

## NOVEL EXPERIENCE WITH COMBINED FIX-DOSE THERAPY FOR HYPERTENSION

Ted Trajceski

Clinical Hospital Tetovo, Republic of North Macedonia

### Abstract

In spite of the general improvement in treatment strategy and novel medications for hypertension, still there are many patients with unsatisfactory results. In this study we retrospectively analyzed the local registry for 280 hypertension patients, referred during 18 months. Aims: To access the efficacy and safety of combined fix-dose therapy approach. Patients were grouped according to the number of antihypertensive medications and mono or fix-combined therapy and followed for 1 month in respect of obtaining target blood pressure control. Patients were informed about taking proper measurements and in respect of drug side effects. Clinical data on previous medical history findings were obtained. Statistical analysis was performed using SPSS 23.0 software package. Parameters were expressed as mean  $\pm$  SD and percentages for nominal values. Comparative analysis was performed using  $X^2$  test. Statistical significance was set at  $p < 0.05$ . Results: The mean age of study participants was over 60 years and there were 47 percentage of men. Obesity was present in almost 20% and quarter were active smokers. Most of the patients were in stage 1 (40%), 37% were in stage 3. The most of the patients and nearly half of all, were treated with fix-dose combined therapy, exporting 48%. Dual therapy with two separate pills was applied in 34% and with only one medicament were treated 16% of patients. The triple therapy was given to only 2% of patients. Patients treated with fix-dose combined therapy were compared with all other patients treated with mono, dual or triple therapy. The two groups of patients did not differ in respect of presence of Diabetes ( $p=0.676$ ). Those treated with fix combinations were significantly younger ( $p=0.045$ ), less male (0.001), more burdened with obesity ( $p=0.028$ ) and more frequently smokers ( $p=0.0001$ ). After one month in 95% of patients the blood pressure reached the recommended targets. In 5% the follow up was not completed. Considering drug side effects, three patients treated with mono ACE therapy complained of dry cough and the treatment was replaced with a propriate dose medicament. Conclusion: Combined fox-dose therapy is shown to be of high efficacy and safety in patients with poor control of hypertension, especially in patients with low therapy adherence and at higher cardiovascular risk.

**Key words:** hypertension, combined fix-dose treatment, mono therapy, blood pressure control, compliance

### Introduction

In spite of the general improvement in treatment strategy and novel medications for hypertension, still there are many patients with unsatisfactory results. This rate is highly heterogeneous between countries, but overall, no more than 15% to 20% of the world hypertensive population has been shown to achieve blood pressure control when the target blood pressure is set at  $<140/90$  mm Hg [1,2]. Patients with uncontrolled hypertension are burdened by a higher risk of cardiovascular events and death [3], and hypertension remains the main cause of death for the world population [4] thereby representing a fundamental problem for public health.

Many factors contribute to the difficulty of HTA management. The therapeutic pathway consists from the factors influenced by doctors, patients, community and social surroundings. Adoption of current guidelines and inertia to modify the therapy vary among doctors. Insufficient implementation of National healthcare policies of prevention also worsen the treatment results when patients refer to cardiologists. Also, patients non-adherence to treatment schedule, nutritional habits, cultural differences, physical inactivity and sedentary life, significantly contribute to less control of blood pressure. The is significant consideration weather the way of medications intake can influence the outcome of blood pressure control. It is a common fact that modern blood pressure therapy strongly relies on long duration medications or expressing their effete longer than 24 hours, rather than short acting agents. By giving these medications the common wisdom suggests that the expression would be similar. Newer the less we are seen on the market combinations of medications

consisting of well-known groups and combinations of therapeutic strategies. It is a challenge to see whether the outcome would differ although the molecules and the doses are the same but separately administered.

The guidelines for hypertension treatment from the seventies and eighties recommended to fully exploit the blood pressure-lowering potential of monotherapy, by progressively increasing the dose of the initially prescribed drug until no further incremental blood pressure response was obtained [5,6]. The problem that emerged from the progressive increase in the drug dose was a substantial increase in the drug-related side effects [7]. As commonly used drug classes, such as diuretics,  $\beta$ -blockers, and calcium channel blockers, were also the most related to such complications. Finally, side effects were found to be the most important cause of treatment discontinuation with a further amplification of the problem [8], inducing increased cardiovascular risk and deaths. These facts led to new guidelines leaving this treatment strategy as fully inapplicable even for small groups of patients [9]. In the last two decades the guidelines recommended a step-care treatment. It covered the complexity of blood pressure regulation coming from the variety and the interplay among many pathophysiological factors inducing hypertension [10,11]. Although many patients reached the targets for blood pressure and side effects were reduced, approximately one third of patients become non-adherent to the novel treatment strategy due to the daily multiple pill use [12]. In 2003 the American [13] and four years later the European Society of Cardiology/European Society of Hypertension guidelines [14,15] recommended initial use of 2 antihypertensive drugs in selected hypertensive groups of patients. This strategy was to be implemented when the baseline blood pressure was over 160/100 mmHg or at least 20 mmHg above the systolic or 10mmHg above diastolic target. Patients with higher high or very high cardiovascular risk, with a history of cardiovascular or renal event were also recommended for this therapeutic approach. In this study we analyzed retrospectively the local registry for hypertension patients in order to see the results of implementation of combined fix-dose therapy approach.

### **Material and methods**

We conducted a retrospective analysis on registry data of 280 patients referred for blood pressure control at a single cardiology unit during 18 months. Patients were referred from general practitioners. The strict target blood pressure values for different patient groups in respect of comorbidities and age were driven by current guidelines [14]. Inclusion criteria was age above 18 years. Pregnant women and patients suffering from malignancies with life expectation less than a year were excluded. Patients were grouped according to the number of antihypertensive medications and mono or fix-combined therapy and followed for 1 month in respect of obtaining target blood pressure control. Measurement of blood pressure was obtained two times a day at home and notified in a diary. Patients were informed about taking proper measurements. In respect of drug side effects, patients were informed to provide accurate data. Clinical data on previous medical history findings were obtained (Cardiovascular comorbidities and events (past Myocardial Infarction, past Percutaneous Interventions, Coronary Artery by-pass grafting, Peripheral Vascular Disease, Percutaneous Peripheral Intervention, Peripheral by-pass, Ischemic stroke, Hemorrhagic stroke, significant Carotid Artery Disease, implantation of PCI or surgical intervention – enterectomy, history of need of oral anticoagulant treatment, risk factors for coronary artery disease: hyperlipidemia, diabetes, smoking, obesity, family history, laboratory data on kidney function, presence of diabetes, family history for hypertension and CAD). At baseline ECG was performed and patients with notified LVH signs were investigated further with echocardiography. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) 23.0 software package (Version 23, SPSS Inc., Chicago, IL, USA). Parameters were expressed as mean  $\pm$  SD and percentages for nominal values. Comparative analysis was performed using  $X^2$  test. Statistical significance was set at  $p < 0.05$ .

### **Results**

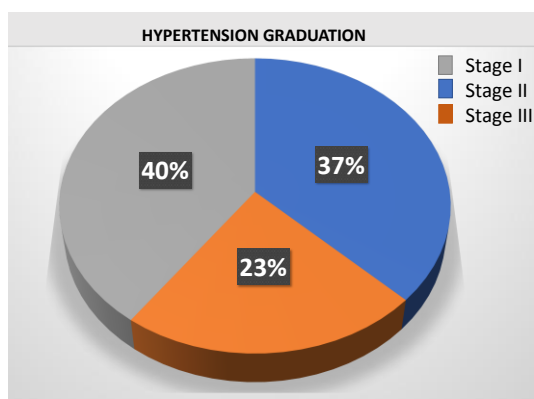
The patients characteristics are shown in Table 1. The mean age of study participants was over 60 years and there were 47 percentage of men. Obesity was present in almost 20% and quarter were active smokers. Hyperlipidemia was notified in the vast majority of patients (73%). Many patients (22%) suffered from Myocardial infarction and one third underwent Percutaneous Coronary

Intervention. Also, more than 20% of patients were genetically burdened for coronary disease. Diabetes was present in one quarter of patients.

Variable N=280	mean±SD No (%)
Age (years)	63.43 ± 14.45
Men	131 (47%)
Obesity	53 (19%)
Active smokers	67 (24%)
Hyperlipidemia	204 (73%)
History of	
Myocardial Infarction	62 (22%)
Heart Failure	20 (7%)
Stroke	8 (3%)
Peripheral Vascular Disease	19 (7%)
Chronic Kidney Disease	19 (7%)
Percutaneous Coronary Intervention	87 (31%)
Valvular Disease	3 (1%)
Family History of Coronary Heart Disease	68 (24%)
Diabetes	70 (25%)

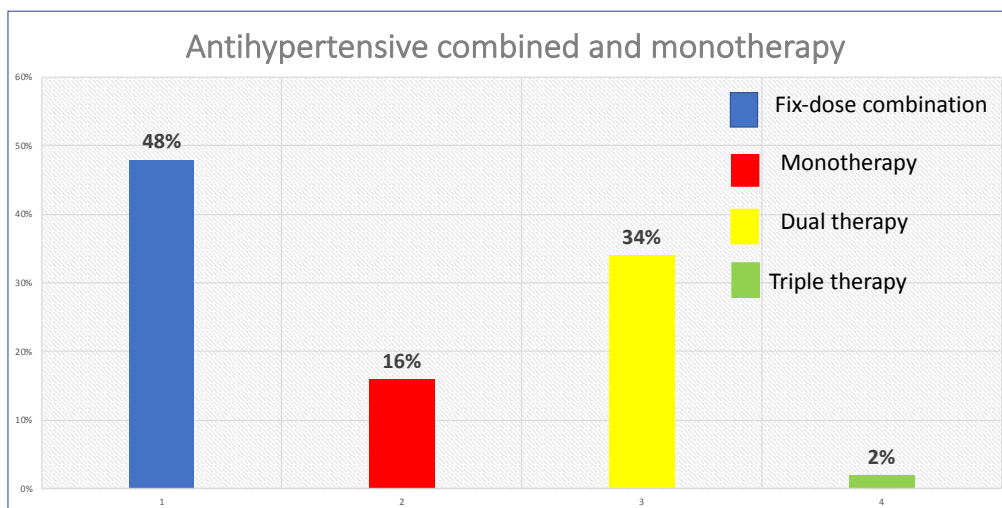
**Table 1.** Patient characteristics

At baseline, patients were stratified by hypertension graduation, as shown on Graphic 1. Most of the patients were in stage 1 (40%), a little bit smaller percentage (37%) was fulfilled by patients in stage 3 and the smallest number of patients entered the group of stage 3.



**Graphic 1.** Patients stratification by hypertension grade

Considering the antihypertensive therapy, the distribution of patients is presented in Graphic 2. The most of the patients and nearly half of all, were treated with fix-dose combined therapy, exporting 48%. Dual therapy with two separate pills was applied in 34%, with only one medicament were treated 16% of patients. The triple therapy was given to only small number of patients exporting 2% of all participants.



**Graphic 2.** Distribution of patients considering mono and combined antihypertensive therapy

The types of fix-dose combinations of antihypertensive treatments is shown in Table 2. Most of the patients (36%) were treated with the combination of Angiotensin Converting Enzyme inhibitor, Calcium blocker and Diuretic. Angiotensin Converting Enzyme inhibitor in dual combination with Calcium blocker was more often applied than when combined with diuretic (6%; 3.7%), respectively. The less frequently used combination was the one among Angiotensin Receptor Blocker with diuretic (0.7%)

Combined fix-dose therapy	
ACE inhibitor/Calcium blocker/Diuretic	100 (36%)
ACE inhibitor/Calcium blocker	17 (6%)
ACE inhibitor/diuretic	11 (3.7%)
ARB/diuretic	2 (0.7%)

**Table 2.** The types of fix-dose combinations of antihypertensive treatments

ACE – Angiotensin Converting Enzyme  
ARB- Angiotensin Receptor Blocker

Patients treated with fix-dose combined therapy were compared with all other patients treated with mono, dual or triple therapy. The comparative analysis is shown in Table 3. The two groups of patients did not differ in respect of presence of Diabetes (p=0.676). Those treated with fix combinations were significantly younger (p=0.045), less male (0.001), more burdened with obesity (p=0.028) and more frequently smokers (p= 0.0001).

	Fix-dose combined treatment N= 134	Mono, dual or triple therapy N=146	p (sig)
Age (years)	63.37±13.69	64.09 ± 15.09	0.045
Male gender	46 (36%)	82 (56%)	0.001
Obesity	44 (33%)	12 (8%)	0.028
Smoking	37 (28%)	26 (17%)	0.0001

Diabet es	39 (29%)	39 (27%)	76	0.6
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**Table 3.** Comparative analysis between patients on fix-dose combined treatment and mono, dual or triple medicament treatment

After one month in 95% of patients the blood pressure reached the recommended targets. In 5% the follow up was not completed. Considering drug side effects, three patients treated with mono ACE therapy complained of dry cough and the treatment was replaced with a propiate dose medicament. No hypotension episodes were notified.

### Discussion

The novel guidelines for the treatment of hypertension coming from both United States and Europe have recommended the concomitant use of 2 antihypertensive drugs in nearly all hypertensive patients [16,17]. This treatment approach significantly improves the protection of the patients with high cardiovascular risk. In our real life study conducted on 280 referred patients for hypertension, nearly half of them were treated with more than one medicament. More than 20% of patients already had a history of cardiovascular event or cardiovascular genetic burden. Newer the less, risk factors implying a patient's bad compliance as obesity and smoking were also present in a large number of our patients. Compared to the other western countries our patients have rather high prevalence of smoking, in spite of the doctors advices [18], considering the cardiovascular risk. Patients with grade 1 hypertension with a treatment based on the initial administration of 2 antihypertensive agents in the HOPE-3 trial (Heart Outcomes Prevention Evaluation-3), showed more than twenty percentage of reduction in the risk of cardiovascular outcomes [19]. From the distribution of our patients in respect of the stage of hypertension we found 40% in stage I, 37% in stage II and 23% in stage III. Nearly all patients with stage II and III were treated with combined fix-dose therapy, but patients in stage I were predominantly treated with monotherapy, as recommended per recent guidelines [17]. The combined therapy consisted of angiotensin converting enzyme inhibitor or angiotensin receptor antagonist plus calcium channel blocker or diuretic. The triple combination was applied in 48% of patents. This discrepancy from the HOPE trial we explain because of not having initial treatment in our patients, but those were referred as patients with poor control. After the introduction of the proper treatment and the follow up, 95% of patients had reached recommended thresholds for blood pressure control. Patients with higher risk for cardiovascular events were administrated with combined therapy. When we compared them with patients with not treated with combined therapy, they were significantly younger ( $p=0.045$ ), less male ( $0.001$ ), more burdened with obesity ( $p=0.028$ ) and more frequently smokers ( $p= 0.0001$ ). Since those patients also reached the thresholds for blood pressure control, we speculate that the adherence to treatment increased when one single pill was introduced for treatment of hypertension. The increasing adherence to antihypertensive treatment is known to be positively related to the achieved blood pressure values [20,21]. Manu published studies have also confirmed this effect and attenuation of cardiovascular risks from randomized trials and in real-life medicine, as it is in line with our results [22-24]. In the follow up of one month, patients were advised to notify adverse reactions related to novel antihypertension treatment. Only minor number of patients complained on caught which diminished after introducing another appropriate drug, replacing angiotensin converting enzyme inhibitor with angiotensin receptor blocker. In respect of hypotension, elderly, old and frail patients are known to be at risk at some extent [17]. In our study, the introduction of the combined therapy was gradual with increasing the dose until reaching recommended targets without significant hypotensive episodes.

### Conclusions:

Combined fox-dose therapy is shown to be of high efficacy and safety in patients with poor control of hypertension, especially in patients with low therapy adherence and at higher cardiovascular risk.

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