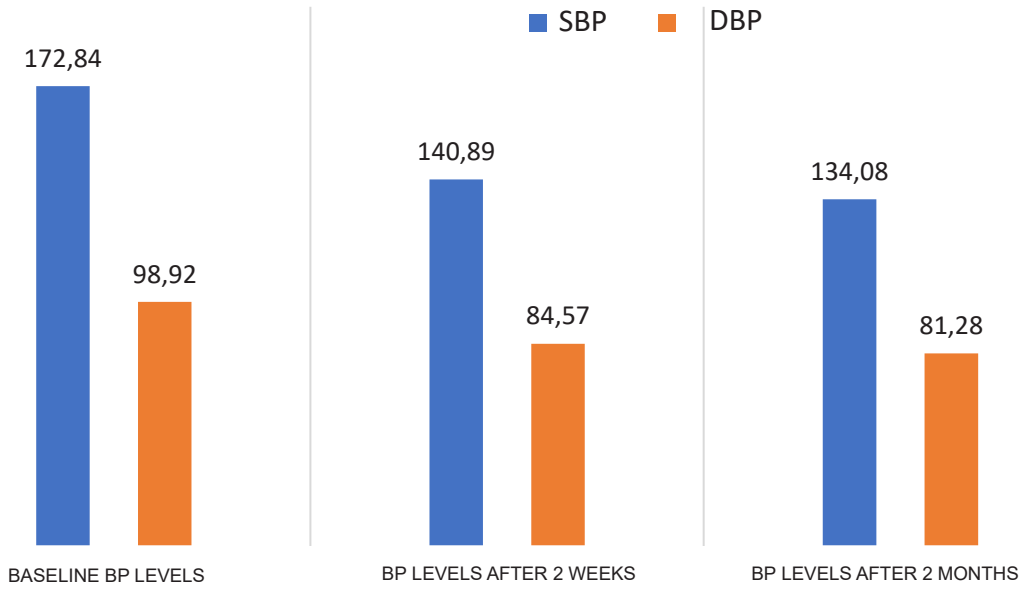

Figure 3. **Dynamic pattern of BP reduction in response to the combination of the original triple SPC of perindopril arginine/indapamide/amlodipine+BB (n=2012, p<0.001).**

well tolerated – adverse events were observed in 0.63 % (Tr. 1), 1 % (Tr. 3) and 1.86 % (Tr. 2) of cases, which can be explained by the previous administration of two (65 %) or three (35 %) antihypertensive drugs comprising the SPC to the patients.

3. One of the important criteria for choosing the dose of a triple SPC is the baseline BP values. The higher the degree of hypertension, the higher the dose prescribed by physicians. The minimum dose of SPC of perindopril arginine/indapamide/amlodipine (5/1.25/5 mg) was prescribed for stage 1 hypertension in 62 %, stage 2 hypertension in 38 %, and stage 3 hypertension in 15 % of patients; the maximum dose (10/2.5/10 mg) was prescribed for stage 1 hypertension in 9 %, stage 2 hypertension in 15 %, and stage 3 hypertension in 43 % of patients enrolled in the study ($p<0.05$).

4. In all patients with varying degrees of hypertension severity, a gradual significant decrease in BP was observed (1–2 weeks up to 2 month). The intensity of BP reduction depended on the baseline BP values.

Cardiologists used the maximum dose of the drug almost twice as often as family practitioners, which led to more effective BP control (≤ 130/80 mm Hg) in a larger group of patients (69.7 % vs. 59.1 % with family practitioners – TRIUMF-3 data).

5. Beta-blockers (BB, n=2012 (33.7 %)) were prescribed due to the presence of a comorbidity (coronary heart disease, angina pectoris – 33.5 %) rather than due to lowered BP. The combination of perindopril arginine/indapamide/amlodipine with BB was well tolerated; after 2 months, 83.9 % of patients achieved BP of 140/90 mm Hg or lower, and after 2 months, another 9.36 % achieved BP of 130/80 mm Hg or lower.

6. Regular medical supervision (cardiologists, family practitioners), high antihypertensive efficacy, convenience of administration (one pill instead of three) and good tolerability of the original single pill combination of perindopril arginine/indapamide/amlodipine led to a significant improvement in adherence to treatment (TRIUMF-2, TRIUMF-3) in most patients (75 and 70 %). Based on the results of a pooled analysis of 5960 patients with a history of taking combination therapy (2 drugs – 65 %, 3 drugs – 35 %), this allowed to achieve target BP levels (140/90 and lower) in 84 % of cases after 2 months of therapy with SPC of perindopril arginine/indapamide/amlodipine.

Study Limitations

The study did not prospectively evaluate the effectiveness of previous antihypertensive therapy with a combination of individual drugs. This data was obtained through targeted history taking. This is especially true for the evaluation of patients who were treated with simultaneous combination of certain drugs from the groups of ACE inhibitors, diuretics, CCBs.

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Зведений аналіз серії досліджень ТРІУМФ: ефективність використання потрійної фіксованої комбінації антигіпертензивних препаратів у практиці лікарів різних ланок в Україні

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Мета дослідження – порівняти дані, отримані у дослідженнях серії ТРІУМФ (антигіперТензивна теРапІя в Україні – оптиМізація артеріального тиску у Фокусі), зокрема ТРІУМФ-1, ТРІУМФ-2, ТРІУМФ-3, для визначення можливих закономірностей та вагомих факторів, що впливають на контроль артеріального тиску (АТ) в пацієнтів, які приймали 2 і більше антигіпертензивних препаратів, та перейшли на використання оригінальної потрійної фіксованої комбінації (ФК) периндоприл + індапамід + амлодипін.

Матеріали і методи. Для проведення зведеного аналізу за даними трьох досліджень серії ТРІУМФ було відібрано дані 5960 пацієнтів. Всі ці дослідження були мультицентровими проспективними та проводились у різні терміни на території України із залученням лікарів загальної практики (ТР-1), спеціалістів-кардіологів (ТР-2) і сімейних лікарів (ТР-3). Відповідно до критеріїв у дослідження могли бути залучені пацієнти з артеріальною гіпертензією (АГ), віком понад 18 років, які за даними анамнезу попередньо приймали 2 або 3 антигіпертензивні препарати не менше ніж 1 місяць, але АТ у них залишався вище ніж 140/90 мм рт. ст. Препаратом вибору для подальшої терапії стала ФК периндоприлу аргініну, амлодипіну та індапаміду – «Трипліксам» («Серв'є», Франція). Тривалість спостереження кожного пацієнта становила 3 місяці. Пацієнти відвідували лікарів через 1–2 тижні, 2 та 3 місяці від початку дослідження та відповідної корекції терапії. До (спостереження?) і через 2 місяці оцінювали показник прихильності до лікування. Окремо проаналізовано використання бета-блокаторів (ББ) в терапії досліджуваної когорти пацієнтів з АГ. Остаточний аналіз містив порівняння даних, отриманих у дослідженнях серії ТРІУМФ.

Результати та обговорення. Застосування ФК периндоприлу аргініну, індапаміду та амлодипіну (П/І/А) дало змогу досягнути цільових рівнів АТ (140/90 і менше) через 2 місяці терапії у 84 % пацієнтів, які попередньо (за даними анамнезу) приймали комбіновану терапію (2 препарати – 65 %, 3 препарати – 35 %). Одним із важливих критеріїв вибору дози потрійної ФК слід вважати вихідні цифри АТ. Чим вищий ступінь АГ, тим вища доза, призначена лікарями. Мінімальна доза ФК П/І/А (5/1,25/5 мг) призначалась при АГ I ступеня – у 62 %, АГ II – у 38 %, АГ III – у 15 % пацієнтів; максимальна (10/2,5/10 мг) – при АГ I – у 9 %, АГ II – у 15 %, АГ III – у 43 % залучених у дослідження пацієнтів ($p<0,05$). Терапія потрійною ФК П/І/А характеризувалася доброю переносимістю: побічні дії спостерігались у 0,63 % (ТР-1), 1 % (ТР-3) та 1,86 % (ТР-2) випадків, що значною мірою зумовлено попереднім застосуванням у обстежених пацієнтів двох (65 %) або трьох (35 %) антигіпертензивних засобів, що входять у ФК. Призначення ББ (n=2012) обумовлювалось не стільки зниженням АТ, скільки наявністю супутньої патології (ішемічна хвороба серця, стенокардія – 33,5 %, серцева недостатність – 28,3 %). Комбінація периндоприл / індапамід / амлодипін з ББ добре переносилась і через 2 місяці прийому у 83,9 % пацієнтів було досягнуто АТ ≤ 140/90 мм рт. ст., а у 9,36 % ≤ 130/80 мм рт. ст. Відзначено суттєве поліпшення прихильності до лікування (ТР-2, ТР-3) у більшості пацієнтів (відповідно 75 та 70 %), що зумовлено високою антигіпертензивною ефективністю, зручністю прийому (одна таблетка замість трьох) та доброю переносимістю оригінальної ФК.

Висновки. Регулярний лікарський нагляд (кардіологи, сімейні лікарі, лікарі загальної практики), висока антигіпертензивна ефективність ФК (цільових рівнів АТ через 2 місяці терапії досягли 84 % пацієнтів), зручність прийому (одна таблетка замість трьох), висока прихильність до лікування, підтверджена в дослідженнях ТР-2, ТР-3 у більшості пацієнтів та добра переносимість оригінальної фіксованої комбінації периндоприлу, індапаміду та амлодипіну обумовили суттєве поліпшення ефективності лікування пацієнтів з АГ.

Ключові слова: артеріальна гіпертензія, антигіпертензивна терапія, фіксована комбінація, прихильність до лікування.

Appendix 1

DOSING of the original triple SPC of perindopril arginine/indapamide/amlodipine.

1.1 Patient characteristics

Criterion	Total population n=5960		D1 (n=1828; 30.7 %)		D2 (n=389; 6.5 %)		D3 (n=2184; 36.6 %)		D4 (n=1559; 26.2 %)	
	n/value	%	n/value	%	n/value	%	n/value	%	n/value	%
Male	2281	38.3	668	36.5	139	35.8	842	38.6	632	40.5
Female	3677	61.7	1160	63.5	249	64.2	1341	61.4	927	59.5
Av. age, years Male	60.7		59.26		60.05		61.44		61.47	
Female	64.8		63.08		64.93		65.24		66.45	
Av. dur. of hyperten, years	11.65		9.42		11.29		11.81		14.07	
Av. SBP, mm Hg	171.92		163.9		168.42		172.24		181.71	
Av. DBP, mm Hg	98.73		95.6		97.47		98.73		102.71	
Stage 1 hypertension		9.4		19		9		6		3
Stage 2 hypertension		49.5		61		60		53		29
Stage 3 hypertension		41.1		20		31		41		68
Risk factors										
Smoking		21.7		21.8		25.4		22.4		19.7
CV mortality in family history		28.7		26.4		32.9		29		30
Obesity BMI ≥ 30 kg/m^2		41.9		36.4		37.5		44.8		45.5
Laboratory tests										
Total cholesterol, mmol/l	N= 4731 5.97									
Cholesterol > 5.0 mmol/l	3754	79.3		74.3		84.9		81.6		80.6
Glucose	N=5107 5.58									
7.0 mmol/L and >	611	12.0		7.6		10.1		11.3		19.2
Creatinine, mkmol/L	N=2993 88.9									
< 115 mkmol/L men or 107 mkmol/L women	2524	84.3		87.1		83.2		84.7		81.3
155–133 mkmol/L men or 107–124 mkmol/L women	370	12.4		9.7		10.1		12.5		15.3
>133 mkmol/L men or 124 mkmol/L women	99	3.3		3.2		6.7		2.8		3.4
Comorbidities										
DM	1195	20.1	259	14.2	62	15.9	441	20.2	433	27.8
Angina pectoris	1996	33.5	488	26.7	104	26.7	769	35.2	635	40.7
MI	635	10.7	164	9.0	33	8.5	249	11.4	189	12.1
Lesions of peripheral vessels	854	14.3	233	12.7	48	12.3	314	14.4	259	16.6
LVH	4591	77.0	1265	69.2	295	75.8	1746	79.9	1285	82.4
AF	370	6.2	106	5.8	12	3.1	135	6.2	117	7.5
HF	1686	28.3	383	21.0	110	28.3	659	30.2	534	34.3
Stroke	604	10.1	148	8.1	35	9.0	208	9.5	213	13.7
Kidney disease	497	8.3	144	7.9	37	9.5	172	7.9	144	9.2
Treatment										
SPC	2498	47	1828		389		2184		1558	
Combination of individual pills	2834	53	111		14		130		174	
Number of AH drugs 2	3159	65	1103	72.9	212	64.6	1234	65.8	780	60.2
3	1682	35	411	27.1	116	35.4	640	34.2	515	39.8

1.2. Analysis of achievement of BP control after 2 months

Parameter	D1 (n=1793)		D2 (n=383)		D3 (n=2156)		D4 (n=1532)	
	n	%	n	%	n	%	n	%
Less than or equal to 140 and 90	1657	92.4	318	83.0	1820	84.4	1171	76.4
Less than 130/80	297	16.6	36	9.4	178	8.3	109	7.1

1.3. BP dynamics

Criterion	Total population		D1 (n=1828; 30.7%)		D2 (n=389; 6.5 %)		D3 (n=2184; 36.6 %)		D4 (n=1559; 26.2 %)	
	n	value	n	value	n	value	n	value	n	value
Entire population										
Average SBP, mm Hg										
Initial	5182	172.25	1557	164.13	342	168.28	1862	172.69	1281	182.29
Rep. after 1 week or 2 weeks	5182	141.15	1557	136.81	342	141.93	1862	142.27	1281	144.48
Rep. after 2 months	5117	133.58	1553	130.2	341	134.52	1858	134.4	1280	136.23
Mean DBP, mm Hg										
Initial	5182	98.85	1557	95.67	342	97.12	1862	99	1281	102.75
Rep. after 1 week or 2 weeks	5182	84.71	1557	82.62	342	84.50	1862	85.36	1281	86.30
Rep. after 2 months	5117	80.89	1553	79.18	341	80.94	1858	81.24	1280	82.48
In patient (1 week)										
Average SBP, mm Hg										
Initial	1799	173.90	552	165.59	103	169.47	648	173.84	496	184.14
Rep. after 1 week	1799	145.54	552	139.69	103	146.23	648	147.21	496	149.71
Rep. after 2 months	1755	132.61	526	126.42	97	128.09	624	130.88	474	131.11
Mean DBP, mm Hg										
Initial	1799	100	552	96.78	103	97.72	648	99.94	496	104.31
Rep. after 1 week	1799	87.1	552	84.28	103	86.34	648	87.74	496	89.40
Rep. after 2 months	1755	80.9	526	77.9	97	79.36	624	80.37	474	80.55

Appendix 2

Characteristics of patients treated with a combination of the original triple SPC of perindopril arginine/indapamide/amlodipine + BB

Criterion	Total population (n=5960)		On BB (n=1925)		BB added at Visit 1 (n=122)	
	n/value	%	n/value	%	n/value	%
Male	2281	38.3	778	40.4	46	38
Female	3677	61.7	1146	59.6	76	62
Av. age, years Male	60.73		61.4		60.48	
Female	64.85		65.9		62.62	
Av. dur. of hyperten., years	11.65		12.19		11.58	
Av. SBP, mm Hg	171.92		172.66		180.18	
Av. DBP, mm Hg	98.73		98.87		102.02	
Stage 1 hypertension		9.4		9		3
Stage 2 hypertension		49.5		46		41
Stage 3 hypertension		41.1		45		56
Smoking		22		22		18
CV mortality in family history		28.71		32		25
Obesity BMI ≥ 30 kg/m^2		41.9		35		48.98
Total cholesterol, mmol/L	N=4731/5.97		1679/5.91			99/6.0
Cholesterol > 5.0	3754	79.3	1061	63.2	78	78
Glucose, mmol/L	N=5107/5.58		5.64		108/5.93	
7.0 mmol/L and >	611	12		13.4		19.6
Creatinine, mkmol/L	N=2993/88.9		89.3			91.8
below 115 mkmol/L men or 107 mkmol/L women	2524	84.3		84.9		80.56
155–133 mkmol/L men or 107–124 mkmol/L women	370	12.4		11.5		19.44
>133 mkmol/L men or 124 mkmol/L women	99	3.3		3.6		0
DM	1195	20.1	444	23		29
Angina pectoris	1996	33.5	812	42		30
MI	635	10.7	329	17		7
Lesions of peripheral vessels	854	14.3	304	16		11
LVH	4591	77	1500	78		79
AF	370	6.2	160	8		5
HF	1686	28.3	658	34		24
Stroke	604	10.1	216	11		11
Kidney disease	497	8.3	176	9		9
SPC	2498	47				
Combination of individual tablets	2834	53				
Number of AH drugs 2	3159	65				
3	1682	35				
Dose of Triplixam				BB + Triplixam		
5/1.25/5	1828	30.7	598		29	
5/1.25/10	389	6.5	128		6	
10/2.5/5	2184	36.6	703		34	
10/2.5/10	1559	26.2	618		30	