Benefits of Fixed Dose Combination of Ramipril/Amlodipine in Hypertensive Diabetic Patients: A Subgroup Analysis of RAMONA Trial

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Abstract

**Background:** Combination of angiotensin-converting enzyme inhibitors and calcium channel blockers has been successfully used in the antihypertensive therapy for many years. Fixed dose combinations of ramipril/amlodipine have a benefit effect for patients to achieve target blood pressure (BP). This study aimed to assess the efficacy and safety of fixed dose combinations of ramipril and amlodipine (Egiramlon®) in hypertensive diabetic patients.

**Methods:** Hypertensive diabetic patients who were enrolled into the RAMONA trial were included in this open, prospective, Phase IV observational clinical study. Patients had mild-to-moderate hypertension and failed to reach target BP levels through their previous therapy. During the four months of observation, patients took part in three visits (1st day = visit 1, 1st month = visit 2, and 4th month = visit 3) where they received a fixed dose combination of 5/5, 5/10, 10/5, or 10/10 mg ramipril/amlodipine, respectively, with the possibly required dose titrations, based on the decision of their attending physician. Target BP for diabetic patients was <140/85 mmHg. BP levels were measured in all visits, by taking two readings at 2-min interval. Laboratory tests including full blood count, renal function test, electrolytes, blood glucose, serum cholesterol, uric acid, triglycerides, liver function test, creatinine kinase, and midstream urinalysis were performed at visit 1 and visit 3.

**Results:** The 6423 patients completed the study. Among these patients, 1276 (19.9%) patients suffered from type 2 diabetes mellitus. The mean age of these diabetic patients was 64.2 ± 10.0 years; 707 (55.4%) patients were males. Target BP was achieved by 891 (69.8%) of diabetic patients at visit 3 (primary endpoint). BP decreased from 157.5/91.3 ± 9.6/7.6 mmHg (visit 1) to 130.9/79.6 ± 7.4/5.8 mmHg (visit 3). As for the secondary endpoint of the study, total cholesterol decreased from 5.50 ± 1.13 mmol/L (visit 1) to 5.20 ± 0.95 mmol/L (visit 3) (P = 0.000), low-density lipoprotein cholesterol decreased from 3.20 ± 0.93 mmol/L to 3.00 ± 0.77 mmol/L (P = 0.000), triglyceride decreased from 2.20 ± 1.14 mmol/L to 2.00 ± 1.97 mmol/L (P = 0.000), while high-density lipoprotein cholesterol increased from 1.30 ± 0.42 to 1.35 ± 0.30 mmol/L (P = 0.001) until the end of the 4th month (visit 3). Fasting blood glucose of the hypertensive diabetic patients decreased from 7.20 ± 1.88 mmol/L to 6.70 ± 1.38 mmol/L (P = 0.000), while HbA1c decreased from 7.90 ± 1.78% to 7.60 ± 1.83% (P = 0.000). Various fixed dose combinations of ramipril/amlodipine were well tolerated and no adverse event related to the use of the medicine has appeared.

**Conclusions:** The fixed dose combination of ramipril/amlodipine was effective in hypertensive diabetic patients who failed to reach target BP previously.

**Key words:** Diabetes Mellitus; Hypertension; Ramipril/Amlodipine Fixed Dose Combination

**Introduction**

It is well known that incidence of type 2 diabetes mellitus has been growing all over the world and in Hungary as well. Mortality and morbidity of diabetic people are nearly four times higher compared to the general population. The frequency of hypertension is increasing in patients with type 2 diabetes mellitus. In the Framingham study, hypertension...
occurred 1.5-fold more frequently in diabetic patients than nondiabetic subjects. In addition, according to the data of the Hungarian Hypertension Register, 80% of patients with type 2 diabetes mellitus have high blood pressure (BP). In the UK Prospective Diabetes Study, effects of strict and less strict BP control have been examined in patients with type 2 diabetes during a median 8.4-year follow-up. Mean BP during follow-up was significantly reduced in the group assigned tight BP control (144/82 mmHg; 1 mmHg = 0.133 KPa) compared with the group assigned to less tight control (154/87 mmHg; \( P = 0.000 \)). Reductions in risk in the group assigned to tight control compared with that assigned to less tight control were 24% in diabetes-related end points, 32% in deaths related to diabetes, 44% in strokes, and 37% in microvascular end points. As the important findings of this study, approximately one-third of the patients in the group assigned to tight control required three or more medicines to lower BP to achieve BP control.

The most recent guidelines of the European Society of Hypertension/European Society of Cardiology (ESH/ESC) and the Hungarian Hypertension Society recommended a target BP levels of below 140/85 mmHg. According to the guidelines, pharmacotherapy of diabetic patients with untreated hypertension should be started with a combination of two medicines at once, using medicines with 24-h long effect daily. The single daily dosage has a beneficial effect on patient adherence, and at the same time, it reduces the fluctuation of BP. The effect is even more preferential if the medicines with 24-h long effect are administered in fixed combinations.

In the subgroup of diabetic patients participating in the Heart Outcomes Prevention Evaluation (HOPE) study (MICRO-HOPE), the reduction in the risk of cardiovascular (CV) events has proven to be more explicit, as the cumulated primary CV endpoints decreased by 25%. This included 22% less myocardial infarction and 33% less stroke. Moreover, the incidence of microvascular complications in diabetic patients showed a significant decrease, as nephropathy occurred 24% less frequently, while the incidence of retinopathy requiring laser therapy was reduced by 22%. The incidence of combined microvascular events (nephropathy, dialysis, and laser therapy) decreased by 16%.

The combination of angiotensin-converting enzyme inhibitors (ACEIs) and calcium channel blockers (CCBs) can influence the renin-angiotensin-aldosterone system (RAAS) and the increased vascular resistance concomitantly and has been successfully used in the antihypertensive therapy for many years. CCBs also exert a mild diuretic effect, increasing the activities of both sympathetic nervous system and RAAS, but ACEIs decrease these effects, therefore, they can complement each other. ACEIs can reduce crural edema caused by the dihydropyridine-type CCBs. Metabolic and central nervous system adverse effects are not observed during the use of either drug.

In the Hungarian RAMONA trial, the efficacy and safety of fixed-dose combinations including various doses of ramipril and amlodipine have been studied in pretreated hypertensive patients (\( n = 6423 \)) who had mild–moderate hypertension and did not achieve target BP despite previous antihypertensive therapy. In this open-label, prospective trial, the mean BP (initially observed as 157/91 mmHg) decreased by 26.4/11.8 mmHg at the end of the study. Under the treatment with the fixed dose combination of ramipril/amlodipine, 52.4% of the patients attained target BP. Considering that diabetes mellitus is associated with high CV risk, an effective and metabolically neutral BP control is particularly important in this group of patients. This study was to primarily evaluate the efficacy of fixed dose combination of ramipril/amlodipine (Egamlon®) therapy during the 4-month treatment in hypertensive diabetic patients who failed to achieve their predetermined target BP despite the previous antihypertensive therapy, and this study also assessed tolerability and how metabolic parameters were influenced by fix dose combination of ramipril/amlodipine.

**Methods**

**Study population and data collection**

The RAMONA study was a Phase IV, prospective, observational, open-label clinical study, and aimed to monitor the effectiveness and safety of the fixed dose combination of ramipril and amlodipine in patients suffering from mild or moderate hypertension despite previous antihypertensive treatment (registration numbers: TUKEB No: 16927-1/2012/EKU (294/PI/12)).

Based on the results of this RAMONA study, we analyzed the data of hypertensive diabetic patients older than 18 years, with mild-to-moderate hypertension, who were enrolled into the RAMONA trial and had failed to reach their target BP during measurements at the outpatient clinics while on their previous antihypertensive therapy. According to the most recent ESH/ESC guidelines, the target BP for hypertensive diabetic patients is <140/85 mmHg.

Exclusion criteria were as follow: patients who did not sign the informed consent, poor adherence, known hypersensitivity to calcium channel antagonists and/or ACEIs, secondary hypertension, pregnancy, neoplastic disease with short life expectancy, poorly controlled diabetes, severe cardiac defect, laboratory abnormalities determined as clinical significant by the investigator, particularly hyperkalemia, as well as the other known contraindications to ramipril or amlodipine therapy.

This study was performed in accordance with the ethical standards described in the Declaration of Helsinki and was approved by the appropriate ethics committee (ETT-TUKEB-NIT approval number: 16927-1/2012/ EKU [294/PI/12]). All patients provided written informed consent before enrollment in this study.

**Blood pressure measurements and laboratory tests**

During the 4 months of observation, the patients took part in three visits (1st day = visit 1, 1st month = visit 2, and
4th month = visit 3), and BP was measured in all three visits with validated sphygmomanometers by taking two readings at 2-min interval in each case. Each patient received one of four fixed dose combinations (5/5, 5/10, 10/5, or 10/10 mg) determined by their attending physician based on BP levels, and the possibly dose titrations could be required for the patients based on the decision of their attending physician.

Laboratory tests including full blood count, renal function test, electrolytes, blood glucose, serum cholesterol, uric acid, triglycerides, liver function test, creatinine kinase, and midstream urinalysis were performed in the fasting state at visit 1 and visit 3.

**Statistical analysis**

Baseline characteristics were shown as mean ± standard deviations (SD) for continuous variables and numbers (percentages) for categorical variables. Web2 Research Kft. (Budapest, Hungary), an independent statistics company, analyzed all study data using SAS software version 9.3 (SAS Institute Inc., Cary, NC, USA). A P < 0.05 was considered statistically significant.

**RESULTS**

**Baseline characteristics**

A total of 9169 patients were enrolled into the RAMONA study, and 6423 patients completed this study. Of these 6423 patients, 1276 (19.9%) patients were diabetic. Mean age of the diabetic patients was 64.2 ± 10.0 years, 707 (55.4%) were males, and 569 (44.6%) were females. Their body mass index (BMI) was 30.1 ± 5.1 kg/m², while their BP was 157.5/91.3 ± 7.6/7.6 mmHg prior to their enrollment into the study. Hypertension had existed for 12.7 ± 8.4 years. At the enrollment, 514 (40.3%) hypertensive diabetic patients belonged to the mild hypertension, and 762 (59.7%) to moderate hypertension.

Among these 1276 diabetic patients, 1255 (98.4%) had risk factors for CV diseases. Dyslipidemia was the most common risk factor found in 1077 (84.4%) of patients, other factors included age (male >55 years, female >65 years) in 826 (64.7%), obesity (BMI ≥30 kg/m²) in 586 (45.9%), smoking in 298 (23.4%), family history (early acute myocardial infarction) in 277 (21.7%), and hyperuricemia in 269 (21.1%) of patients. Target organ lesions were present in 622 (48.7%) of patients, with left ventricular hypertrophy in 415 (32.5%), arterial carotid plaque in 285 (22.3%), elevated serum creatinine level in 71 (5.6%), microalbuminuria in 117 (9.2%), and glomerular filtration rate <60 ml·min⁻¹·1.73 m² in 106 (8.3%) of patients. The majority of hypertensive diabetic patients had target organ damage at the beginning of the study.

**Effects of fixed dose combination of ramipril/amlodipine**

Target BP was achieved by 891 (69.8%) of patients (primary endpoint) at the 4th month of the study (visit 3). A great number of patients took various antihypertensive medications (e.g., β-blockers [BB], calcium-channel blockers, diuretics, etc.) and antihyperlipidemic agents (e.g., statins) at baseline [Table 1]. The attending physicians chose the preferable dose of ramipril/amlodipine fixed dose combination according to BP levels of the patients measured on each visit. The consequently applied doses are specified in Table 2.

The BP significantly decreased from 157.5/91.3 ± 7.6/7.6 mmHg (visit 1) to 130.9/79.6 ± 7.4/5.9 mmHg, with significant decreasing by 16.6/12.3% (visit 3; P = 0.000). At visit 2 and visit 3, 32.3% and 69.8% of the patients reached target BP, respectively, (P = 0.000) the rate of reaching the target BP was dose-dependent. At visit 3, 24.1% of patients who received 10/10 mg, 21.8% of those who received 5/5 mg, 20.5% of those who received 10/5 mg, and 1.8% of those who received 5/10 mg reached target BP [Table 3]. Reduction of BP was accompanied by changes in heart rate. Heart rate decreased from 78.0 ± 8.5/min (visit 1) to 72.9 ± 6.0/min (visit 3), with significant decreasing by 5.1 ± 7.5/min (P = 0.000).

As for the secondary endpoint of this study, we assessed the safety and metabolic effects of fixed dose combination of ramipril/amlodipine on the subgroup of diabetic patients. Regarding the lipid status, total cholesterol decreased from...
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An overactive 5 mg then 10 mg, respectively. In this Brazil study, the ramipril/amlodipine 5/5 mg then 10/10 mg or amlodipine 2.5 mg, then the doses were titrated, based on BP, to stages 1 or 2 essential hypertension were enrolled, and received ramipril/amlodipine 2.5/2.5 mg or amlodipine 2.5 mg, then the doses were titrated, based on BP, to ramipril/amlodipine 5/5 mg then 10/10 mg or amlodipine 5 mg then 10 mg, respectively. In this Brazil study, the study in Brazil was to compare the efficacy and tolerability a similar 18-week, prospective, randomized, double-blind CV events. The rate of reaching the target BP could be even higher by further adding the doses of the ramipril/amlodipine fixed combination to its maximum (10/10 mg) since only approximately 37.5% of patients have taken maximal dose up to the visit 3. Considering that 84.4% of patients in this study had dyslipidemia, the metabolic effects of ramipril/amlodipine antihypertensive therapy could not be neglected either. All lipid parameters showed a significant improvement until the 4th month of the study (visit 3), which was also particularly important in the antihypertensive therapy of diabetic patients. In addition, preferable changes could be observed in carbohydrate metabolism, as both fasting glucose and HbA1c decreased moderately but significantly. No adverse effects had developed during the 4-month period.

A similar 18-week, prospective, randomized, double-blind study in Brazil was to compare the efficacy and tolerability of an amlodipine/ramipril fixed dose combination.[11] Patients with stages 1 or 2 essential hypertension were enrolled, and received ramipril/amlodipine 2.5/2.5 mg or amlodipine 2.5 mg, then the doses were titrated, based on BP, to ramipril/amlodipine 5/5 mg then 10/10 mg or amlodipine 5 mg then 10 mg, respectively. In this Brazil study, the mean changes in systolic BP and diastolic BP, as measured using 24-h ambulatory BP monitoring in the physician’s office, were significantly greater in patients with fixed dose combination of ramipril/amlodipine therapy than patients with monotherapy.

Recent ESC/ESH recommendations have emphasized the importance of inhibiting RAAS activity in the treatment of primary hypertension.[6] An overactive RAAS activity inhibition may be achieved either with ACEIs or angiotensin-receptor blockers (ARBs). A recent meta-analysis has shown that ACEIs reduced all-cause mortality, CV mortality, and major CV events in patients with diabetes mellitus, whereas ARBs had no benefits on these outcomes. Thus, ACEIs should be considered as the first-line therapy to limit excess mortality and morbidity in this population. ACEIs may be better at reducing the risk of CV and all-cause mortality.[12] ACEIs combined with CCBs have a synergistic antihypertensive effects, which can offer an added advantage of minimizing adverse effects of individual components (e.g., edema with dihydropyridine CCBs). The Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm showed that an ACEI and CCB combination was more effective in lowering BP and reducing the risk of mortality and major CV events than traditional therapy with a BB – thiazide combination.[13] This study had several limitations. This single-arm, open-label study did not use randomized protocols, and only short-term benefit effects were evaluated. However, our findings did give an evidence of the value of ramipril/amlodipine fixed-dose combination in real-life clinical practice.[11]

In conclusion, the fixed dose combination of ramipril/amlodipine was effective in hypertensive diabetic patients with high CV risk who failed to reach target BP previously. In addition, it is well tolerated and has been proven to have very preferable metabolic effects.

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Conflicts of interest
There are no conflicts of interest.

References
1. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA 1979;241:2035-8. doi: 10.1001/jama.1979.03290450033020.
2. Lago RM, Singh PP, Nesto RW. Diabetes and hypertension. Nat Clin Pract Endocrinol Metab 2007;3:667. doi: 10.1038/ncpendmet0638.
3. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr., Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the national cholesterol education program adult treatment panel III guidelines. Circulation 2004;110:227-39. doi: 10.1161/01.CIR.0000133317.49796.0E.
4. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ 1998;317:703-13. doi: 10.1136/bmj.317.7160.703.
5. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R,
Germano G, et al. 2007 guidelines for the management of arterial hypertension: The task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007;25:1105‑87. doi: 10.1097/HJH.0b013e3281fc975a.

6. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: The task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013;31:1281‑357. doi: 10.1097/HJH.0000431740.32696.cc.

7. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO‑HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. Lancet 2000;355:253‑9.

8. Weir MR. Targeting mechanisms of hypertensive vascular disease with dual calcium channel and renin-angiotensin system blockade. J Hum Hypertens 2007;21:770‑9. doi: 10.1038/sj.jhh.1002254.

9. Tomcsányi J. Monitoring of the blood pressure lowering effectiveness of ramipril‑amlodipine fix combination – A non-interventional trial (RAMONA study) (Hungarian). Hypertonia es Nephrologia 2013;17:34‑8.

10. Kikuya M, Hozawa A, Ohokubo T, Tsuji I, Michimata M, Matsubara M, et al. Prognostic significance of blood pressure and heart rate variabilities: The Ohasama study. Hypertension 2000;36:901‑6.

11. Miranda RD, Mion D Jr., Rocha JC, Kohlmann O Jr., Gomes MA, Saraiva JF, et al. An 18-week, prospective, randomized, double-blind, multicenter study of amlodipine/ramipril combination versus amlodipine monotherapy in the treatment of hypertension: The assessment of combination therapy of amlodipine/ramipril (ATAR) study. Clin Ther 2008;30:1618‑28. doi: 10.1016/j.clinthera.2008.09.008.

12. Cheng J, Zhang W, Zhang X, Han F, Li X, He X, et al. Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on all-cause mortality, cardiovascular deaths, and cardiovascular events in patients with diabetes mellitus: A meta-analysis. JAMA Intern Med 2014;174:773‑85. doi: 10.1001/jamainternmed.2014.348.

13. Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the anglo‑scandinavian cardiac outcomes trial‑blood pressure lowering arm (ASCOT‑BPLA): A multicentre randomised controlled trial. Lancet 2005;366:895‑906.