

# The Incidence of Antihypertensive Drug-induced Side Effects in Patients with Diabetes Mellitus Type 2 and Hypertension

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## ABSTRACT

**Objective:** To determine types and frequency of side effects of antihypertensive drugs in patients with diabetes mellitus (DM) type 2 and hypertension. **Subjects and Methods:** We performed a prospective study of 79 patients with DM type 2 and hypertension, randomly selected by systematic sampling, who were followed over a period of six months. Patients were assessed at baseline and once a month measuring following parameters: types of used antihypertensive drugs and frequency of side effects, the values (mmHg) of systolic (SBP) and diastolic blood pressure (DBP). **Results:** Out of 79 patients, 48/79 (60.8%) were males and 31/79 (39.2%) were females. The median age in males was 53 years (IQR=48 to 55 years), in females 53 years (IQR=49 to 56 years). There was no statistically significant difference in median age between males and females ( $P=0.368$ ). There is a statistically significant difference in the values of SBP [ $\chi^2(5)=312.296$ ,  $P<0.001$ ] and DBP [ $\chi^2(5)=216.051$ ,  $P<0.001$ ] over a period of six months follow-up. The drug side effects were noted in 9/79 (11.4%) patients between 1-2 months, in 6/79 (7.6%) between 2-3 months, in 1/79 (1.3%) between 3-4 months. The most common side effect was cough (11/79 or 13.9%) associated with the combination of ACE inhibitor and thiazide diuretics. In 5/79 (6.3%) patients there were reports of: flushing, palpitations, headache, dizziness and leg edema associated with Ca blockers. **Conclusion:** The most common side effect of antihypertensive treatment was cough (13.9%) associated with the combination of ACE inhibitor and thiazide diuretic.

**Key words:** diabetes mellitus type 2, hypertension, antihypertensive drugs, side effects

## 1. INTRODUCTION

Hypertension is a common comorbidity of diabetes mellitus (DM) and it occurs in 20-60% of people with DM (1). The application of combined antihypertensive treatment proved to be necessary in diabetics, kidney patients and patients at high risk, and generally whenever a lower blood pressure (BP) value is desired (2). In view of the increasing number of available antihypertensive agents, clinicians are faced with the need to become familiar with the potential side effects of these drugs. In order to minimize the incidence of drug-induced side effects, several facts need to be remembered: (a) the most important side effect of diuretics is hypokalemia, which can cause cardiac arrhythmias and may be dangerous in patients who are taking digitalis, ones with chronic arrhythmias and acute myocardial infarction; (b)  $\beta$ -blockers ( $\beta$ -B) can induce bronchoconstriction, peripheral vasoconstriction, glycogenolysis, inhibition of insulin secretion and sometimes induce severe bradycardia. They can also cause cold

limbs, faster fatigue, nightmares, insomnia and depression; (c) calcium channel blockers (CaB) of the first generation, particularly nifedipine, a representative of dihydropyridine, causes a number of side effects: sudden drop in blood pressure (BP) value, sympathetic activation and reflex tachycardia, especially dangerous in coronary patients, facial flushing and headache; (d) angiotensin-converting enzyme (ACE) inhibitors' side effects are rare and the two of them are specific: cough and angio neurotic edema. They are associated with the action on the bradykinin system (3).

Unfortunately, adverse antihypertensive drugs reactions cannot always be predicted from the pharmacological profile and only prolonged clinical experience will reveal their's adverse effects.

In this study, we evaluated the incidence of adverse effects of antihypertensive drugs in patients with diabetes mellitus type 2 and hypertension.

## 2. PATIENTS AND METHODS

A clinical, prospective study was conducted at the Department of Internal Medicine, Clinical Center University of Sarajevo (CCUS) during 2012-2013. The study was conducted with the consent of the Ethical Committee of the CCUS.

### 2.1. Patients

The study included 79 patients with DM type 2 and hypertension, randomly selected by systematic sampling who were followed over a period of six months. The *inclusion criteria* were: patients with DM type 2 and arterial hypertension (blood pressure measured in the sitting position after at least 5 minutes rest, average of three readings at the last run-in-visit, should range from 140 to 179 mmHg systolic or from 90 to 109 mmHg diastolic—grades 1 or 2 of hypertension; women or men with uncomplicated hypertension within the age range from 40 to 60 years old, because of the lesser likelihood of the existence of any vascular incidents as a complication of DM. The exclusion criteria were: a history of cardiovascular disease; secondary hypertension; renal dysfunction; recent treatment with two or more antihypertensive drugs or a contraindication to discontinue blood pressure lowering agents; severe non-cardiovascular disease; known contraindications for the first-line study medications, pregnant and lactating women. All participants signed informed consents for participation in this study.

### 2.2. Methods

Patients were assessed at baseline and once a month by measuring following parameters: types of used antihypertensive drugs and frequency of side effects, the values (mmHg) of systolic (SBP) and diastolic blood pressure (DBP). The incidence rate of adverse effects was the primary outcome variable calculated according to the formula: the number of new cases with side effects that occurred during a specified period of time/the total number of treated patients during that period of time expressed as a percentage. Sitting SBP and DBP (average of three readings) were secondary outcome variables.

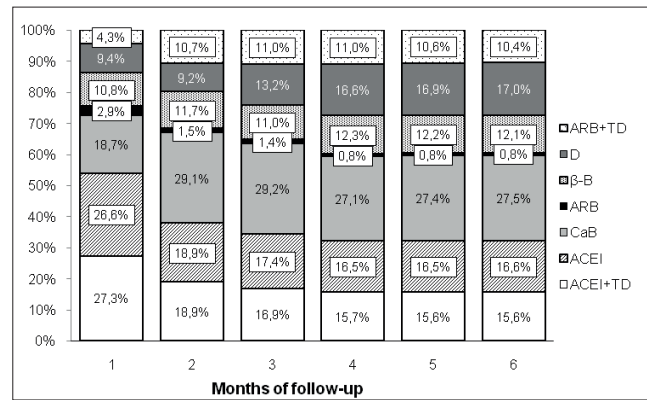
### 2.3. Statistical analysis

The Kolmogorov–Smirnov statistic Test with a Lilliefors significance level was used for testing normality. In case of categorical variables, counts and percentages were reported. A P-value <0.05 was considered as significant. The Friedman Test is used to test differences between different periods. *Post-hoc* analysis with Wilcoxon Signed-Rank Tests was conducted applying Bonferroni correction, resulting in a significance level set at  $P < 0.003$ . Statistical analysis was performed by using the Statistical Package for the Social Sciences (SPSS Release 21.0; SPSS Inc., Chicago, Illinois, United States of America) software.

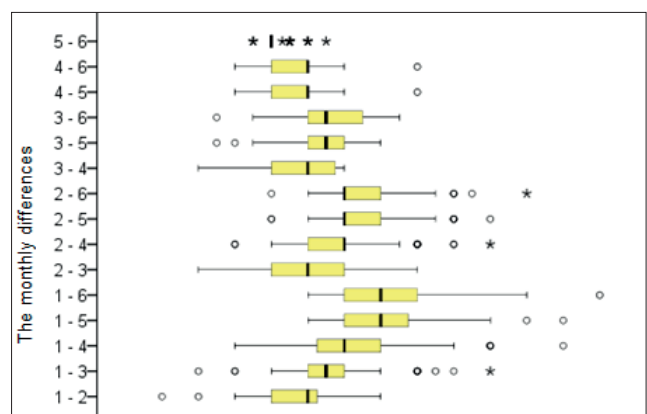
## 3. RESULTS

Out of 79 patients, 48/79 (60.8%) were males and 31/79 (39.2%) were females ( $\chi^2(1)=3.658$ ;  $P=0.056$ ). The median age in males was 53 years (IQR=48 to 55 years) and in females was 53 years (IQR=49 to 56 years). There was no statistically significant difference in median age between males and females ( $P=0.368$ ).

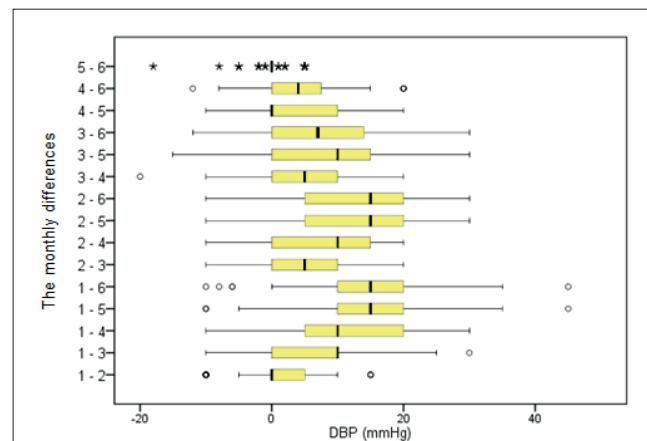
The most commonly proscribed therapy was the combination of three antihypertensive drugs (35.4%), followed



**Figure 1.** The frequency of use of antihypertensive drugs over a six-months follow-up period (ACEI—angiotensin-converting enzyme (ACE) inhibitors; TD—thiazide diuretics; CaB—calcium channel blockers; ARB—angiotensin receptor antagonists; β-B—β-Blockers; D—diuretics)



**Figure 2.** The monthly difference of systolic blood pressure in patients with diabetes mellitus type 2 and hypertension (n=79) treated with antihypertensive drugs over a period of six months (All P-values < .001, between 5-6 months  $P > .05$ ).



**Figure 3.** The monthly difference of diastolic blood pressure in patients with diabetes mellitus type 2 and hypertension (n=79) treated with antihypertensive drugs over a period of six months (All P-values < .001, between 1-2 months and 5-6 months  $P > .05$ ).

with the combination of four antihypertensive drugs (31.9%), two antihypertensive drugs (15.7%) and five antihypertensive drugs (9.1%). The monotherapy is used in 5.1% and the combination of six antihypertensive drugs in 2.8%.

The drug side effects were noted in 9/79 (11.4%) patients between 1- 2 months, where eight subjects 8/79 (10.1%) were reported with cough associated with ACEI

+ TD, while one patient 1/79 (1.3%) experienced dizziness and flushing associated with Cab. Between 2-3 month, the drug side effects were noted in 6/79 (7,6%), where three patients 3/79 (3.8%) were reported with cough, associated with ACEI + TD, while the other three patients, 3/79 (3.8%) experienced side effects associated with CaB: allergies, headache, flushing and leg edema.

Dizziness and palpitations associated with CaB appeared between 3-4 months in one patient 1/79 (1.3%). The drug side effects were not recorded during 4-5 and 5-6 months periods.

At the beginning of the study, the median value of SBP was 150 mmHg (IQR=150 to160 mmHg), and after six-month treatment was 125 mmHg (IQR=120 to130 mmHg), which represents a reduction of SBP for 25 mmHg. There was a statistically significant difference in the SBP values over the six-month use of the antihypertensive therapy ( $\chi^2(5) = 312.296$ ;  $P < .001$ ).

At the beginning of the study, the median value of DBP was 100 mmHg (IQR=90 to100mmHg), and after six months of treatment was 80 mmHg (IQR=80 to 85mmHg), which represents a reduction of DBP for 20mmHg. The DBP value in patients ( $n=79$ ) significantly changed during the six months of therapy with antihypertensive drugs ( $n=79$ ) ( $\chi^2(5) = 216.051$ ;  $P < .001$ ).

#### 4. DISCUSSION

In this prospective study, we found that the most common side effect of antihypertensive treatment was cough (13.9%) associated with the combination of ACEI + TD used between 1-2 months and 2-3 months of follow-up. Between 3-6 month these antihypertensive drugs were used in 15.6%–16.9% of patients and there were no adverse effects associated with them during this period. A dry cough occurs in 10-15% of patients treated with ACE inhibitors, due to the accumulation of bradykinin, substance P and/or prostaglandin in the lungs (3), which coincides with our results. Thiazide diuretics are one of the cheapest and most commonly used antihypertensive drugs worldwide. Thiazides, however, have significant side-effect profile and often, as monotherapy, are insufficient to normalize blood pressure value. Ng Lp et al. were conducted a retrospective study to identify patients who discontinued the use of ACE inhibitors and they found that 30.4% of patients discontinued the use of ACE inhibitors due to cough (4). Caldeira et al. conducted systematic review and meta-analysis to evaluate the tolerability of ARBs in patients with intolerance to ACE inhibitors and they found that ARBs had fewer cough events versus ACE inhibitors (5). In our study, the incidence of adverse reactions to CaB was 6.3%. Out of the total number of patients with adverse effects to CaB ( $n=5$ ), two of them were females who experienced flushing. Kajiwarra et al. study revealed that vasodilation-related adverse symptoms to dihydropyridine calcium channel blockers occurred significantly more often in females than in males (OR 1.87, 95 % CI 1.28-2.71,  $p = 0.001$ ) and furthermore, exclusively among females. The younger age group (<50 years) complained more frequently of vasodilation-related symptoms (OR 2.39, 95 % CI 1.02-5.59,  $p = 0.045$ ) (6). Peripheral edema, particularly of the lower limbs, is one of the

most common adverse effects of dihydropyridine calcium channel blockers and may result in the need of dose reduction or drug withdrawal, both of which can adversely affect antihypertensive efficacy (7). In our study, one patient had leg edema associated with CaB. In the study conducted by Luis MR, side effects such as: headaches and dizziness were more frequent in the group of olmesartan/hydrochlorothiazide compared to olmesartan group, hydrochlorothiazide group and the placebo group (8). Barrios et al. found that the treatment with medoksomilolmesartan, 40 mg/per day, was associated with a lower frequency of side effects compared to the combinational therapy of olmesartan medoksomil/hydrochlorothiazide (21.5% vs. 28.3%) (9). In the study conducted by Pool J Let al., 1,346 patients were randomized into eight groups: valsartan (VAL) 160 and 320mg; hydrochlorothiazide (HCTZ) 12.5 and 25mg; VAL/HCTZ160/12,5;320/12,5; 320/25mg and placebo groups (10). Each of these combinations was associated with a significant reduction in SBP values and DBP values compared to monotherapy and placebo groups (all  $P < .001$ ). The incidence of hypokalemia was lower in the combination of valsartan/hydrochlorothiazide (1.8%-6.1%) compared to monotherapy with hydrochlorothiazide (7.1%-13.3%). The study by Bangalore S et al. (11) questioned whether the therapy with the targeted normal SBP value (<120 mm Hg) reduces the incidence of the large cardiovascular incidents in patients with type 2 diabetes and cardiovascular disease or additional risk factors. The total number of 4,733 patients with type 2 diabetes (10-year median), aged 40-88 years (mean 62 year), were randomized to intensive or standard therapy for achieving SBP<120 mmHg and<140 mmHg, respectively. Serious side effects, which are attributed to antihypertensive treatment, appeared in 77(3.3%) subjects with intensive therapy and in 30 (1.3%) patients with a standard therapy ( $P < .0001$ ).

#### 5. CONCLUSION

The most common side effect of antihypertensive treatment was cough (13.9%) associated with the combination of ACE inhibitor and thiazide diuretic. The optimal choice and antihypertensive drug dosage should be done in accordance with the guidelines, by taking into consideration all patients characteristics.

**CONFLICT OF INTEREST: NONE DECLARED.**

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