

Treatment of hypertension with a fixed-dose combination of bisoprolol and amlodipine in daily practice: Results of a multinational non-investigational study

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Abstract

Objective: Primary study objective was assessing patient adherence to the fixed dose combination (FDC) of bisoprolol and amlodipine in daily practice. Secondary study objectives included the assessment of blood pressure values and heart rate.

Material and methods: This non-investigational study was carried out in six countries in Eastern Europe, namely Czech Republic, Hungary, Poland, Romania, Serbia, and Slovakia. 12,424 patients > 18 years of age with essential hypertension were recruited if they had been switched from a free combination to the FDC at least 4 weeks prior to recruitment. Exclusion criteria included pregnancy, lactation, any contraindication to the FDC and other antihypertensive treatment. Adherence was measured by tablet count (tablets taken divided by tablets prescribed, times 100) and defined as follows: excellent >90%, good 76-90%, moderate 50-75%, bad <50%. Other patient data, clinical findings such as systolic and diastolic blood pressure, pulse pressure and heart rate were recorded upon availability at study start and after 6 months of FDC treatment.

Results: Data of 12,242 patients (mean age: 59.1 years' gender: 49% female, 51% male) were documented. The average daily doses of the FDC were 5.8mg bisoprolol and 6.3mg amlodipine, differing only slightly from those of the free combination (5.5mg and 6.1mg, respectively). After 6 months of FDC-treatment, 99% of the participants of the study showed an excellent or a good adherence. This good or excellent adherence may have led to the observed reduction of the systolic and the diastolic blood pressure of 16.5mmHg for systolic and 9.5mmHg for diastolic blood pressure values. (Cohen's D Efficient-size 1.26 and 1.04). In addition, pulse pressure decreased by 7.1mmHg (Cohen's D Efficient-size 0.6). The heart rate decreased by a mean of 7.7bpm (Cohen's D Efficient-size 0.85). There was a certain influence of the baseline BMI values on the blood pressure values at study start, but not on the blood pressure values after 6 months of FDC treatment.

Conclusion: These study results demonstrate that the FDC leads to an excellent patient adherence and therefore may result. Patients enrolled in the study also demonstrated good blood pressure control under the FDC that is crucial in the risk reduction of cardiovascular events. The key limitation of this study is that the study design does not allow a direct comparison of patient adherence under the free and the fixed dose combination.

Introduction and study objective

Hypertension is recognized as a major risk factor for coronary, cerebral, and renal vascular diseases [1]. There are about 600 million hypertensive people in the world [2]. Hypertension is responsible for 57% of all stroke-related deaths and 24% of all coronary heart disease-related deaths [3]. There is a need for increased awareness, diagnosis, and management of hypertension.

The recent European Society of Cardiology/European Society of Hypertension guidelines for the management of hypertension state that 'monotherapy allows to achieve blood pressure (BP) target in only a limited number of hypertensive subjects' and that 'use of more than 1 agent is necessary to achieve target BP in most subjects' [4]. The 7th Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends that when the BP is more than 20/10 mmHg above goal, consideration should be given to initiating therapy with 2 drugs, either as separate prescriptions or in FDC [5]. In the randomized trials of antihypertensive therapy conducted during the 1970s and 1980s, in which very large doses of single drug were employed as initial therapy, more than 50% of subjects required treatment with combination therapy to achieve the BP goal

indicated in the trial protocol. This implies that an increase in the dose of the initial antihypertensive agent does not usually significantly increase the effectiveness of monotherapy. It is well known that high doses of almost all antihypertensive agents increase the risk and the severity of adverse effects. Adverse effects of drugs are the main cause for the low adherence of subjects with antihypertensive therapy in clinical practice. Essential hypertension has multiple mechanisms, and rational combination therapy allows interference with more than 1 of these mechanisms. Rational combination therapy not only reduces adverse effects because of the use of low doses of each combined agent, but can also take advantage of counteractions that each of the combined agents can exert on the undesirable actions of the other

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agent [6]. Hence, it is logical, and has been practically demonstrated that low dose combination agents, because of additive effect on BP, would expose subjects to fewer side-effects, with equal or better BP control. Thus, combination therapy has an important place in the routine management of hypertension.

However, it must be considered that for many, especially elderly, patients, the rules for taking multiple medications can be very distressing and lead to misconduct and to inadequate adherence. Because of the above-mentioned facts, a fixed combination tablet of the beta-blocker bisoprolol and the calcium channel blocker amlodipine in the strengths of 5mg/5mg, 5mg/10mg, 10mg/5mg and 10mg/10mg was developed as substitution for the free combination. Bisoprolol is a highly beta₁-adrenoceptor-selective antagonist devoid of any intrinsic sympathomimetic activity (ISA). Pharmacological features of bisoprolol are essentially related to its high beta₁-selectivity and confer substantial clinical advantages to the drug compared with non-selective agents in terms of their respiratory, hemodynamic, and metabolic effects [7-9]. Amlodipine is a long-acting calcium channel blocker of the dihydropyridine class. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells [10-12]. Both bisoprolol and amlodipine are widely used antihypertensive drugs. The combination of amlodipine and bisoprolol demonstrates an additive effect since both the drugs have different and complementary modes of actions to reduce BP: for example, a vascular selective calcium antagonist like amlodipine lowers total peripheral resistance and a β-1 selective blocker like bisoprolol lowers heart rate (HR) and, thus, cardiac output [13-15]. There have been several studies that have evaluated the effects of bisoprolol and amlodipine separately, as monotherapy, in the management of essential hypertension [16]. There also have been some studies that have evaluated the FDC of Bisoprolol and Amlodipine, not only to evaluate bioequivalence, but also the efficacy and safety on the treatment of hypertension [17-21]. The first study on the FDC of Bisoprolol and Amlodipine was carried out by Mehta *et al.* [17]. The study investigated the efficacy and safety of the FDC in 106 subjects suffering from mild to moderate essential hypertension. The study showed that a once daily administration of the FDC of Amlodipine/Bisoprolol 5 mg/2.5 mg significantly lowered both SBP and DBP, and was well tolerated and safe at the end of 8 weeks of treatment. Response rate was 98%.

Further experiences with a FDC of Bisoprolol and Amlodipine were gained from an observational study of 801 subjects with stage II essential hypertension [18]. Patients received a FDC of 5 mg Bisoprolol and 5 mg Amlodipine once daily for 4 weeks. Responders were supposed to have a SBP <140 mmHg and a DBP <90 mmHg at the end of treatment. The responder rate after 4 weeks of treatment was 82.5%. Excellent to good efficacy and tolerability were scored in 91.4% and 90.3% of the patients. The most frequently reported AE was edema in 8% of the patients. Other adverse events were headache (4%), fatigue (3%), leg cramps (3%), and dry mouth (1%). All AEs were mild. The authors concluded that the daily application of a FDC of Bisoprolol 5 mg and Amlodipine 5 mg in stage II essential hypertension was effective, safe, and well tolerated. Shirure *et al.* [19] demonstrated the superiority of the FDC of Bisoprolol 5 mg and Amlodipine 5 mg in 60 hypertensive patients, aged 40-65 years. In those patients not responding to either Amlodipine 5 mg or Bisoprolol 5 mg alone, after addition of the second agent, mean SBP and DBP values decreased significantly after 2 weeks. Hostalek *et al.* [20] carried out an observational study with Concor AM in several thousand patients in Poland. The study results clearly

demonstrate the strong adherence under the FDC of Bisoprolol and Amlodipine. Consequently, BP control was improved and, thus, the risk of cardiovascular events decreased. The primary objective of the phase III trial by Hostalek *et al.* [21] 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 on pre-study Amlodipine monotherapy and subjects on pre-study Bisoprolol monotherapy 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 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 SBP. 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). The most important advantage of a FDC compared to the free combination is the expected better patient adherence. Thus, the present study was conducted as a non-investigational study to evaluate the adherence of the FDC in daily practice in patients who had been switched from the free to the fixed dose combination prior to recruitment.

Methods

Hypertensive patients aged over 18 years from Czech Republic, Hungary, Poland, Romania, Serbia, and Slovakia, who had been switched from a free combination of bisoprolol and amlodipine to the fixed dose combination (FDC) at least four weeks prior to recruitment were included in this non-interventional study. 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 determined upon availability. Follow-up examinations occurred after 6 months. At this point, 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 and heart rate values were also documented upon availability. Blood pressure was measured in a supine position after at least 5 minutes' rest. Additionally, patients were asked to assess the new treatment concept subjectively.

Analysis

All entries in the CRFs were transferred for evaluation in the BIAS file (Biometric analysis of samples, Hanns Ackerman, Univ. Frankfurt). As methods were used calculation of mean, standard deviation, median, quartiles, and the Cohen's D for Effect-size (M1-M2/s-pooled).

Results

12,424 hypertensive patients were recruited for the study in six CEE countries. In 995 patients, the documentation did not allow the evaluation of the primary target parameter adherence. All patients had been previously prescribed bisoprolol and amlodipine in free combination and had been switched to the FDC prior to recruitment. Demographic data are summarized in Table 1 and 2. There were 49% female and 51% male patients. The mean age was 59.1 years with a broad range. The youngest patient was 19 years and the oldest 99 years old. There was no influence of the gender nor of the age on the blood pressure values at study start. There were 4,828 patients with concomitant cardiovascular disease (39%) and 2,644 patients with type

2 diabetes (21%). 13% of the patients had concomitant CV diseases and type 2 diabetes. 6,542 (54%) of the patients were overweight (BMI>25) and another 3,289 (27%) obese (BMI>30). Almost half of the patients stated to be non-smokers (50%). 25% each was still smoking or had quit smoking. 38% of the patients were not drinking any alcohol, the rest was consuming slightly (50%), moderately (11%), or regularly (1%).

All patients had been pretreated once daily with a free combination of bisoprolol (mean 5.5 ± 1.5mg) and amlodipine (mean 6.1 ± 2mg). Most patients (8,497, 72%) were treated with the lowest possible combination of 5mg bisoprolol and 5mg amlodipine. The average duration of free combination treatment prior to switch to FDC was 16.8 months (SD ± 15). The mean duration of the hypertension was 8.8 ± 6 years.

Mean, median, and quartile 1 and 3 values for systolic and diastolic blood pressure at study start demonstrate that a big part of patients did not reach the target value for systolic blood pressure of <140 mmHg,

namely 4,179 (34%). Mean duration of hypertension prior to study recruitment was 8.8 years (SD ± 6).

The average dose in the fixed combination (bisoprolol: 5.8mg ± 2, amlodipine: 6.3mg ± 3) was not considerably different from the previous dose of both products in the free combinations. Table 3 compares the dosage strengths of bisoprolol and amlodipine in free and fixed dose combination. When switching from the free to the fixed dose combinations no changes in single doses of bisoprolol and amlodipine were performed in about 80% of the cases. Adherence data after 6 months of treatment are only available for 11,429 (92%) of the patients. The data is summarized in Table 4. It was expected that more than 90% of the patients at Visit 5 show an excellent or good adherence. The adherence of 99% of the patients was good to excellent. Systolic blood pressure decreased by 16.5 mmHg (Effect size: d=1.26), and the diastolic blood pressure by 9.5mmHg (Effect size d=1.04). Similarly, the pulse pressure and heart rate values fell over the 6 months of treatment (Table 5). The changes in blood pressure values are described in Table 6.

Table 1. Demographic data I.

	N	%
Participants	12,424	
Gender, n=12,368		
Male	6,314	51
Female	6,054	49
Cardiovascular co-morbidities n=12,216	4,828	39
Diabetes type 2 n=12,216	2,644	21
CV co-morbidity plus diabetes, n=12,216	1,598	13
Liver disease n=12,089	210	2
Kidney damage n=12,256	410	3
Smoking habits, n=12,152		
Smoker	3,013	25
Ex-smoker	3,033	25
No smoking	6,106	50
Alcohol consumption, n=12,148		
No alcohol	4,566	38
Little alcohol (1x weekly)	6,075	50
moderate alcohol (2-4x weekly)	1,354	11
regular (5-7x weekly)	137	1
Diet, n=12,122		
normal	11,906	98
vegetarian	194	2
vegan	20	0

Table 2. Demographic data II.

Parameters	Mean (SD)	median	Q1-Q3
Age (years) n=12,343	59.1 (11)	60	52-67
Height (cm) n=12,343	169.9 (9)	170	164- 177
Weight (kg) n=12,335	81.5 (13)	80	72 - 90
BMI (kg/m²) n=12,190	28.2 (4)	28.5	25.6 - 31.3
Systolic blood pressure (mmHg) n=12,383	147.6 (16)	148	138 - 160
Diastolic blood pressure (mmHg) n=12,373	88.3 (10)	90	80 - 95
Pulse beat/min n=12,333	75.8 (10)	76	68 - 82
Pulse Pressure n=12,369	59.3 (13)	60	50 - 70
Duration of hypertension (years) n=12,103	8.8 (6)	6	3 - 12
Duration of free combination prior to switch (months) n=11,974	16.8 (15)	12	6 - 24
Dosages (free combination)			
Bisoprolol (mg daily) n=12,244	5.5 (2)	5	5 - 5
Amlodipine (mg daily) n=12,251	6.1 (2)	5	5 - 5
Dosages FDC			
Bisoprolol (mg daily) n=12,244	5.8 (1.5)	5	5 - 5
Amlodipine (mg daily) n=12,251	6.3 (2)	5	5 - 10
Time of FDC prior to recruitment (weeks) n=12,041	4.9 (15)	4	4 - 6

Table 3. Comparison of dosing between free and fixed-dose combination.

	Free combination n=11,869 n (%)	FDC n=11,818 n (%)
Bisoprolol 5 mg/Amlodipine 5 mg	8,498 (72)	7,690 (65)
Bisoprolol 10 mg/Amlodipine 5 mg	729 (6)	933 (8)
Bisoprolol 5 mg/Amlodipine 10 mg	2,031 (17)	2,222 (19)
Bisoprolol 10 mg/Amlodipine 10 mg	611 (5)	973 (8)
Daily Doses	Mean (SD) Median; Q1-Q3	Mean (SD) Median; Q1-Q3
Bisoprolol mg/d	5.5 (1.5) 5; 5-5	5.8 (2) 5; 5-5
Amlodipine mg/d	6.1 (2) 5; 5-5	6.3 (2) 5; 5-10

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

Adherence N=11,429	N	%
Excellent (>90% of prescribed tablets taken)	9,610	84
Good (76-90% of prescribed tablets taken)	1,689	15
Moderate (51-75% of prescribed tablets taken)	107	1
Bad (<50% of prescribed tablets taken)	23	
Total	11,429	100.0
Good to excellent (≥76%) adherence	11,299	99

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

	SBP (mmHg)	DBP (mmHg)	Pulse pressure (mmHg)	Heart rate (bpm)
	N Mean (SD) median Q1 - Q3	N Mean (SD) median Q1 - Q3	N Mean (SD) median Q1 - Q3	N Mean (SD) median Q1 - Q3
Visit I (Study start)	12,383 147.6 (16) 148 138 - 160	12,373 88.3 (10) 90 80 - 95	12,369 59.3 (13) 60 50 - 70	12,333 75.8 (10) 76 68 - 82
Visit IV (after 6 months)	11,472 131.2 (10) 130 125 - 139	11,463 78.9 (7) 80 75 - 83	11,457 52.3 (10) 50 45 - 60	11,408 68.4 (7) 68 64 - 72
Difference mean+/-SD	11,433 16.5 (15) 15 5 - 27	11,417 9.5 (11) 10 0 - 16	11,407 7.1 (14) 5 0 - 15	11,322 7.7 (10) 7 0 - 14
Cohen's effect size	1.26	1.04	0.6	0.85

*Cohen's Effect-size: 0.2 =small, 0.5 =medium, 0.8 =large

Table 6. Changes in blood and pulse pressure values.

	Increase >10 mmHg	Increase 0-10 mmHg	Decrease 1-10 mmHg	Decrease >10 mmHg
	N (%)	N (%)	N (%)	N (%)
SBP	554 (5)	1,478 (13)	3,031 (27)	6,370 (55)
DBP	630 (5)	2,468 (22)	4,064 (36)	4,255 (37)
Pulse Pressure	1,279 (11)	3,053 (27)	3,614 (32)	3,461 (30)

Table 7. Blood pressure, pulse pressure and heart at study start and after 6 months' FDC treatment per BMI group.

	Group 1 BMI <19 kg/m ²	Group 2 BMI >19-25 kg/m ²	Group 3 BMI >25-30 kg/m ²	Group 4 BMI >30 kg/m ²
Study Start	n mean ± SD median; Q1 - Q3	n mean ± SD median; Q1 - Q3	n mean ± SD median; Q1 - Q3	n mean ± SD median; Q1 - Q3
Systolic blood pressure (mmHg)	32 144.3 ± 19 141; 130-157	2322 144.8 ± 16 143.5; 132-155	6527 147.2 ± 15 146; 138-160	3277 150.3 ± 16 150; 140-160
Diastolic blood pressure (mmHg)	32 86.1 ± 12 89; 72.5-99	2319 86.7 ± 10 87; 80-95	6527 88.2 ± 10 90; 80-95	3272 89.8 ± 11 90; 80-100
Pulse pressure (mmHg)	32 58.3 ± 13 60; 50-65	2319 58.1 ± 13 56; 50-65	6528 59.1 ± 12 60; 50-65	3271 60.5 ± 13 60; 50-70
Heart rate (bpm)	32 73.2 ± 11 72; 63-81	2315 75.1 ± 11 75; 68-80	6528 75.8 ± 10 76; 68-82	3267 76.3 ± 10 76; 69-84
After 6 months				
Systolic blood pressure (mmHg)	29 128.3 ± 12 130; 120-130	2097 130.3 ± 10 130; 120-138	6030 131.1 ± 10 130; 125-138	3090 131.8 ± 10 130; 125-140
Diastolic blood pressure (mmHg)	29 76.6 ± 7 77; 70-80	2093 78.5 ± 7 80; 75-82	6030 78.9 ± 7 80; 75-82	3088 79.3 ± 7 80; 75-85
Pulse pressure (mmHg)	29 51.6 ± 9 50; 45-60	2092 51.8 ± 10 50; 45-60	6027 52.2 ± 10 50; 45-60	3086 52.5 ± 10 50; 45-60
Heart rate (bpm)	29 66.7 ± 7 65; 61.5-72	2091 68.3 ± 7 68; 64-72	5995 68.4 ± 7 68; 64-72	3086 68.3 ± 7 68; 64-72

At study start, 3,664 patients (30%) were not blood pressure controlled. After six months of treatment, this was only the case in 130 patients (1%). The positive effect of the FDC treatment on blood pressure, pulse pressure and heart rate was true for all BMI groups (Table 7). Data on preference is available for 7,982 patients. Thereof, 7,184 (90%) declared they would prefer treatment by the fixed combination.

Adverse events

Totally, 101 adverse events were reported. Most the adverse events were peripheral swelling [24] and joint swelling [11], followed by bradycardia, dizziness, and headache (5 each). Only 8 adverse events were considered serious, three cases of atrial fibrillation (one not related), two cases of cardiac failure, one case of cerebrovascular insufficiency, one case of angioedema and one head injury leading to death (not related) (Table 7). Totally, only 9 patients out of 12,424 patients (0.07%) discontinued the study due to adverse events.

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

Discussion

In long-term treatment of chronic diseases, such as hypertension, patient adherence is a severe problem. Patients often fail to control their blood pressure because they do not comply with pharmacologic therapy [19]. 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. On the other hand, strict blood pressure control is crucial to decrease the risk for cardiovascular events, particularly in hypertensive patients with additional risk factors such as type 2 diabetes. The general goal of antihypertensive therapy is to minimize the risks associated with blood pressure elevation without adversely affecting quality of life.

The importance of achieving goal BP in individual patients cannot be overemphasized. In major clinical trials, small differences in on-treatment BP frequently translate into major differences in clinical event rates. Recent data also suggest that inadequate BP control is itself an independent risk factor for the development of diabetes in hypertensive patients [20]. The biggest advantage of the FDC of bisoprolol and amlodipine is the reduction of tablets to be taken. It could be, therefore, assumed that the FDC will improve patient adherence [17,18]. 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 [21].

First analyses of Polish patient populations from this study [17,19] demonstrated already 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. This reinforces previous data with improved adherence under FDC [22]. With a sample size of more than 12,000 patients from six European countries, the present multicenter study can be considered as representative, covering a wide range of ages. 22% of patients were aged

below 50 years and 16% were older than 70 years, so that, as expected, most patients suffering from high blood pressure were between 50 and 70 years of age.

In this patient population, 30% of the patients was not blood pressure controlled at study start. There was a clinically relevant reduction of systolic and diastolic blood pressure values during the study. This may be at least partly due to the good to very good adherence in 99% of the patients under the FDC. Same is true for the pulse pressure and heart rate. The high acceptance of the FDC by the patient was also shown by the fact that 90% of the patients preferred the FDC to the free combination at study end.

Conclusion

The FDC of bisoprolol and amlodipine leads to an excellent patient adherence. Patients enrolled in the study also demonstrated good blood pressure control under the FDC that is crucial in the risk reduction of cardiovascular events.

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.

U. Hostalek contributed to the conception and design of the study. EMW Koch and U. Hostalek were involved in the data analysis and interpretation. EMW Koch drafted this article. No assistance in the preparation of this article is to be declared.

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