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Efficacy, safety, and tolerability of antihypertensive therapy with aliskiren/amlodipine in clinical practice in Austria. The RALLY (Rasilamlo long lasting efficacy) study

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Summary
Background This observational study evaluated the efficacy and tolerability of 3-month aliskiren/amlodipine therapy under outpatient conditions.

Methods This Austria-wide observational study included 579 hypertensive patients (566 [98 %] who could be analyzed biometrically) under the care of 140 physicians. The average age of the patient collective was 64 ± 11 years and the mean duration of hypertension was 10 ± 7 years. Regarding 92 % of the study participants, an antihypertensive therapy already existed. Efficacy was assessed in accordance with the Austrian hypertension guidelines while tolerability was evaluated on the basis of adverse events. A descriptive physician judgment based on efficacy, tolerability, and compliance was available for 539 patients (95 %). Office blood pressure values were used for the evaluation.

Results On average, the systolic and diastolic blood pressures were reduced from 161 ± 14 to 135 ± 10 mmHg and 93 ± 9 to 81 ± 6 mmHg, respectively. Blood pressure values of < 140/90 mmHg and < 130/80 mmHg were achieved in 56 and 7 % patients, respectively. A subgroup analysis of 242 patients (43 %) with diabetes mellitus and/or renal disease, as well as those with a high cardiovascular risk, demonstrated nearly identical results compared to the total population. Overall, 44 adverse events were documented in 41 patients, and physicians reported that 94 % of patients were compliant in a final survey on evaluation of therapy.

Conclusion The fixed-dose combination of aliskiren/amlodipine provided clinically relevant blood pressure reductions along with good tolerance and compliance. During the 3-month duration of observation under outpatient conditions, it was seen that aliskiren and amlodipine reduced the systolic and diastolic blood pressures on average by 26 and 13 mmHg, respectively.

Keywords Hypertension · Observational study · Aliskiren/amlodipine · Fixed-dose combination therapy · Renin–angiotensin–aldosterone system (RAAS)

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Introduction

Arterial hypertension affects about 1 billion people worldwide and, as a substantial risk factor for cardiac, cerebrovascular, and renal diseases, is still the leading cause of death [1]. One-fifth of the population (21 %) in Austria is affected by this disease, and the prevalence clearly rises to 48 % in the age group over 60 years [2]. In cases of uncomplicated hypertension, the Austrian guidelines recommend a target blood pressure of < 140/90 mmHg, while a level of < 130/80 mmHg is still presently recommended for those demonstrating hypertension along with diabetes mellitus, renal insufficiency, or a high cardiovascular risk (stroke or myocardial infarction in their medical history) [3]. This has meanwhile changed in the recently published European guidelines for the treatment of hypertension: with diabetes, cardio/cerebrovascular diseases, peripheral arterial occlusive disease, metabolic syndrome, or renal disease, a target systolic blood pressure of < 140 mmHg is recommended, while a level of < 130 mmHg is to be strived for only in the event of an evident proteinuria [4]. A diastolic blood pressure of < 90 mmHg is always to be targeted, while a level of < 85 mmHg is only recommended for patients with diabetes [4]. In order to reach such blood pressure target val-

ues, especially in patients demonstrating systolic blood pressure values >160 mmHg and with a high cardiovascular risk, it is reasonable to initiate a combination antihypertensive therapy early [4]. Thereby, the therapeutic goal can be achieved faster and the rate of cardiovascular events can be consequently decreased [5, 6].

Because of the multifactorial nature of hypertension, combinations of at least two active substances with different modes of action are preferred [3, 4], with one agent based primarily on the renin–angiotensin–aldosterone system (RAAS), which plays a large role in blood pressure regulation as well as in the pathogenesis of hypertension. A likely selection is the combination of the direct renin inhibitor aliskiren with the calcium-channel blocker amlodipine. While amlodipine inhibits the influx of calcium into the muscle cells of vessels, thereby preventing vasoconstriction and decreasing vessel resistance, aliskiren works at the origin of the RAAS through direct renin blockade, thereby suppressing angiotensin II production. The combination of aliskiren and amlodipine results in an efficient and long-persisting blood pressure reduction [7]. Both substances have long-term half-lives (aliskiren, about 50 h and amlodipine, about 40 h) in comparison with other antihypertensive agents [7]. Continuous blood pressure control is thereby guaranteed for more than 24 h, which is particularly important in the early morning hours during which blood pressure frequently rises and can cause a heart attack or stroke [8]. More intensive reduction in blood pressure through the aliskiren/amlodipine combination therapy compared with the respective monotherapies is well documented [9]. Moreover, amlodipine can also be considered to demonstrate end-organ protection, which is supported by well-documented data [10–12]. The rationale for the present observational study, was the recording of efficacy and tolerability of a 3-month antihypertensive therapy with aliskiren/amlodipine under outpatient conditions.

Patients, materials, and methods

The RALLY study was an observational study carried out from October 1, 2011 to April 30, 2012. A total of 140 physicians in private practices for general or internal medicine participated in this study. Each physician's office received study records for five patients with hypertension, while the duration of observation of the patients was set for 3 months.

As of January 10, 2012, the basic conditions had to be changed because the application of aliskiren in combination with angiotensin receptor blockers (ARBs) or angiotensin converting enzyme inhibitors (ACEIs) in patients with diabetes mellitus or impaired renal function had been recognized as a new contraindication. The study physicians were informed that (i) no new patient should be recruited, (ii) aliskiren/amlodipine for patients under simultaneous ACEI or ARB therapy should be discontinued, and (iii) only patients without such comedications should continue.

Observational data

The characteristics to be evaluated involved blood pressure and pulse values (as measured in the physician's office), the administered dose of aliskiren/amlodipine (and other relevant medications), as well as the reported adverse events (AEs). Demographic as well as history data were collected. The recommended dose of aliskiren/amlodipine is 150/5 or 150/10 mg, and should be administered once daily, preferably in the morning. Physicians did choose the dosage at their discretion and in agreement with the patients. In the course of this study, the following characteristics and data were documented in a total of three visits: patient data, history, previous medication, current medication, heart rate, blood pressure, and weight at visit 1 and current medication, heart rate, blood pressure, weight, and undesirable events at visits 2 and 3.

Efficacy

The National Guidelines of the Austrian Society for Hypertension, 2007, were applied during the study and during the preparation of this manuscript. The proportion of patients found to be within the blood pressure target values for aliskiren/amlodipine was evaluated according to the efficacy, defined as <140/90 mmHg as well as <130/80 mmHg for patients with diabetes and/or renal disease as well as for high-risk patients (e.g., after stroke or myocardial infarction).

Tolerability

The evaluation of tolerability was made by a descriptive analysis of all AEs. Reported or observed AEs were documented in an observation form, including the date of start and end of the AE along with the cause and outcome of the aliskiren/amlodipine treatment. A severe adverse event (SAE) was to be additionally reported in the form according to the Pharmacovigilance Ordinance.

Treatment satisfaction

Efficacy, tolerability, and compliance (adherence to therapy) of the aliskiren/amlodipine therapy were finally assessed descriptively by the study physicians. The attributes for this physician evaluation that could be selected were very good, good, satisfactory, or unsatisfactory.

Statistical analysis

All study variables were evaluated descriptively and statistically. Mean, standard deviation, median, quartiles, minimum and maximum values, as well as frequencies were summarized in a table. The changes of the goal variables of blood pressure values over the observation time

Table 1 Patient demographics and baseline characteristics

a) Patient data (*n*=566)	Male		Female		Overall	
Age (years)—*n*, mean ± SD	300	61.4 ± 10.7	261	66.5 ± 11.4	561	63.8 ± 11.3
<65 years—*n*, %	180	59.4 %	199	38.0 %	280	49.5 %
≥65 years—*n*, %	120	39.6 %	161	61.2 %	281	49.6 %
Missing data—*n*, %	3	1.0 %	2	0.8 %	5	0.9 %
Gender—*n*, %	303	53.5 %	263	46.5 %	566	100 %
Height (cm)[a]—*n*, mean ± SD	302	176 ± 6.4	263	163.5 ± 6.0	565	170.2 ± 8.8
Weight (kg)[a]—*n*, mean ± SD	302	90.9 ± 14.5	263	75.5 ± 13.2	565	83.8 ± 15.8
BMI[a]—*n*, mean ± SD	302	29.2 ± 4.5	263	28.3 ± 4.8	565	28.8 ± 4.7
Hypertension for (years)—*n*, mean ± SD	291	9 ± 7.0	250	10.1 ± 7.7	541	9.6 ± 7.3
Missing data—*n*, %					25	4.4 %
b) Medical history data	***n***			**%**		
Essential hypertension	528			93.3 %		
Predisposing factors *(multiple citations, sorted according to frequency):*						
Hypercholesterolemia	376			66.4 %		
Cardio/cerebrovascular co-morbidity (CVD, PAOD, heart failure, status post insult/TIA, status post MI)	269			47.5 %		
Abdominal circumference (men ≥102 cm, women ≥88 cm)	245			43.3 %		
Nicotine abuse	199			35.2 %		
Diabetes mellitus	198			35.0 %		
Metabolic syndrome[b]	134			23.7 %		
Renal insufficiency (microalbuminuria, chron. renal insufficiency)	90			15.9 %		
Antihypertensive medications to date:						
None	45			8 %		
Yes	521			92 %		

SD standard deviation, *BMI* body mass index, *CVD* cardiovascular disease, *PAOD* peripheral arterial occlusive disease, *TIA* transient ischemic attack, *MI* myocardial infarction
[a]One missing data
[b]Defined as adiposity, hypertension, dyslipidemia, insulin resistance

period were compared by means of Friedman's as well as Wilcoxon's tests. Comparisons between the subgroups were analyzed by means of the chi-square test as well as the Mann–Whitney U-test. These tests and the resultant *p* values were interpreted in a descriptive sense and without any hypothetical evaluation.

Ethics

The RALLY study has been approved by the local ethics committee.

Results

Patient characteristics

Overall, 579 patients from 140 doctors' offices were included in the study. Thirteen patients (2 %) did not have documented data with regard to aliskiren/amlodipine. The results are therefore based on 566 evaluable patient forms. Patient demographics, baseline characteristics, and medical history data are compiled in Table 1. Table 2 shows an overview of the aliskiren/amlodipine medication as well as the number of antihypertensive comedications before and during the study. Altogether, we are dealing with a study population that has had hypertension for quite some time, allowing for a subgroup analysis of 242 high-risk patients.

Efficacy

After 3 months of treatment, a mean blood pressure decrease of 26 mmHg systolic and 13 mmHg diastolic was observed ($p<0.0001$). Blood pressure values of <140/90 mmHg and <130/80 mmHg were attained in 56 and 7 % patients, respectively (Figs. 1 and 2). A detailed analysis according to age groups and gender did not reveal any significant differences in efficacy. At the start of the study, 66 % of the patients received aliskiren/amlodipine at a dose of 150/5 mg and 28 % were given 150/10 mg (Table 2). Three percent of patients received

Table 2 Medication before and during the study

Medication ($n=566$)	**1st visit** (initial values)		**2nd visit** (after approx. 1 month)		**3rd visit** (after approx. 3 months)	
Daily dose of aliskiren/amlodipine:	***n***	***%***	***n***	***%***	***n***	***%***
150/5 mg	371	65.5	270	47.7	247	43.6
150/10 mg	158	27.9	221	39.0	210	37.1
300/5 mg	18	3.2	18	3.2	17	3.0
300/10 mg	19	3.4	27	4.8	31	5.5
No information	–	–	28	4.9	57	10.1
Discontinued	–	–	2	0.4	4	0.7
Antihypertensive co-medication:	***n***	***%***	***n***	***%***	***n***	***%***
None	347	61.3	343	60.6	370	65.4
1	219	38.7	223	39.4	209	36.9
2	56	9.9	54	9.5	45	8.0
≥3	8	1.4	8	1.4	4	0.7

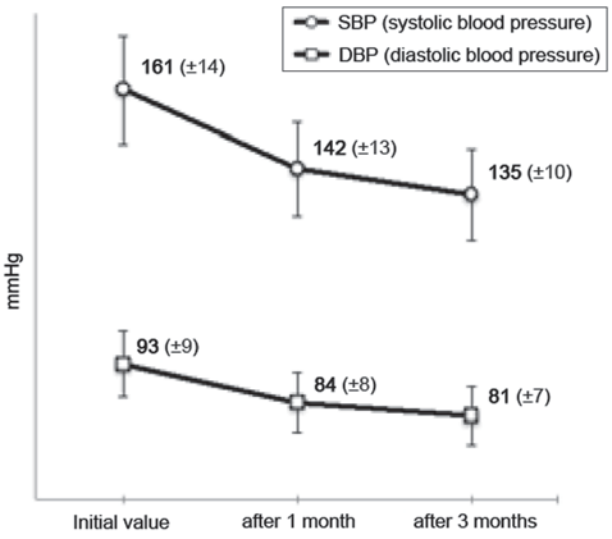

Fig. 1 Blood pressure decrease in mmHg (all patients)

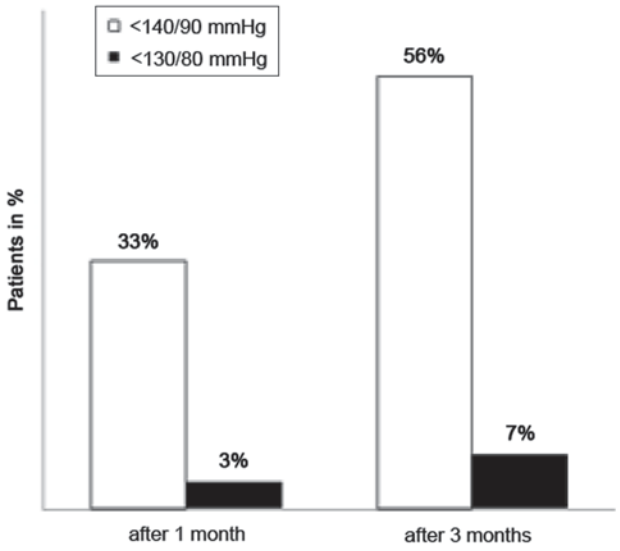

Fig. 2 Proportion of patients (in %) with blood pressure decrease to <140/90 or <130/80 mmHg (all patients)

a daily dose of 300/5 mg and another 3% of patients received 300/10 mg. After 3 months, 44% of the patients received the 150/5 mg dose whereas 37% of the patients received the 150/10 mg dose. On the other hand, 3 and 5.5% patients received the 300/5 and 300/10 mg dose, respectively, after 3 months.

Risk factors were identified in 242 patients (43%), whereby a subgroup analysis was performed (data not shown). Altogether, these 242 high-risk patients demonstrated 376 comorbidities (according to multiple answers). The most frequently cited comorbidity was diabetes mellitus (35%), followed by renal (16%) and cardiovascular diseases (16%). Results in this subgroup indicated that the systolic blood pressure was reduced in average by 25 mmHg and the diastolic blood pressure was reduced in average by 13 mmHg (Fig. 3) ($p<0.0001$), similar to the overall collective. More than half (52%) of the patients in this subgroup attained blood pressure values of <140/90 mmHg and 7% achieved blood pressure values of <130/80 mmHg after 3 months (Fig. 4).

Tolerability

A total of 44 AEs were observed in 41 patients (7%). The most common AEs (10 [23%]) were edemas or swelling of the lower extremities or ankles. Peripheral edemas are a known, dose-dependent side effect of amlodipine, and were also observed under aliskiren/amlodipine therapy. In the framework of the examination, it was not checked whether the edemas/swellings had already existed previously or not; that is to say whether they were the result of

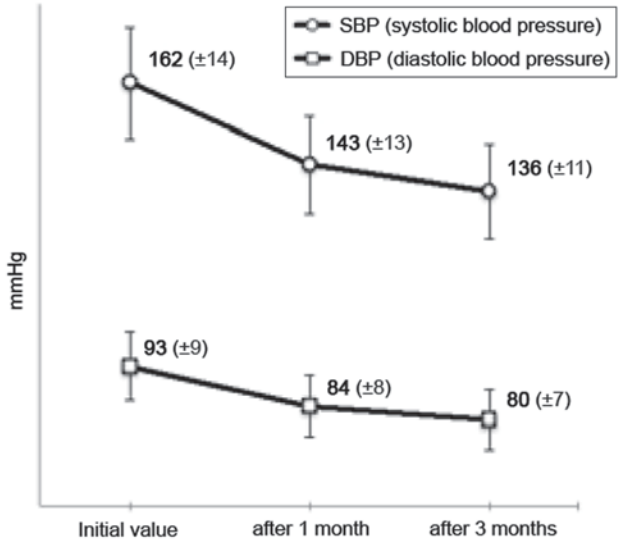

Fig. 3 Blood pressure decrease in mmHg for subgroup of high-risk patients

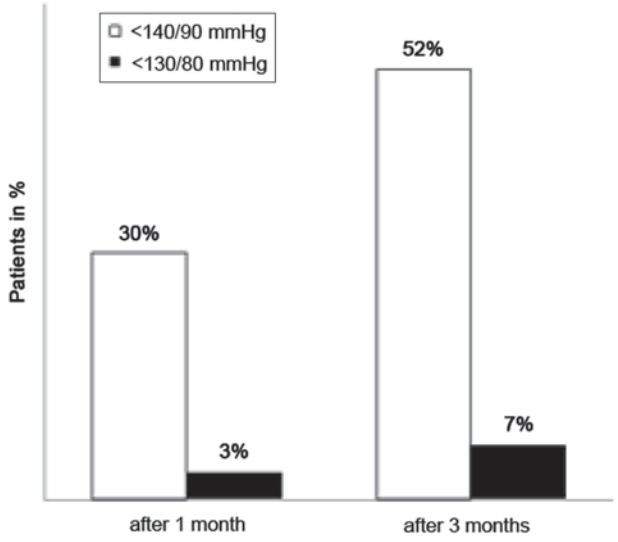

Fig. 4 Proportion of patients (in %) with blood pressure reduction to <140/90 or <130/80 mmHg (subgroup of high-risk patients)

the disease or the treatment. Eight AEs were incidences of increase in diastolic blood pressure, six AEs were incidences of lack of efficacy, and two AEs were incidences of hypotension and increase in pulse rate. None of the AEs were classified as SAEs by the study physicians. A total of seven patients (1 %) discontinued therapy due to their AE. Two fatalities were noted during the study—one patient was murdered and the other died for unknown reasons. According to the investigating physician, the second fatality had no relationship to the aliskiren/amlodipine therapy.

Treatment satisfaction

The final medical evaluation reflected the satisfaction of the study physicians with regard to the efficacy, tolerability, and compliance of the aliskiren/amlodipine therapy. No statements were made in this regard on 6 % of the patient forms. The efficacy was assessed as being very good or good in 90 % of the cases (65 or 25 %, respectively), the tolerability was evaluated as being very good or good in 91 % of the cases (69 or 22 %, respectively) and the compliance was also considered to be very good or good in 91 % of the cases (66 or 25 %, respectively). When accounting for the proportion of patients who evaluated the parameters as "satisfactory" (efficacy 4 %, tolerability 2 %, compliance 3 %), an altogether positive physician evaluation was seen in 94 % of patients for efficacy and tolerability, as well as 93 % for compliance. No information was available for 5 % (efficacy) and 6 % (tolerability, compliance) of the patients. 0.4 % of the patients evaluated the compliance as being "unsatisfactory," while the efficacy and tolerability were each rated to be "unsatisfactory" by 1 % of the patients.

Discussion

It is estimated that the prevalence of hypertension will continue to grow worldwide and that the number of adults with hypertension will increase by 60 % to about 1.6 billion by the year 2025 [13]. In contrast, the problem in Europe is that 73 % of patients with hypertension are untreated and that the target values are not reached in approximately 70 % of the patients with hypertension receiving treatment [14]. The main goal of antihypertensive therapy is to reduce of the overall risk for cardiovascular disease [4]. A systolic blood pressure reduction of 2 mmHg reduces the cardiovascular mortality by 7–10 %, or, expressed differently, the risk of cardiovascular events doubles exponentially with every increase by about 20/10 mmHg [15]. Compliance with therapy plays an important role in reducing blood pressure: 1 year after beginning therapy, the therapeutic adherence drops to just below 60 % and, after the first 10 years, only 40 % of the patients continue to take their medication [16]. Fixed-combination preparations with a single dose are being employed increasingly as they simplify the administration and improve the adherence. The target blood pressure is consequently attained more frequently and the risk of hospitalization is decreased [17].

The present observational study, with the goal of evaluating the efficacy and tolerability of a 3-month aliskiren/amlodipine combination in outpatient settings, revealed a significant average blood pressure reduction of 26 mmHg systolic and 13 mmHg diastolic with a high degree of treatment satisfaction reported by the study physicians (94 % positive final evaluations).

The rate of renal insufficiency seems to be rather low within the examined collective, which could be a reflection of frequent "under diagnosis" demonstrated in a recent study: even in a general internal medicine setting involv-

ing inpatients, renal insufficiency is not recognized in more than 60% of the patients with this illness in spite of the availability of kidney function parameters and is therefore not mentioned in the physicians' discharge letters [18]. In this respect, although Austria is better than other European countries, this could nevertheless have dramatic consequences for the treatment and prevention of chronic renal insufficiency and its associated complications [18].

As a consequence of the continuing increase of hypertension and diabetes mellitus over the past decades, the prevalence of chronic renal insufficiency has also increased [18]. In order to choose the most appropriate medicinal therapies among the myriad of possibilities, it is extremely important that an overall evaluation of all risk factors be carried out. The renal elimination pathways for cardiovascular medications and oral antidiabetic agents, as well as other drugs (e.g., antibiotics, analgesics), must also be considered in this context. From a nephrological point of view, antihypertensive agents with additional protective effects should be favored by all means. The end organ protection of amlodipine on the other hand has been verified many times [10–12]. The combination of aliskiren and amlodipine and their synergistic effects result in a greater reduction in blood pressure than that observed for the respective monosubstances, which is especially beneficial for patients with hypertension who are also suffering from diabetes and/or from impaired renal function [9]. The favorable results of the aliskiren/amlodipine effects seen in the RALLY study are substantiated by the high contentment with the therapy.

Conclusion

Data from the 566 patients enrolled in this observational study provide a good insight into the Austrian real-life practice and demonstrate strong efficacy with aliskiren/amlodipine: A clinically relevant blood pressure reduction was achieved with good tolerability and adherence to therapy (compliance) after 3 months of treatment. These results confirm the clinical study data of the aliskiren/amlodipine combination in a nonselected patient population under the conditions of real-life practice.

Limitations of the study

This study has not yet been subjected to the new regulations that also demand a monitoring in observational studies. Accordingly, it has certain limitations as assessed by present-day criteria, for instance, with regard to side effects (AEs). Whether it was induced pathogenetically or medicinally, a 23% rate of edema is principally not surprising for antihypertensive treatments. Comorbidities such as cardiomyopathy, heart failure, pulmonary hypertension, or renal insufficiency can result in edema, similar to approved and newer antihypertensive agents. The rate of edema in this observational study is consistent with data from other clinical amlodipine studies, although it is greater than that observed in other clinical aliskiren/amlodipine studies [9, 19].

A further limitation of this observational study became clear immediately after beginning the study, when the results of the major clinical endpoint study, ALTITUDE, in patients with diabetes and renal impairment who received either aliskiren or placebo in addition to their antihypertensive therapy (ACE inhibitors or ARBs) were published. The ALTITUDE study was prematurely terminated because a benefit was not foreseeable in the aliskiren group. An interim analysis revealed an elevated risk to the dual RAAS blockade arm, which consequently led to a contraindication of the addition of aliskiren treatment to patients with diabetes mellitus or impaired renal function who are already on either ACEI or ARB therapy. This observation from the ALTITUDE study is consistent with the results with the combination of the ACE inhibitor ramipril with telmisartan in the ONTARGET study [20]. Therefore, the study protocol had to be amended for the RALLY study, and the study investigators were instructed to avoid a simultaneous ACEI or ARB therapy. This amendment certainly influenced the patient number and selection, although the extent to which this was influenced cannot, naturally, be determined.

With reference to the usually necessary administration of several antihypertensive agents—as can be seen in the patient data of the Austrian observational study—the results of the ALTITUDE study are taken into account in the current European recommendations: in order to avoid the risks associated with a double RAAS blockage [4], Aliskiren should not be used in combination with ACE inhibitors or ARBs for hypertensive patients suffering also from diabetes or with renal impairment. This was also taken into account in the framework of the RALLY study thanks to the prompt safety information provided by the study physicians.

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Conflict of interest
A.R. Rosenkranz received speakers fee from Novartis, M. Ratzinger was an employee of Novartis.

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