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Ramipril + amlodipine and ramipril + hydrochlorothiazide fixed-dose combinations in relation to patient adherence

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Abstract

Objective: To compare 1-year treatment adherence of ramipril + amlodipine and ramipril + hydroclorothiazide fixed-dose combination therapies in patients with hypertension.

Methods: Data were extracted from the database of the National Health Insurance Fund of Hungary. Treatment adherence was modelled using survival analysis.

Results: At 2 months after initiation of treatment, 42% of patients using ramipril + hydrochlorothiazide ($n = 28,800$) had discontinued treatment, compared with 0% of patients using ramipril + amlodipine ($n = 10,295$). At 1 year, treatment adherence was 29% in the ramipril + hydrochlorothiazide group and 54% in the ramipril + amlodipine group. The hazard ratio for discontinuing ramipril + hydrochlorothiazide vs ramipril + amlodipine was 2.318 (95% confidence intervals 2.246, 2.392).

Conclusion: Ramipril + amlodipine had significantly higher 1-year treatment adherence than ramipril + hydrochlorothiazide in patients with hypertension.

Keywords

Adherence, antihypertensive therapy, ramipril + amlodipine fixed-dose combination, ramipril + hydrochlorothiazide fixed-dose combination

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Introduction

Cardiovascular disease is a leading cause of mortality in Hungary,[1] and hypertension is one of the most widespread modifiable cardiovascular risk factors. Uncontrolled hypertension leads to cardiovascular target organ damage and disease.[2]

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An appropriate lowering of blood pressure is important for the prevention of cardiovascular complications, but almost half of patients receiving antihypertensive therapy in Hungary do not reach target blood pressure values[3] (according to the 2013 guidelines of the European Society of Hypertension [ESH] and the European Society of Cardiology [ESC][4]). In addition, target blood pressures are lower in patients with high cardiometabolic risk than in low risk patients, requiring the use of combined antihypertensive therapy.[4] Combined therapy is associated with fewer side effects than individual therapy, which may improve patient adherence.[5]

To the best of our knowledge, there have been no studies comparing patient adherence with ramipril + amlodipine and ramipril + hydrochlorothiazide fixed dose combination therapy. The aim of this retrospective study, therefore, was to evaluate adherence to these drug regimens in a group of previously untreated patients with hypertension.

Patients and methods

Study population

This retrospective study included patients with hypertension who were prescribed fixed-dose combinations of ramipril + amlodipine or ramipril + hydrochlorothiazide as initial antihypertensive therapy between 1 October 2012 and 30 September 2013. Patients were required to have not received the study drugs for at least 1 year prior to study entry, and were identified from the database of the single Hungarian health insurance company, the National Health Insurance Fund of Hungary (NHIFH). As the NHIFH covers the entire population, these data can be considered representative of the population of Hungary as a whole.

Study parameters

Prescriptions were followed for 14 months for all patients, with the date of first prescription considered the start of treatment. The percentage of patients remaining on therapy in each given month following the start of treatment was noted, with 2-month discontinuations of medication excluded (60-day grace period).[6] Treatment was considered to be discontinued if a patient did not obtain a repeat prescription for at least 60 days, according to the recommendation of the International Society of Pharmacoeconomics and Outcomes Research (ISPOR).[7]

Statistical analyses

Adherence curves were modelled using survival analysis, where survival time was the time to discontinuation and the explanatory variable was the type of medication (ramipril + hydrochlorothiazide vs. ramipril + amlodipine). Discrete time survival analysis with a generalized linear model employing complementary log-log link function was used, since the number of patients taking medication was available at 30-day intervals.[8] The proportionality of the hazard was checked by adding the interaction of the drug and time to the model, and comparing the fit of this saturated model to the original one.[9] If non-proportionality was not substantial, hazard ratio was calculated (ramipril + amlodipine fixed-dose combination as reference). Restricted mean survival (adherence) time was calculated,[10] restricted to 360 days. Patients who died during follow-up were excluded from the analysis. Statistical analyses were performed with R program package[11] version 3.2.3, using a custom script developed for this purpose that is available from the corresponding author on request.

Results

A total of 39 095 patients in the NHIFH database fulfilled the study criteria ($n = 10$

295 ramipril + amlodipine; $n = 28$ 800 ramipril + hydrochlorothiazide).

Data regarding treatment adherence are shown in Figure 1 and Table 1. At 2 months after initiation of treatment, 42% of patients using ramipril + hydrochlorothiazide had discontinued treatment, compared with 0% of patients using ramipril + amlodipine. After 1 year, treatment adherence in the ramipril + hydrochlorothiazide group was 29%, compared with 54% in the ramipril + amlodipine group.

The 360-day restricted mean adherence time was 9.0 months (SE 0.036 months) for ramipril + amlodipine and 5.9 months (SE 0.026 months) for ramipril + hydrochlorothiazide. The hazard ratio for discontinuing ramipril + hydrochlorothiazide vs ramipril + amlodipine was 2.318 (95% confidence intervals 2.246, 2.392), $p < 0.001$.

Table 1. Treatment adherence of patients with hypertension receiving ramipril + amplodipine or ramipril + hydrochlorothiazide fixed-dose combination therapy.

Day	Ramipril + amlodipine $n = 10\,295$	Ramipril + hydrochlorothiazide $n = 28\,800$
30	10295 (100)	25558 (89)
60	10295 (100)	16609 (58)
90	8804 (86)	15371 (53)
120	7992 (78)	13148 (46)
150	7699 (75)	12112 (42)
180	6912 (67)	11106 (39)
210	6616 (64)	10435 (36)
240	6292 (61)	9881 (34)
270	6086 (59)	9417 (33)
300	5887 (57)	9026 (31)
330	5724 (56)	8670 (30)
360	5540 (54)	8386 (29)

Data presented as *n* (%).

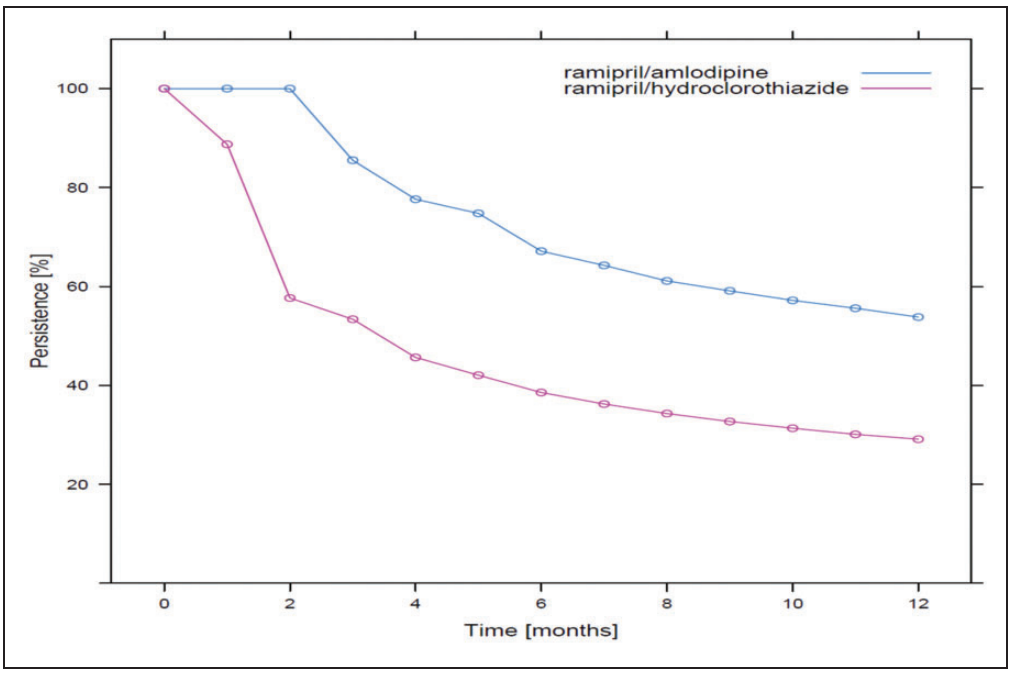

Figure 1. Treatment adherence of patients with hypertension receiving ramipril + amplodipine ($n = 10\,295$) or ramipril + hydrochlorothiazide ($n = 28\,800$) fixed-dose combination therapy.

Discussion

The findings of the present study indicate that 1-year treatment adherence is significantly higher with ramipril + amlodipine than ramipril + hydrochlorothiazide in patients with hypertension. When assessed based on a 60-day grace period, the percentage of patients who adhered to ramipril + hydrochlorothiazide treatment was 29% after 1 year, compared with 54% in patients receiving ramipril + amlodipine.

Others have shown that there may be significant differences in treatment adherence between the groups of active substances used in antihypertensive treatment. A 10-year retrospective study in the Netherlands found a total non-adherence rate (for all antihypertensive therapies) of 39%, but the rate of non-adherence was considerably higher in patients taking diuretics or beta blockers than those taking an angiotensin-converting enzyme inhibitor (ACEI) or combination therapy.[12] A meta-analysis found that adherence to antihypertensive therapy varied significantly according to drug type. In comparison to diuretics, all other types of treatment (angiotensin II receptor blockers [ARBs], ACEIs, calcium channel blockers [CCBs], beta blockers) were associated with better adherence. No difference was found between ACEIs and ARBs.[13]

As with all long-term treatment, appropriate patient co-operation is essential in antihypertensive therapy. There is a higher risk of developing cardiovascular events/diseases (e.g. chronic renal disease, left ventricular hypertrophy, stroke, cardiac failure, etc) in non-adherent patients.[14] The 2013 guidelines of ESH/ESC prefer a fixed-dose combination of two antihypertensive medicines, as patient adherence and the ratio of patients with controlled blood pressure are inversely related to the number of medications taken daily.[4]

It has been shown that benazepril + amlodipine (ACEI + calcium channel blocker) results in a 20% lower risk of major cardiovascular events compared with benazepril + hydrochlorothiazide (HCT; ACEI + diuretic), with no clinically significant between-group difference in blood pressure.[15] An analysis of Swiss prescription data indicated a decrease in diuretic sales and an increase in calcium channel blocker sales over a 5-year period.[16] Treatment adherence was significantly better with ramipril +amlodipine than ramipril + hydrochlorothiazide in the present study, in accordance with evidence supporting advantages of ACEI + calcium channel blocker combinations.[17]

The present study has several limitations. First, it was not possible to account for primary non-adherence as this was outside the scope of our study. Also, due to limitations of the database, we could not separate adherence data by date of entry into the study (i.e. adherence from 1 October 2012 to 30 September 2013 was equivalent to adherence from 30 September 2013 to 29 September 2014), and were therefore unable to model the changes during the study period that may have influenced adherence. Methodologically, the most important limitation of the present study is the non-availability of information on potential confounders, such as sex, age or socioeconomic status. However, given the clinical practice on how these therapies are chosen in Hungary, this effect does not seem to have a profound impact.

In conclusion, 1-year treatment adherence was significantly higher with ramipril + amlodipine than ramipril + hydrochlorothiazide in patients with hypertension.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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