

Effectiveness of Hypertension Therapy by Using Fixed Combinations and Monocomponent Drugs—A Prospective Study from Croatia

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Purpose: Arterial hypertension is the leading risk mortality factor in the world according to the report by the World Health Organization. The aim of this research was to compare fixed-dose combination with free-drug combination therapy and prove that fixed-dose combination improve patient compliance and persistence, measuring blood pressure among hypertensive patients in a Croatian Adriatic city. **Methods:** The study included 202 patients, 101 women and 101 men, mean age 66.8 ± 9.4 with previous diagnosis of hypertension. **Results:** Mean blood pressure was $152.8 \pm 18.8/87.3 \pm 10.3$ mmHg. Blood pressure control ($\leq 140/90$ mmHg) was achieved in 24.8% of patients, 13.9% of women and 10.9% of men. Mean blood pressure in the group with fixed-dose combination was $149.2 \pm 17.9/86.2 \pm 8.5$ mmHg, and $156.7 \pm 18.9/88.4 \pm 11.8$ mmHg in the group with free-drug combination therapy. **Conclusions:** Results suggest that blood pressure control was better in patients with fixed-dose combinations than in patients with free-drug combinations. Fixed-drug combination improved compliance and adherence in patients with antihypertensive therapy. Results of the study indicate that fixed-drug combination should be considered in patients with hypertension according to the guidelines.

Key words: Hypertension, fixed -dose combinations, compliance, adherence, Croatia.

1. Introduction

According to a Kearney et al. [1] study from year 2000, currently one quarter of world population suffers from hypertension and it is estimated that by year 2025 this number might increase by 60%. With these numbers, 73% of hypertensive European population remains untreated [2]. In Croatia, arterial hypertension prevalence is 37.5%, whereas of 59% treated patients only 19.4% has controlled ABP (arterial blood pressure) [3].

Primary goal of treating patients with arterial hypertension is to achieve maximum decrease of the long-term risk of CV (cardiovascular) diseases. The

ABP must be decreased at least below the 140/90 mmHg threshold, as with each increase in 20 mmHg of SBP (systolic blood pressure) and 10 mmHg of DBP (diastolic blood pressure) the risk of CVI (cerebrovascular incident) and MI (myocardial infarction) increases by double [4].

Although the treatment starts with monotherapy, combination of drugs enables a pharmacology “strike” toward two and more systems and will have better impact on ABP decrease compared to monotherapy [5]. Preferred combinations include rennin-angiotensin-aldosterone system inhibitors and calcium channel blockers. Common adverse effect of calcium channel monotherapy is peripheral oedema. In combination with rennin-angiotensin-aldosterone system inhibitors this adverse effect is alleviated. Also,

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combination of diuretics and RAAS blockers results in additive blood pressure reduction. Diuretic-induced vasodilation reduces ABP by inducing mild sodium depletion and reducing plasma volume. Consequently, diuretics may indirectly stimulate the RAAS, which may attenuate their efficacy. Acceptable combinations include beta—blockers and diuretics, calcium channel blockers with diuretics or beta—blockers. [6]. Further strengths of combo therapy include: better tolerability, decreasing time and frustration of finding the effective monotherapy for patient, damaging organs due to lack of efficacy, availability of fixed combinations and better adherence and compliance [7]. Low therapy adherence is not only an issue identified with patients but also by doctors [8].

1.1 Compliance and Adherence to Therapy

The role of a doctor is crucial in controlling the ABP especially due to clinical inertia (failure to strengthen the therapy when therapeutic goals are not reached). Decrease in clinical inertia of 50% may bring increase of controlled patients by 1/5 [9]. Most usual reasons for clinical inertia include fear of potential side effects due to increasing drug dosage, lack of additional disease symptoms and accepting higher ABP values as well controlled [10]. However, the role of pharmacists is thus more important, especially for compliance and adherence, the main reasons for failure to achieve controlled ABP [11]. It is estimated that 24-58% patients lack adherence or compliance [12]. The second reason is the complexity of therapeutic regime, meaning number of prescribed drugs and dosing, which brings worse compliance by 35% with four times daily dosing compared to once a day dosing [13]. Thus the fixed combination of two drugs coming from different antihypertension drugs increases both the compliance and the adherence, also decreases side effects [14, 15].

1.2 Study Goals

The main goal of this study was to compare FC

(fixed combinations) and MC (mono component) antihypertensive drugs and to identify whether fixed combinations improve compliance and adherence, as measured according to valid guidelines [16]. Secondary goal was to prove importance of a pharmacist patient support reflected in better adherence, compliance and adding up to better control of ABP.

2. Materials and Methods

2.1 Data Collection and Outcome Measures

Informed consent was collected from all patients prior to data collection. Data from patients were coded and anonymized before analyses.

The research was conducted in a community pharmacy in a Croatian Adriatic City of Kastel Sucurac during February 2013 as a prospective study for patients diagnosed with arterial hypertension, taking anti hypertension therapy. The study included a non-probabilistic sample of 202 adult patients both male and female, routinely coming to the pharmacy to collect their medications. The inclusion criteria were: previously diagnosed hypertension, taking 2 anti-hypertensives, and written statement that they have been taking their drugs three days prior to measurement. The exclusion criteria were: newly prescribed antihypertension therapy, taking only 1 antihypertensive drug, written statement that they have not been taking their drugs three days prior to measurement.

All respondents had ABP measured and data collected on age, sex, drug type, number of antihypertensive drugs and values of measured ABP. After the data collection respondents were grouped whether they were taking fixed (2 or more active substances in one tablet or pill) or mono component (only one active substance) AH therapy.

Adherence was defined as patient behaviour reflecting prescribed therapeutic regimen, expressed as a ration of prescribed and taken doses in a specific time interval. Compliance was defined through

continuous usage of prescribed therapy measured with time accumulation from the beginning to the end of therapy. Controlled ABP was defined as being $\leq 140/90$ mmHg.

2.2 Statistical Analysis

Descriptive statistics was used, including *t*-test for statistical significance and χ^2 -test or Fisher exact test for testing observed differences of continuous variables. The two groups differences (FC vs. MC) were tested using the Z-test, with significance threshold of 0.05, all using Statistica software (version 10, StatSoft Inc, SAD).

3. Results and Analysis

Out of 202 patients, there was an equal ration of women/men; average age was 66.8 ± 9.4 yrs, every adult with inclusion criteria could take part in this study. All patients used 2-5 antihypertension drugs. Fixed combinations were used in 104 and mono components by 98 patients. Most used FC was ramipril/hydrochlorothiazide (32%) and ramipril/hydrochlorothiazide (16.3%), the rest was highly variable.

Most frequently MC was amlodipine (28.2%), out of which in mono components 46 and 11 on fixed combo. Mean ABP was $152.8 \pm 18.8/87.3 \pm 10.3$ mmHg (Table 1). Totally 17 (8.42%) patients had SBP > 180 mmHg and DBP > 110 mmHg was found

with 2 patients (0.99%). As mentioned, ABP values of $\geq 180/110$ mmHg refer to severe hypertension.

In total 24.8% respondents had ABP values $\leq 140/90$ mmHg, out of which 13.9% women and 10.9% men, showing no statistically significant difference among observed values for men and women (Table 2).

When observing the ABP in two treatment groups (FC and MC) there were in total 64 patients (32.7%) on FC therapy and 16 patients (16.3%) on MC therapy who had ABP values $\leq 140/90$ mmHg (Table 2).

Mean observed ABP for patients with FC was $149.2 \pm 17.9/86.2 \pm 8.5$ mmHg, and for MC therapy mean ABP was $156.7 \pm 18.9/88.4 \pm 11.8$ mmHg. Using Z test it was accepted that mean values of SBP and DBP were lower for FC taking patients, than for MC patients ($p < 0.05$).

Following graph (Fig. 1) shows distribution of patients related to SBP and type of anti-hypertensive therapy (fixed or mono).

Observed SBP which ranged 140-160 mmHg was most frequent in both treatment groups (39.4% for FC and 38.8% for MC), whereas the second highest grade for FC was 120-140 mmHg (33.6%), while MC was 160-180 mmHg (32.6%). Most frequent DBP level differed between the groups for FC group the highest percentage was (58.7%) measured in range of 75-90 mmHg, while MC was in range of 90-105 mmHg (46.9%).

Table 1 Measured values of arterial blood pressure.

Outcomes	All patients
SBP (mmHg) mean \pm SD	152.8 ± 18.8
DBP (mmHg) mean \pm SD	87.3 ± 10.3
SBP 180 mmHg n (%)	17 (8.42%)
DBP 110 mmHg n (%)	2 (0.99%)

SBP—Systolic blood pressure, DBP—Diastolic blood pressure.

Table 2 Observed ABP for both patient groups.

	Fixed combo	Mono component	<i>p</i>
N patients	104	98	
SBP (mmHg)	149.2 ± 17.9	156.7 ± 18.9	< 0.05
DBP (mmHg)	86.2 ± 8.5	88.4 ± 11.8	< 0.05

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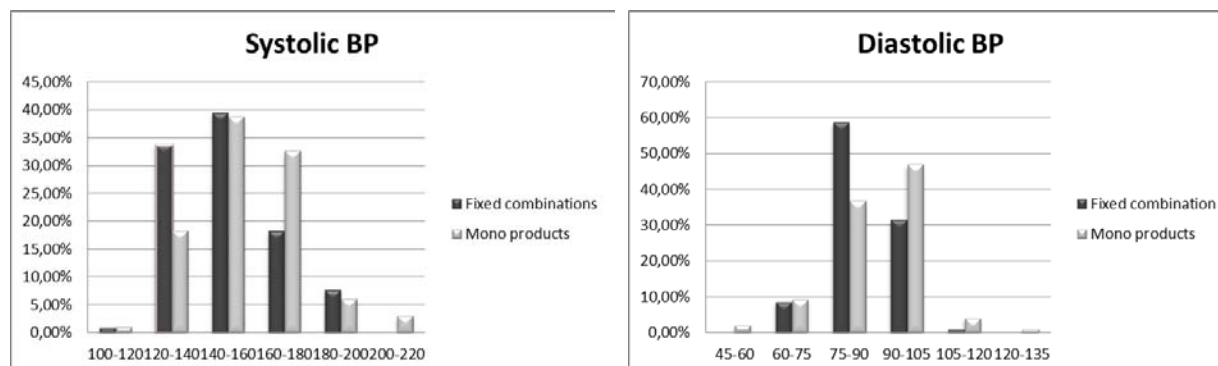


Fig. 1 Comparison of observed SBP/DBP values for patients on fixed combinations and mono-component antihypertensive drugs.

4. Discussion

Main findings of this research were: ABP was not adequately controlled in most of hypertonic patients receiving AH therapy on the observed area. Patients taking FC had better controlled ABP compared to those taking MC. FC drugs have the capacity to improve compliance and adherence of therapy [5, 6].

Most prescribed FC was of ramipril & hydrochlorothiazide (30.8%) and MC was amlodipine (28.2%), which correlates with data published by Agency for Medicinal Products and Medical Devices of Croatia showing that ramipril was second most used drug measured by DDD/1,000 inhabitants/days [17]. As ramipril together with hydrochlorothiazide most prescribed FC and respondents had it prescribed also in combination with felodipine, we may assume that part of respondents received it as part of FC; so total ramipril consumption is actually much higher. When observing FC per groups most prescribed were the ACE—inhibitors mostly combined with diuretics and then with Ca channel blockers. Pharmacokinetics studies suggest that usefulness of fixed combination in the treatment of patients with hypertension require more prompt, intensive, and sustained blood pressure reduction, according to guidelines recommendation. Results of the clinical trials based on zofenopril plus hydrochlorothiazide show that this combination provides a good blood pressure control in a larger proportion of patients than would be achievable with monotherapy with zofenopril, while maintaining the

tolerability profile observed with each individual agent [18]. Recent study with perindopril and amlodipine in fixed dose and free dose combination has result in an advantage of the reduction of BP in group with fixed dose combination [19].

When observing the mean ABP ($152.8 \pm 18.8/87.3 \pm 10.3$ mmHg) it is clear that ABP control is unsatisfying, having only 24.8% patients with $ABP \leq 140/90$ mmHg). According to previous research in Croatia 19.4% of hypertonic patients had controlled ABP [3]. Similar results on control of ABP and CV risk were observed in Central and Eastern Europe, with ABP control obtained at 27.1% patients and mean ABP of $149.3 \pm 17/88.8 \pm 11$ mmHg [20]. Although this study was conducted in the period of six weeks and on smaller sample the results do not differ significantly from two mentioned studies. In Croatia, mentioned results show that more significant ABP control was achieved for women. Due to sample size, this study does not show any statistically significant difference in sex when observing ABP, SBP or DBP. Another Croatian research demonstrated also lack of significant difference among men and women in values of SBP and DBP, with only statistical difference observed for patients older than 65 years in DBP [21]. These findings might be explained by white coat effect. In some countries, ABP values $\leq 140/90$ mmHg for treated patients are explained with unequal (lack of) access to health care services for certain patients [22]. However Croatian health care system does enable equal access to all patients, especially on

primary health care level. Other publications explain inadequate ABP control with lack of clinical guidelines, which are accepted in Croatia [2, 23].

Some parts of explanation may lay in the failure of doctors to achieve therapy goals and some part in lack of compliance and adherence of patients. Clinical inertia is based on doctor's resistance to combine several AH drugs as they see such therapy as aggressive and unnecessary, especially for patients with lower CV risk [24]. The ALLHAT study [4] has shown that highest percentage of controlled ABPs (75.5%) was correlated with doctors having lowest rate of clinical inertia. Patients' resistance is mostly correlated with drug side effects, dosing regimen more than once a day, number of tablets taken and total drug costs [25].

For patients with high CV risk it is hard to achieve hypertension control; this study observed SBP ≥ 180 mmHg in 8.42% respondents and DBP in 0.99% patients, which is similar to findings of a study examining also high CV risk patients (SBP ≥ 180 mmHg of 9.6% patients and DBP ≥ 110 mmHg 1.2% patients) [26]. Problem of uncontrolled ABP for these patients is correlated to other risk factors, which further emphasize importance of FC drugs [27]. Respondents on FC therapy in this research had better control of ABP than the ones on MC. Although the measurements were taken in a non-isolated environment (a community pharmacy), this finding might have an important clinical significance related to potential of decreasing unwanted CV events.

Studies that researched patients with FC vs. MC showed better compliance and adherence, eliminating number of tablets, especially in the first six months of therapy and bringing lower costs of therapy as a result of decreasing hospitalizations and CV events [9, 28].

Focused attention of this study was also on supporting control of hypertension in everyday pharmacy practice where there is vast potential for improvement through numerous motivational programmes, social support and reminder methods.

Evidence point to impact of education, regular controls of pharmacist and drug packs with time monitoring may improve adherence by 34% and improve decrease of SBP [29], concluding that pharmacy care shows promising potential in controlling arterial hypertension.

So far mentioned studies showed that key success factors in successful antihypertensive therapy are: accepting valid guidelines, determination to achieve therapeutic goal values, efficacy and tolerance to therapy as well as patient compliance and adherence; all of them can be found in fixed combinations. As a result, better control brings decrease of CV morbidity and mortality.

5. Conclusions

Main findings of this research were: ABP was not adequately controlled in most of hypertensive patients receiving AH therapy on the observed area. Patients taking FC of hypertensives had better controlled ABP compared to those taking MC hypertensives. Fixed combinations have the capacity to improve compliance and adherence of therapy. The pharmacist plays an important role and offers potential in better hypertension control offering support for adherence and compliance. Based on the research results fixed combinations should be used more frequently and according to guidelines for specific stages of hypertension. Future researches might focus more on the ways how the role of a pharmacist might improve hypertension control through better adherence and compliance.

Conflict of Interest

The authors declare that they have no conflicts of interest. Author Vanesa Benkovic expressed views strictly from the personal point of view which does not reflect the position of Novartis Croatia where she acts as an employee. Benkovic did not give, or receive any resources related to this study, nor is included in selling or promoting any of Novartis drugs.

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