**RESEARCH ARTICLE**

# A fixed-dose combination of bisoprolol and amlodipine in daily practice treatment of hypertension: Results of a non-investigational study in the Czech Republic

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## Summary

Objective:

This non-investigational study with the primary goal to assess patient adherence to the fixed dose combination (FDC) of bisoprolol and amlodipine in daily practice was carried out in six countries in Eastern Europe, in Czech Republic, Hungary, Poland, Romania, Serbia and Slovakia. In this paper, the results of 740 patients recruited in Czech Republic are presented. Secondary objectives included the assessment of blood pressure, pulse pressure values and heart rate.

Material and Methods

Patients eligible for recruitment were over 18 years of age, had essential hypertension, had already been switched from a free combination of bisoprolol 5–10mg/d and amlodipine 5–10mg/d to the FDC at least 4 weeks prior to recruitment, and gave informed consent. Women in childbearing age were under reliable contraception.

Exclusion criteria included pregnancy, lactation, any contraindication to the FDC according to the local label and any other antihypertensive medication.

The primary target parameter was patient adherence under the FDC. Adherence was measured by tablet count (tablets taken divided by tablets prescribed, times 100). The definition was as follows: excellent >90%, good 76-90%, moderate 51-75%, bad ≤50%. The study hypothesis was that at least 90% of the patients showed good to excellent adherence.

All other patient data, clinical findings and laboratory values were recorded upon availability at study start and after 6 months.

Results

There were more male (383, 52%) than female (357, 48%) patients. The mean age was 58.8 years with a Q1 – Q3 interval of 51 to 68 years. The youngest patient was 23 years and the oldest 95 years old. All patients had been pretreated once daily with a free combination of bisoprolol (mean 5.8mg) and amlodipine (mean 5.9mg). In most patients, the doses were not changed at the switch to the FDC or later during the study, resulting in a mean of 6.2mg for bisoprolol and 5.9mg for amlodipine.

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Over the 6 months of treatment, the adherence of 98% of the patients was good to excellent. Thus, the study expectation was more than met.

Potentially due to the excellent adherence, there was a 12.1mmHg reduction in mean systolic and a 6.9mmHg reduction in mean diastolic blood pressure after 6 months compared to study start. The benefits of patient adherence on blood pressure control are confirmed by the improvement of the pulse pressure by an average of 59.1mmHg±13 at study start versus 54.1mmHg±10 after 6 month of treatment. Heart rate decreased by a mean of 5.6bpm.

Only in 2 patients (0.3%), two adverse drug reactions probably related to the study medication were documented after 6 months: one case of hypotension and one case of edema. None of the adverse drug reactions (ADR) was considered serious and both patients fully recovered. Overall, the FDC of bisoprolol and amlodipine was well tolerated.

The study results clearly show that the high adherence under the FDC of bisoprolol and amlodipine may contribute to better blood pressure control and, thus, to a better risk reduction for cardiovascular events.

**Keywords:** Adherence, hypertension, bisoprolol, amlodipine, fixed dose combination.

## Introduction and Study Objective

Hypertension is related to an increased cardiovascular (CV) risk, and arterial hypertension is one of the most prevalent cardiovascular diseases in the industrialized nations (1). Thus, in hypertensive patients, the primary goal of treatment is to achieve maximum reduction in the long-term total risk of CV disease (2).

The 2013 European Society of Cardiology (ESC) guidelines on the management of hypertension recommend the initiation of antihypertensive drugs in all patients with a systolic blood pressure (SBP) of 140mmHg or more and/or a diastolic blood pressure (DBP) of 90mmHg or more. They further recommend drug treatment to be initiated within a lower BP range, that is, a SBP between 130 and 139mmHg and a DBP between 85 and 89mmHg in patients with diabetes or a history of cardiovascular or renal disease, aiming at achieving SBP/DBP values <130/80mmHg (2).

Large-scale meta-analyses of available data confirm that major antihypertensive drug classes, that is, diuretics, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, angiotensin receptor blocker (ARB), and beta-blockers do not differ significantly in their overall efficacy to reduce BP in hypertension (2).

As arterial hypertension is usually a multifactorial disease, this treatment goal can be reached in ≥75% of the hypertensive patients only by giving a combination therapy (2,3). A drug therapy directed at only one component routinely evokes compensatory (counter-regulatory) responses. Thus, a combination of two complementary agents, targeting different pathways of hypertension and preferably balancing each other' counter-regulatory activities, improves response rates and tolerability (3, 4). Preferably, the combined agents don't show any pharmacokinetic drug-drug interaction.

Combination therapy is usually recommended for patients with BP ≥160/100mmHg ("stage 2 hypertension") and for those whose BP cannot be controlled under monotherapy (2, 5).

The combination of a beta-blocker with a dihydropyridine (DHP) calcium channel blocker is one of several preferred

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combinations of antihypertensive agents recommended by international guidelines, such as the European Society of Hypertension (ESH) and ESC guidelines (2) for hypertensive patients with angina pectoris or after myocardial infarction. They target three pathways of hypertension (sympathetic nerve system, renin release and vasodilatation) that favor synergism in terms of antihypertensive efficacy and tolerability (6-9).

However, the complexity of therapy and pill burden has a direct negative impact on treatment adherence. More medications are associated with a lower likelihood of adherence (10). Fixed-dose combinations (FDC) may overcome this adherence hurdle by decreasing the number of tablets to be taken, particularly if they are suitable for a once daily intake.

For bisoprolol and amlodipine, a fixed dose combination tablet in the strengths of 5mg/5mg, 5mg/10mg, 10mg/5mg and 10mg/10mg was developed as substitution therapy at same doses for patients, whose blood pressure can be adequately controlled by a free combination of bisoprolol and amlodipine. These four strengths cover all potential free combinations and, thus, do not limit the flexibility of dosing.

A first open, non-comparative, non-investigational study with the fixed combination of bisoprolol and amlodipine was carried out by Metha et al. (2005) (11) in 106 patients with mild to moderate essential hypertension. They were treated with a fixed dose combination of 2.5mg bisoprolol and 5mg amlodipine (dosage strength available in India only) one or (if needed) two tablets once daily for 8 weeks. Treatment response was defined as a SBP below 140mmHg and a DBP below 90mmHg. Mean SBP and DBP were significantly lower after end of treatment compared to baseline ($p<0.0001$). Responder rate was 89%.

These results were confirmed by a second observational study in 801 patients with stage II essential hypertension (12). Patients received a fixed-dose combination of 5mg bisoprolol and 5mg amlodipine once daily for four weeks. 749 patients completed the study. Mean SBP decreased significantly from a baseline of 171.9±17.9mmHg to 152.9±16.4mmHg, 142.1±13.1mmHg and 134.3±10.1mmHg after 1, 2 and 4 weeks, respectively (all $p<0.001$). Mean DBP fell from 103.9±9.6mmHg at baseline to 93.5±8.8mmHg, 88±7.3mmHg and 83.4±6.2mmHg after 1, 2 and 4 weeks, respectively (all $p<0.001$). The responder rate after 4 weeks of treatment was 82.5%. Excellent to good efficacy and tolerability were documented in 91.4% and 90.3% of the patients.

In an open, parallel, comparative, randomised controlled trial conducted among 60 patients aged between 40-65 years with stage 2 hypertension (SBP ≥160 or DBP ≥100mmHg), the effect of amlodipine 5mg, bisoprolol 5mg and a fixed dose combination of amlodipine 5mg + bisoprolol 5mg was studied and compared. Results revealed that patients on the fixed dose combination of amlodipine + bisoprolol achieved significant better blood pressure control with antihypertensive effect greater than individual monotherapy study groups (13).

The primary objective of the phase III trial by Hostalek et al. (2016) (14) was to investigate the efficacy of the FDC of bisoprolol and amlodipine in 200 hypertensive patients, whose BP could not be controlled by either monotherapy (Bisoprolol 5 mg or Amlodipine 5 mg) alone. Based on the primary efficacy endpoint of the trial, subjects reported mean SBP reductions of 24.7 mmHg (95% CI: -27.1; -22.3) and 25.9 mmHg (95% CI: -28.6; -23.3), respectively, from baseline to Week 18 (all p-values were < 0.001). Also, DBP, as well as HR, decreased significantly

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under the FDC compared to the values under either monotherapy ($p<0.001$). Thus, it could be shown that adding the second component of the FDC led to a statistically significant and clinically relevant decrease in blood pressure. In more than 80% of the patients, BP could already be controlled under the lowest strength of the FDC (5mg/5mg) after 6 weeks of treatment.

As the most important advantage of a FDC is the expected better patient adherence, more clinical data are needed on the impact of patient adherence with this fixed combination. Thus, the present study was conducted to evaluate the adherence of the FDC in daily practice. Results from Polish patients from the same study have recently been reported (15, 16).

## Methods

758 hypertensive patients have been asked to participate in the study in the Czech Republic. 18 patients did not meet all inclusion criteria. The remaining 740 patients had been previously prescribed bisoprolol and amlodipine in free combination and had been switched to the FDC at least four weeks prior to recruitment.

Prior to inclusion in the study, patients were informed of the nature, significance and scope of the study and gave their consent to participate and to have their data used in an anonymized way. At the screening examination, past medical history data and clinical findings were recorded and blood pressure values and laboratory values documented upon availability. There were three facultative visits (Visit 2, 3, and 4) at month 1, 2 and 3. Final follow up visit and examinations occurred after 6 months at visit 5. The number of prescribed tablets taken by the patients was checked to assess adherence (>90%=excellent, 76–90%=good, 50–75%=moderate, <50%=poor). Blood pressure, measured in a supine position after at least 5 minutes of rest, and heart rate values were also documented. Additionally, patients were asked to assess the new treatment concept subjectively.

## Analysis

All entries were transferred for evaluation in the file BIAS (Biometric analysis of samples, Hanns Ackermann, University Frankfurt, Germany). For all parameters, mean, standard deviation, median, and quartiles were calculated.

## Results

The demographic data of the 740 patients from Czech Republic are summarized in Table 1 and 2.

**Table 1 Demographic data I**

| | N | % |
|---|---|---|
| **Participants** | 740 | |
| **Male**<br>**Female** | 383<br>357 | 52<br>48 |
| **Cardiovascular co-morbidities** | 165 | 22 |
| **Diabetes type 2** | 172 | 23 |
| **Liver disease** | 16 | 2 |
| **Kidney damage** | 22 | 3 |

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| | | |
|---|---|---|
| **Smoking habits**<br>Smoker<br>Ex-smoker<br>No smoking<br>No data | <br>165<br>123<br>450<br>2 | <br>22<br>17<br>60<br>1 |
| **Alcohol consumption**<br>No alcohol<br>Little alcohol (1x weekly)<br>moderate alcohol (2-4x weekly)<br>no data | <br>192<br>445<br>102<br>1 | <br>26<br>60<br>14 |

There were more 48% female and 52% male patients. The mean age was 58.8 years with a Q1 – Q3 interval of 51 to 68 years. The youngest patient was 23 years and the oldest 95 years old.

There was almost one quarter of patients with concomitant cardiovascular disease (22%) and/or type 2 diabetes (23%). A third of the patients were overweight (BMI$\geq$25kg/m$^2$) and another third obese (BMI$\geq$30kg/m$^2$).

More than half of the patients stated to be non-smokers (61%). The other half was still smoking (22%) or had quitted smoking (17%). 26% of the patients declared to not drinking any alcohol, the rest was consuming slightly (60%) to moderately (14%).

All patients had been pretreated once daily with a free combination of bisoprolol (mean 5.8mg$\pm$2) and amlodipine (mean 5.9mg$\pm$2). The majority of patients (358, 60%) were treated with the lowest possible combination of 5mg bisoprolol and 5mg amlodipine.

**Table 2 Demographic data II**

| **Parameters** | **Mean (SD)** | **median** | **Q1-Q3** |
|---|---|---|---|
| **Age (years) n = 317** | 58.8 (13) | 60 | 51-68 |
| **Height (cm) n = 319** | 170.5 (12) | 170 | 165– 177.8 |
| **Weight (kg) n = 321** | 84.6 (17) | 83 | 73 - 94 |
| **BMI (kg/m$^2$) n = 319** | 28.8 (5) | 28 | 25.3 – 32 |
| **Systolic blood pressure (mmHg) n = 320** | 144.9 (16) | 140 | 131.5 - 155 |
| **Diastolic blood pressure (mmHg) n = 320** | 86.0 (10) | 85 | 80 - 91 |
| **Pulse beat/min n = 316** | 72.0 (15) | 72 | 65 - 80 |
| **Pulse Pressure n = 320** | 59.1 (13) | 59 | 50 - 67 |
| **Duration of hypertension (years) n = 312** | 9.0 (6) | 7 | 4 - 13 |
| **Dosages (free combination)**<br>**Bisoprolol (mg daily) n = 312**<br>**Amlodipine (mg daily) n = 311** | <br>5.8 (2)<br>5.9 (2) | <br>5<br>5 | <br>5 - 5<br>5 - 5 |
| **Time of FDC prior to recruitment (weeks) n = 312** | 5.5 (3) | 4 | 4 - 6 |

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The systolic blood pressure values exceeded 140mmHg in about 50% of the patients (see Figure 1). Thus, half of the patients had not blood pressure controlled at the study start. Regarding diastolic blood pressure, in 45% of patients the blood pressure exceeded 85mmHg. Mean duration of hypertension prior to study recruitment was 9 years (SD±6).

**Figure 1 Distribution of systolic blood pressure at study start**

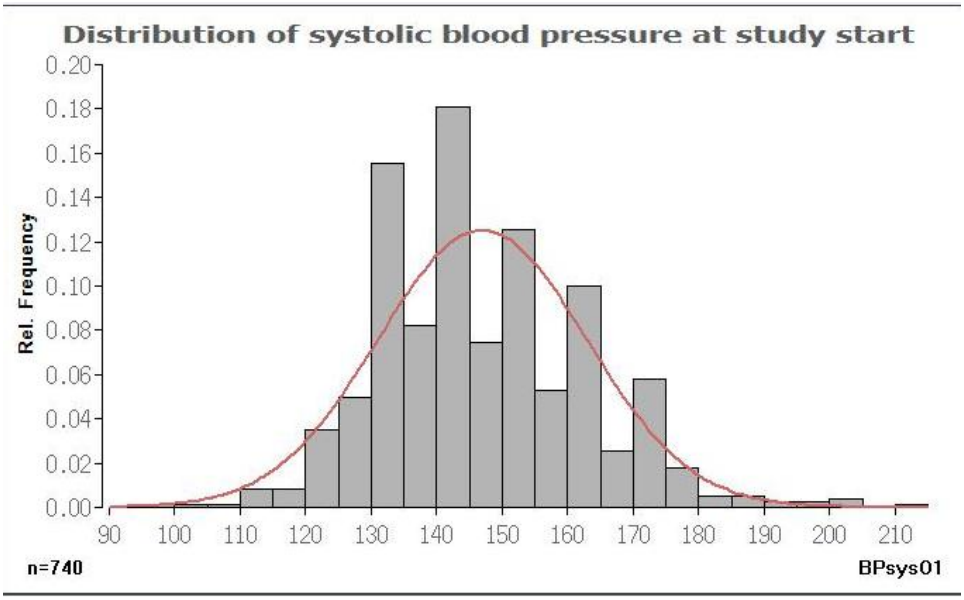


Table 3 shows that the dose regime was altered in some of the subjects when changing from the free combination to the fixed combination. However, only small dose changes were made.

**Table 3 Comparison of dosing**

| | Free combination n (%) | FDC n (%) |
|---|---|---|
| **Bisoprolol 5mg/Amlodipine 5 mg** | 358 (60%) | 431 (62%) |
| **Bisoprolol 10 mg/Amlodipine 5 mg** | 106 (18%) | 139 (20%) |
| **Bisoprolol 5 mg/Amlodipine 10 mg** | 122 (20%) | 105 (15%) |
| **Bisoprolol 10 mg/Amlodipine 10 mg** | 14 (2%) | 23 (3%) |
| **N** | 600 | 698 |
| **Daily Doses** | Mean (SD) | Mean (SD) |
| **Bisoprolol mg/d** | 5.8 (2) | 6.2 (3) |
| **Amlodipine mg/d** | 5.9 (2) | 5.9 (2) |

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With either the free combination or the FDC, 358 patients (60%) or 431 (62%), respectively, of the patients were on the lowest possible dose combination. When switching from the free to the fixed dose combinations no changes in single doses of bisoprolol and amlodipine were made in the majority of cases (88% for bisoprolol and 66% for amlodipine). In 2% and 17% of patients the dose was decreased, and in 10% and 17% of patients increased. For some patients, no comparative dose information was available.

According to the inclusion criteria, patients had to be on the FDC of bisoprolol and amlodipine at least 4 weeks prior to study start. This criterion was met by almost all patients. Mean time of FDC treatment prior to study start was 5.5 (SD±3) weeks.

At the end of the study (after 6 months) data on the main target, the patient adherence, was available for 730 participants (96.3%). The data is summarized in table 4.

**Table 4 Patient adherence at Visit 5 (after 6 months)**

| Adherence | N | % |
|---|---|---|
| **Excellent (>90% of prescribed tablets taken)** | 606 | 83 |
| **Good (76-90% of prescribed tablets taken)** | 107 | 15 |
| **Moderate (51–75% of prescribed tablets taken)** | 17 | 2 |
| **Bad (≤50% of prescribed tablets taken)** | | |
| **Total** | 730 | 100.0 |
| **Good to excellent (≥76%) adherence** | **713** | **98** |

It was expected that more than 90% of the patients at Visit 5 would have an excellent to good adherence. Actually, the adherence of 98% of the patients was good to excellent. Thus, the expectation was more than met.

The results suggest that the additional mean reduction of the blood pressure values may be associated with the high degree of adherence, since in the majority of the patients the FDC of bisoprolol and amlodipine dose was kept unchanged over the study. The detailed evaluation shows the differences of the systolic and diastolic blood pressure values at the start of the observational period and after 6 months. Systolic blood pressure decreased by 12.1mmHg (8.3%), the diastolic blood pressure by 6.9mmHg (8%). Similarly, the pulse pressure values fell by 5.5mmHg (9.3%), and heart rate by 5.6bpm (7.8%) (Table 5).

**Table 5 Changes in blood pressure, pulse pressure and heart rate**

| | SBP (mmHg) | DBP (mmHg) | Pulse pressure (mmHg) | Heart rate (bpm) |
|---|---|---|---|---|
| | **Mean (SD)<br>median<br>Q1 – Q3** | **Mean (SD)<br>median<br>Q1 – Q3)** | **Mean (SD)<br>median<br>Q1 – Q3)** | **Mean (SD)<br>median<br>Q1 – Q3)** |
| **Visit I (Study start)** | 144.9 (16)<br>140<br>131.5-155 | 86 (10)<br>85<br>80-91 | 59.1 (13)<br>59<br>50-67 | 72 (15)<br>72<br>65-80 |
| **Visit IV (after 6 months)** | 133.1(11)<br>130<br>125-140 | 79.1<br>80<br>75-84 | 54.1 (10)<br>50<br>45-60 | 67.4 (9)<br>68<br>60-72 |

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| | | | | |
|---|---|---|---|---|
| **Difference mean+/-SD** | 12.1 (15) | 6.9 (11) | 5.5 (15) | 5.6 (11) |
| **Cohen's effect size** | 0.78 | 0.64 | 0.37 | 0.52 |
| *Cohen´s Effect-size: 0.2 = small, 0.5 = medium, 0.8 = large | | | | |

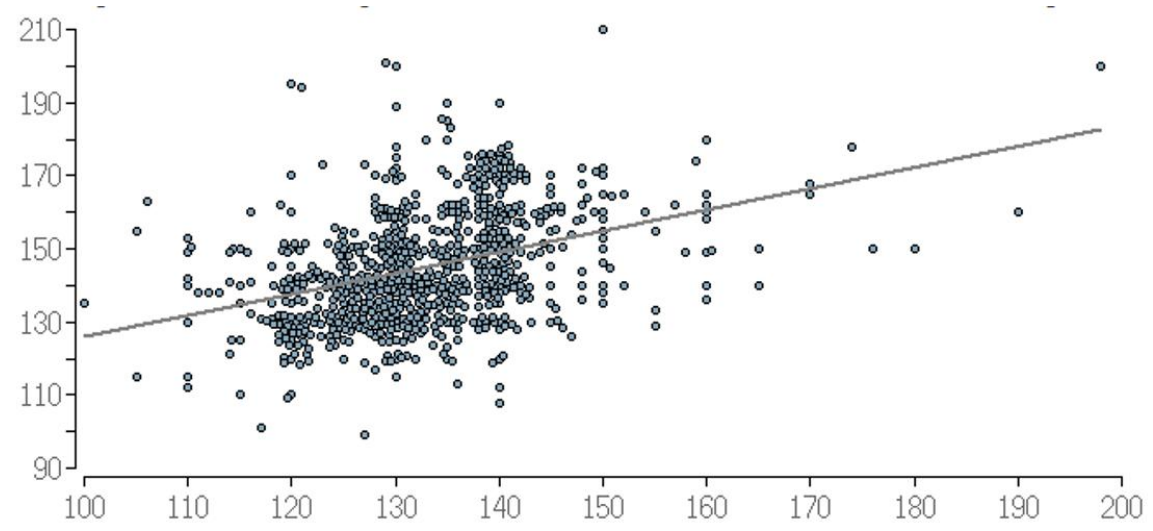
Table 6 shows that the proportion of patients with elevated blood pressure values at study start had significantly decreased values after six months' treatment period with the fixed combination dose without any decisive change in the dose.

**Table 6 Distribution of systolic blood pressure and pulse pressure at study start and after 6 months**

| | Systolic Blood Pressure | | | Pulse Pressure | |
|---|---|---|---|---|---|
| | **Study start** | **After 6 mths** | | **Study start** | **After 6 mths** |
| | **n (%)** | **n (%)** | | **n (%)** | **n (%)** |
| **<100mmHg** | 1 | 0 | **<30mmHg** | 2 | 3 |
| **101-130mmHg** | 184 (25%) | 387 (53%) | **31-50mmHg** | 241 (33%) | 340 (47%) |
| **131-144mmHg** | 188 (25%) | 243 (33%) | **51-60mmHg** | 128 (17%) | 147 (20%) |
| **145-155mmHg** | 187 (25%) | 77 (11%) | **61-67mmHg** | 191 (26%) | 161 (22%) |
| **>155mmHg** | 180 (25%) | 22 (3%) | **>67mmHg** | 178 (24%) | 77 (11%) |
| **Total** | 740 | 729 | **Total** | 740 | 728 |

In 545/726 study participants caused the change of dose regime a reduction in systolic blood pressure (see Figure 2). In 15%, an increase in systolic blood pressure was observed. The values of diastolic blood pressure changed in a similar way (66% reduction, 17% increase).

**Figure 2 SBP at study start and after 6 months**

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From the figure, it can be assumed that the degree of blood pressure reduction depends of the initial value (correlation coefficient: 0.4)

On questioning, 79% of the study participants declared they were very satisfied with the change of the dose regime, a further 21% assessed the new medication as good and only 1 percent was unhappy with the fixed dose regime. Accordingly, 89% of patients reported that they would prefer treatment with the fixed combination, 9% did not see any advantage and only 2% preferred the free dose combination.

**Adverse events**

Only in 2 patients (0.3%), two adverse drug reactions probably related to the study medication were documented after 6 months: one case of hypotension and one case of edema. None of the ADR was considered serious and both patients fully recovered.

There were only few laboratory values documented upon availability for fasted plasma glucose, HbA1C, serum creatinine, GOT (AST), and GPT (ALT). There were no significant changes in these parameters documented during the study.

Overall, the FDC of bisoprolol and amlodipine was well tolerated.

**Discussion**

Strict blood pressure control is crucial in the treatment of hypertension to decrease the risk for cardiovascular events. As the treatment of hypertension is usually life-long and as most of the patients need several drugs to control the blood pressure, patient adherence is a severe problem. Patients often fail to comply with pharmacologic therapy (17). This is particularly true in patients with a high pill burden, e.g. in patients that need a combination of drugs for the treatment of hypertension and further disorders.

The biggest advantage of an FDC over free combinations is the reduction of tablets to be taken. In a meta-analysis of nine studies comparing administration of FDCs or their separate components, the adherence rate was improved by 26% in patients receiving FDCs (3).

First results of a non-investigational study with the FDC of bisoprolol and amlodipine in Poland (15, 16) demonstrated the excellent patient adherence under the FDC of bisoprolol and amlodipine and the beneficial impact of a strong patient adherence on blood pressure, pulse pressure and heart rate control. Data of the present study confirmed the excellent adherence under the FDC. Again, 98% of the patients showed excellent to good adherence over 6 months of treatment duration.

Although there was no relevant dose change in the majority of patients when switching from the free combination to the FDC, a clinically relevant reduction of systolic and diastolic blood pressure values was documented during the study, probably, at least partly, due to the strong adherence. This outcome was associated with a considerable reduction in pulse pressure and heart rate values.

The FDC was well tolerated. At study end, 89% of the patients preferred the FDC over the free combination.

The study results clearly suggest that the high adherence under the FDC of bisoprolol and amlodipine may lead to better blood pressure control and, thus, to risk reduction for cardiovascular events.

**Conclusion**

The FDC of bisoprolol and amlodipine leads to an excellent patient adherence, adding to better control blood pressure that is crucial in the risk reduction of cardiovascular events in hypertensive patients.

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**Transparency**

This study was carried out as a company-sponsored trial by Merck KGaA. U. Hostalek is an employee of Merck KGaA, while EMW Koch is a consultant to the company.

J. Bruthans was the Principal Investigator of this study in the Czech Republic. U. Hostalek contributed to the conception and design of the study. EMW Koch and U. Hostalek were involved in the data analysis and interpretation. No assistance in the preparation of this article is to be declared.

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