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Research Article

Fixed Dose Combination (FDC) of Bisoprolol and Amlodipine in Daily Clinical Practice in Romania: Adherence and Acceptance

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Abstract

Objective: This non-investigational study had the primary goal to assess the adherence of patients with hypertension to the fixed dose combination (FDC) of bisoprolol and amlodipine in daily practice. Secondary objectives included the assessment of blood pressure, pulse pressure values and heart rate before and after 6 month.

Material and Methods: Patients eligible for recruitment were over 18 years of age, had essential hypertension. They had already been switched from a free combination of bisoprolol 5 - 10 mg/d and amlodipine 5 - 10 mg/d to the FDC at least 4 weeks prior to recruitment, and gave informed consent.

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%.

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 (466; 59%) than female (321, 41%) patients. The mean age was 59,9 years with a Q1 - Q3 interval of 51 to 68 years. The youngest patient was 22 years and the oldest 87 years old. All patients had been pretreated once daily with a free combination of bisoprolol (mean 5.2 mg) and amlodipine (mean 6.2 mg). In most patients, the doses were not changed at the switch to the FDC.

Over the 6 months of treatment, the adherence of 85% of the patients was good to excellent, although it should be pointed out that a larger proportion of the physicians failed to provide precise information.

Potentially due to the still good adherence, there was a 23.5 mmHg reduction in mean systolic and a 12.5 mmHg reduction in mean diastolic blood pressure after 6 months compared to study start. The benefits of patient adherence on blood pressure control are also confirmed by the improvement of the pulse pressure by an average 17% after 6 month of treatment.

None of the ADR (2 patients with peripheral edema) 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 ConcorAM may contribute to better blood pressure control and, thus, to risk reduction for cardiovascular events.

Keywords: *Adherence; Hypertension; Bisoprolol; Amlodipine; Fixed Dose Combination*

Introduction

Arterial hypertension is one of the most prevalent cardiovascular diseases in the industrialized world [1]. Thus, hypertensive patients must be treated to achieve an optimal reduction of the blood pressure values to minimize the risk of cardiovascular complications [2].

The European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines recommend the use of two-drug combinations as an initial treatment step, and the possible addition to the antihypertensive treatment regimen of lipid-lowering and antiplatelet agents (Mancia., *et al*. 2013).

The treatment with antihypertensive drugs should be started in all patients with a systolic blood pressure (SBP) of l 40 mmHg or more and/or a diastolic blood pressure (DBP) of 90 mmHg or more. However, in patients with diabetes or a history of cardiovascular or renal disease drug treatment should be initiated within a lower BP range (>130/85 mmHg) aiming at achieving SBP/DBP values < l 30/80 mmHg [2].

The 2007 ESH/ESC guidelines state that diuretics, ACE inhibitors, calcium antagonists, angiotensin receptor antagonists, and beta blockers can all be considered suitable for initiation of antihypertensive treatment, as well as for its maintenance [2].

A combination of two complementary agents improves response rates through blockade of more than one physiologic pathway [3,4]. In this respect, better reductions of the blood pressure values can be realized [5,6].

A meta-analysis of 42 trials with about 11000 patients showed that combining two different antihypertensive classes gives approximately five times greater additional fall in BP than doubling the dose of a single drug (Wald., *et al*. 2009). However, this more complex prescription for medication is often associated with the risk of jeopardizing patients' adherence [7].

Thus, a fixed dose combination (FDC) tablet of the beta blocker bisoprolol and the calcium channel blocker amlodipine in the strengths of 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg was developed as substitution therapy for patients, whose blood pressure can be adequately controlled by simultaneously given amlodipine and bisoprolol of the same doses.

A first open, non-comparative study with the fixed combination of bisoprolol and amlodipine was carried out by Metha., *et al*. [8] in 106 patients suffering from mild to moderate essential hypertension. Patients were treated with a fixed dose combination of 2.5 mg bisoprolol and 5mg amlodipine (dosage strength available in India only) once daily for 8 weeks. In case of insufficient therapeutic effect after 7 or 15 days, this dose could be doubled. Treatment response was defined as a SBP below 140 mmHg and a DBP below 90 mmHg. Mean SBP and DBP were significantly lower after end of treatment compared to baseline ($p < 0.0001$). Responder rate was 89%.

Further experiences with a fixed dose combination of bisoprolol and amlodipine were gained in an observational study in 801 patients with stage II essential hypertension [9]. Patients received a fixed-dose combination of 5 mg bisoprolol and 5 mg amlodipine once daily for four weeks. Mean SBP decreased significantly from a baseline of 171.9 ± 17.9 mmHg to 152.9 ± 16.4 mmHg, 142.1 ± 13.1 mmHg and 134.3 ± 10.1 mmHg after 1, 2 and 4 weeks, respectively (all $p < 0.001$). Mean DBP fell from 103.9 ± 9.6 mmHg at baseline to 93.5 ± 8.8 mmHg, 88 ± 7.3 mmHg and 83.4 ± 6.2 mmHg after 1, 2 and 4 weeks, respectively (all $p < 0.001$). Excellent to good efficacy and tolerability were scored in 91.4% and 90.3% of the patients. The authors conclude that the daily application of a fixed-dose combination of bisoprolol and amlodipine in stage II essential hypertension is effective, safe and well tolerated.

As the most important advantage of a FDC is the expected better patient adherence, but 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. Similar studies with Polish patients [10], with patients from six countries in Eastern Europe [11], and with patients from the Czech Republic [12] have recently been reported.

Trial Design

As the study purpose was to gain data on the adherence of the FDC bisoprolol and amlodipine in daily practice, an observational study design was chosen.

Material and Methods

In the context of this non-interventional study, hypertensive patients aged over 18 years who had been switched from a free combination of bisoprolol and amlodipine to the FDC at least 4 weeks before recruitment were selected. The patients were informed in writing and verbally about the nature, the significance and the scope of the study. A written declaration of consent was a prerequisite for participation. Patients also agreed that their pseudonymized data may be used for statistical evaluation and publication. No additional treatment measures that differed from the clinically appropriate management of the patients were prescribed. Any additional medications or non-pharmacological treatment measures required were used in accordance with medical instructions; co-administration of any other antihypertensive was considered an exclusion criterion.

Blood pressure measurements were taken in the upright seated position after a 5-minute rest period. Patients were given a prescription for a specified number of tablets for the treatment period up to the next follow-up visit (mandatory after 6 months) and their consumption was checked.

The recording of findings from the screening examinations was repeated after 6 months and the results documented. The entries in the case report forms were transferred to the BIAS (Biometric Analysis of Samples, Hanns Ackermann, Frankfurt) analysis program and used for comparative analyses. For all parameters, mean, standard deviation, median, and quartiles were calculated. Tests were Gaussian distribution, Spearman correlation, Mantel Haenszel test for contingency tables, t-test for paired values (parametrics), Wilcoxon matched pairs-test (non-parametric), as well as Cohen's D for effect size were used.

Results

801 hypertensive patients were recruited for the study in Romania. In 15 patients, the documentation of data was too poor for any evaluation. The remaining 786 patients provided sufficient data and had been previously prescribed bisoprolol and amlodipine in free combination and had been switched to the FDC at least four weeks prior to recruitment.

Table 1 summarizes patient data at baseline.

Parameter	N (%)
Participants	786
Female	466 (59)
Male	320 (41)
Co-morbidities	
Cardiovascular disease, n = 750	516 (69)
Type 2 diabetes, n = 782	75 (10)
Liver disease, n = 691	30 (4)
Renal disease, n = 682	14 (2)
Smoking habits, n = 780	
No smoker	560 (72)
Smoker	90 (11)
Ex-smoker	130 (17)
Alcohol intake, n = 748	
No	473 (60)
Little	211 (27)
Moderate	94 (12)

Table 1: *Demographic data I.*

There were 59% female and 41% male patients. The mean age was 59.9 years with a broad range. The youngest patient was 22 years and the oldest 87 years old.

There was a high number of patients with concomitant cardiovascular disease (69%) and/or type 2 diabetes (10%). 389 (53%) of the patients were overweight (BMI > 25) and another 188 (26%) obese (BMI > 30).

Almost all patients had been pretreated once daily with a free combination of bisoprolol (mean 5.2 mg ± l) and amlodipine (mean 6.2 mg ± 3). The majority of patients (71%) 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 11.7 months ± l4. The mean duration of the hypertension was 6.2 ± 5 years.

In table 2, a supplementary compilation of demographic data and outcomes of the study participants prior of the study beginning is given.

Parameter	Mean (SD)	Median	Range
Age (years), n = 775	59.9 (11)	60	22 - 87
Height (cm), n = 776	167.5 (8)	168	145 - 191
Weight (kg), n = 783	80.1 (14)	80	48 - 180
BMI (kg/m^2), n = 772	28.6 (4)	28	16.6 - 47.3
Cardiac parameters			
Systolic blood pressure (mmHg), n = 786	157.9 (18)	160	115 - 250
Diastolic blood pressure (mmHg), n = 786	89.4 (10)	90	58 - 120
Pulse pressure (mmHg), n = 786	68.6 (15)	70	20 - 130
Heart rate (beats/min), n = 780	77.8 (11)	78	48 - 160
History of hypertension			
Duration of hypertension (years), n = 773	6.2 (5)	5	3 - 9
Duration of free combination (months), n = 773	11.7 (14)	7	---
Dosages in free combination			
Bisoprolol (mg/day), n = 764	5.2 (1)	---	5 - 10
Amlodipine (mg/day), n = 758	6.2 (3)	---	5 - 10
Time of FDC prior to recruitment (weeks),	4.4 (2)	4	4 - 23

Table 2: *Demographic data II.*

The systolic blood pressure values exceeded in 77% of the study participants the threshold of 140 mmHg. Thus, more than three quarters of the patients was not blood pressure controlled at study start. Regarding diastolic blood pressure, in 33% of the patients more than 90 mmHg were measured.

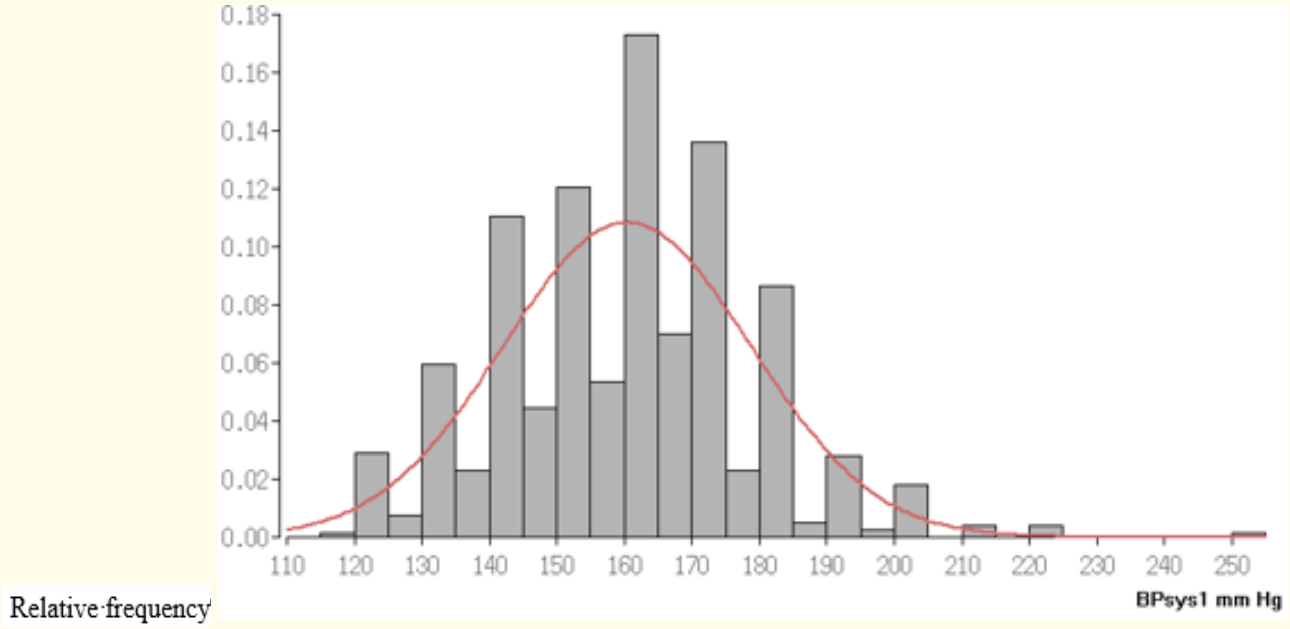

Figure 1: *Distribution of systolic blood pressure at study start. Systolic blood pressure distribution (Chi square).*

Table 3 compares the dosage strengths of bisoprolol and amlodipine in free and fixed-dose combination.

n = 711	Free combination, n (%)	Fixed dose combination, n (%)
Bisoprolol 5 mg/Amlodipine 5 mg	507 (71)	519 (73)
Bisoprolol 10 mg/Amlodipine 5 mg	32 (5)	31 (4)
Bisoprolol 5 mg/Amlodipine 10 mg	166 (23)	160 (23)
Bisoprolol 10 mg/Amlodipine 10 mg	6 (1)	1 (1)
Daily dose (mg/day)	**Mean (SD)**	**Mean (SD)**
Bisoprolol, n = 722	5.3 (1)	5.3 (1)
Amlodipine, n = 711	6.1 (2)	6.1 (2)

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

With either the free combination or the FDC, more than 70% of the patients took the lowest possible dose combination. When switching from the free to the fixed dose combinations changes in single dose of bisoprolol and amlodipine were performed in 8 patients for bisoprolol (1.1%) and in 302 patients (42.5%) for amlodipine. In 136 patients (19.1%), the amlodipine dose was increased and in 166 patients (23.3%) decreased. For 75 patients (10.6%), no comparative dose information was available.

According to the inclusion criteria, patients had to be on the FDC ConcorAM at least 4 weeks prior to study start. This criterion was met by all patients. Mean time of FDC treatment prior to study start was 4.4 (SD +/-2) weeks.

Exact or complete data on the adherence of the patients could only be registered in 268 patients (34%). The data is summarized in table 4.

Adherence, n = 268 (Missing data 518)	N (%)
Excellent (> 90% of prescribed tablets taken)	171 (63)
Good (76 - 90% of prescribed tablets taken)	59 (22)
Moderate (51 - 75% of prescribed tablets taken)	3 (1)
Poor (< 50% of prescribed tablets taken)	35 (13)
Total	268 (100)
Good to excellent (> 76 of prescribed tablets taken)	230 (86)

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

It was expected that more than 90% of the patients at Visit 3 show an excellent to good adherence. Actually, the adherence of 86% of the patients was good to excellent. Thus, at least for the 34% of patients with available data, the expectation was not fully met.

Table 5 shows that the values for systolic blood pressure, diastolic blood pressure, pulse pressure, and heart rate considerably decreased under the six-month treatment with the FDC.

	SBP (mmHg) n = 766	DBP (mmHg) n = 763	Pulse pressure (mmHg) n = 763	Heart rate (beats/min) n = 757
	Mean (SD) median range	Mean (SD) median range	Mean (SD) median range	Mean (SD) median range
Visit 1 (study start)	157.9 (18) 160 115 - 250	89.4 (10) 90 58 - 120	68.6 (15) 70 20-139	77.8 (11) 78 48 - 160
Visit 2 (after 6 months)	134.1 (13) 130 100 - 180	77 (8) 80 50-100	57.2 (12) 55 30-110	66.8 (6) 66 50 - 92
Difference, mean (SD)	-23.5 (18)	-12.5 (11)	-12 (19)	-10.9 (10)
Cohen's effect size*	1.3	1.1	0.66	1.0
*Cohen's Effect-size: 0.2 = small, 0.5 = medium, 0.8 = large				

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

Data from Table 5 show that the values of systolic blood pressure, diastolic blood pressure, pulse pressure and heart considerably decreased under the six-month treatment with the FDC.

The systolic blood pressure decreased in 678 patients (88%). In only 36 cases (5%), there was an increase, and the SBP remained unchanged in 52 patients (7%).

The diastolic blood pressure be decreased in 80% of the patients, increased in 7% and remained unchanged in 13%, whereas the pulse pressure decreased in 69%, increased in 15% and remained unchanged in 16% of the patients.

The clinically relevant improvements in SBP and pulse pressure can be clearly demonstrated by allocating the patients at study start and after 6 months to defined pressure groups (Table 6).

Systolic Blood Pressure			Pulse Pressure		
	Study start	After 6 moths		Study start	After 6 moths
	n (%)	n (%)		n (%)	n (%)
< 145 mmHg	213 (28)	645 (84)	< 20mmHg	298 (39)	147 (19)
146 - 160 mmHg	265 (35)	106 (14)	21 - 60 mmHg	188 (25)	458 (60)
161 - 170 mmHg	155 (20)	9 (1)	61 - 79 mmHg	148 (19)	143 (19)
> 170 mmHg	133 (17)	6 (1)	> 79mmHg	129 (17)	15 (2)
Total	766 (100)	766 (100)	Total	763 (100)	763 (100)

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

On questioning, 89% of the study participants declared they would prefer treatment with the fixed combination, 10% did not see any advantage and only 1% preferred the free dose combination.

The FDC was well tolerated in this study. There were two cases of treatment-related peripheral edema, in both cases non-serious. Both patients recovered after one and four weeks, respectively.

There were no significant changes in the parameters fasted plasma glucose, HbA_{1C}, serum creatinine, GOT (AST), and GPT (ALT) documented during the study.

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 [13]. 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 in order 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 [14].

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 [13,14].

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 [14].

The effectiveness of the combination of bisoprolol and amlodipine has been duly established in clinical studies. However, the specific issue of such studies with a strict selection of well-defined patients limits more or less the validity of the results on this selected group.

In daily practice, however, the physician has to encounter individuals of different ages with different initial findings, comorbidities, concomitant medications and lifestyle habits.

In order to meet the possibilities and limitations of antihypertensive treatment under these circumstances, studies with a large number of cases are required and there must be recruited patients with virtually no limitations of the daily practice. Such studies can only be performed multi-centric.

First analyses of patient populations from other countries participating in this study [10-12] 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. This reinforces previous data with improved adherence under FDC [7].

Data of the present study confirmed a good adherence under the FDC, although the expectation of at least 90% of patients with good or excellent adherence after 6 months could not be met. This is in clear contrast to the previous publications [10-12], in whom 97 to 98% of the patients showed excellent or good adherence. This difference may be due to poor data documentation in the Romanian patients since adherence data after 6 months were only available for 268 (34%) of the patients.

Despite the lower documented adherence, there were clinically relevant improvements in blood pressure and heart rate. At study start, most the patients were not blood pressure controlled. There was a clinically relevant reduction of systolic and diastolic blood pressure values during the study, probably due to the still relatively good adherence. 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 89% of the patients preferred the FDC over the free combination at study end.

The study results suggest that the FDC ConcorAM may improve adherence and lead to better blood pressure control and, thus, to risk reduction for cardiovascular events.

Conclusion

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

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