Research Article

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Safety and effectiveness of combined antihypertensive and cholesterol-lowering therapy in high-/very high-risk patients

Aim: Controlling cardiovascular (CV) risk factors is paramount in reducing atherosclerotic events. This 6-month prospective noninterventional trial assessed the safety and effectiveness of fixed-combination lisinopril–amlodipine plus rosuvastatin. **Patients & methods**: Patients with mild/moderate hypertension and hypercholesterolemia, at high-/very high-CV risk, received lisinopril–amlodipine (10/5, 20/5 or 20/10 mg/day) plus rosuvastatin (10 or 20 mg/day). Primary end points: systolic/diastolic blood pressure, low-density lipoprotein cholesterol. **Results**: At 6 months, 91% of 2241 evaluable patients achieved blood pressure target (<140/90 mHg); low-density lipoprotein cholesterol targets, <3, <2.5 and 1.8 mmol/l, were achieved by 67, 49 and 40% of patients, respectively. Adverse events (4.4%) were mostly mild. **Conclusion**: Lisinopril–amlodipine plus rosuvastatin was well tolerated and effective in patients with mild/moderate hypertension and hypercholesterolemia at high/very high CV risk.

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Keywords: cardiovascular risk • diabetes mellitus • hypercholesterolemia • hypertension • lisinopril–amlodipine • rosuvastatin

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Cardiovascular (CV) diseases are the leading cause of mortality both globally and in Hungary. They are predicted by the WHO to remain a leading cause of death for the next 10 years [1]. Two of the most prevalent but controllable CV risk factors are hypertension and lipid profile abnormalities. Large clinical trials emphasize the need for achieving and maintaining risk parameters (blood pressure, blood lipids) within target range to reduce mortality rates [2–9].

Adequate blood pressure control with monotherapy is achieved in only a small proportion of patients (30%) and antihypertensive combination therapy is required in most patients [7,8]. According to clinical studies (HOT, UKPDS, RENAAL) in high-risk CV populations, the concomitant use of two or more antihypertensives on average was needed to achieve and maintain blood pressure values in the target range [10–12].

Although recent guidelines recommend higher (<140/90 mmHg) target values than 2007 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines for high- and very high-risk patients, two-thirds of these patients will nonetheless require combination therapy. The new guidelines still give priority to the fixed-dose combination of two antihypertensive agents in these high-risk groups, since patient compliance improves if the number of tablets to be taken is reduced [7,8].

The combination of angiotensin-converting enzyme (ACE) inhibitors with calcium channel blockers achieves effective blood pressure control and clinically demonstrable target organ protection (by reducing carotid intima-media thickness and left ventricular hypertrophy), independent of blood pressure values [13–17]. The ACCOMPLISH trial has shown that ACE inhibitor-calcium

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channel blocker combination therapy is superior to ACE inhibitor diuretic combinations for reducing CV events in hypertensive patients, although the two therapies provided similar blood pressure-lowering effects [6].

As early as 1995, the MRFIT study confirmed that simultaneous increases in systolic blood pressure and total cholesterol levels exponentially raised CV morbidity. Since then, many large randomized controlled trials have proven that statins lower CV risk in both primary and secondary prevention [18–23]. Current international (ESC/European Atherosclerosis Society [EAS] 2011) and local (5th Hungarian Cardiovascular Consensus Conference) therapeutic recommendations therefore suggest implementing lipid-lowering therapy using effective, well tolerated statins until target values are reached [9,24]. European guidelines (ESC/EAS), published in July 2011, have significantly broadened the population of very high-risk CV patients and stress the extended use of statins to reach strict target values.

Rosuvastatin is considered a moderate/high-intensity statin according to recent guidelines [25–31]. It is well tolerated and, in most patients, target low-density lipoprotein cholesterol (LDL-C) levels are achieved with the use of rosuvastatin in both primary and secondary prevention (STELLAR, MERCURY I, ASTEROID, METEOR, CENTAURUS) [21,26–29]. Moreover, in the STELLAR trial, rosuvastin therapy was not only more effective than atorvastatin, simvastatin and pravastatin therapy for achieving LDL-C target levels but also produced significantly greater increases in high-density lipoprotein cholesterol (HDL-C) [26].

Lisinopril–amlodipine, an effective and frequently used therapy, is a combination of two long-acting agents with similar pharmacokinetic properties [32]. In Hungary, lisinopril–amlodipine fixed-combination preparations are available in a wide range of doses (10/5, 20/5, 20/10 mg) to better personalize therapy and achieve target blood pressure values.

The proportion of high-risk patients reaching target LDL-C levels in Hungary increased from 14% in 2004 to 40% in 2011, according to general practice data [33,34]. This increase is noteworthy, but 60% of patients (and an even greater percentage of patients at very high CV risk) still do not achieve target values. This gap in achieving efficacy targets needs to be addressed, in view of the CV mortality rate in our country.

The primary aim of our noninterventional trial conducted in Hungary was to examine the efficacy of fixed-combination lisinopril–amlodipine antihypertensive therapy (Lisonorm® Richter Gedeon Nyrt, Budapest, Hungary) plus free-combination rosuvastatin cholesterol-lowering therapy (Xeter® Richter Gedeon Nyrt) in patients with mild or moderate hypertension and hypercholesterolemia who were categorized as high or very high CV risk. Our secondary purpose was to determine the safety and tolerability of lisinopril–amlodipine and rosuvastatin co-therapy in these patients.

Patients & methods

This was a prospective, observational, noninterventional trial. Patients were followed up for a period of 6 months. There were four appointments altogether: baseline, month 1, month 3 and month 6.

Selection of patients

In total, 2452 high- and very high-risk CV patients with mild (grade I) or moderate (grade II) essential hypertension and hypercholesterolemia were enrolled in the trial in 256 locations in Hungary. Examinations and diagnoses were performed by internists, cardiologists, hypertension specialists and general practitioners.

Patients meeting inclusion criteria were aged ≥18 years. Patients either had not previously received antihypertensive treatment or, if previously treated, had not achieved target blood pressure values. The study included patients with hypertension in the following groups: asymptomatic, high CV risk patients (≥140/90 mmHg); patients with diabetes mellitus, metabolic syndrome, coronary and peripheral artery disease (≥130/80 mmHg) and patients aged over 79 years (≥150/90 mmHg).

For hypercholesterolemia, patient inclusion was based on LDL-C levels above target values according to CV risk classification: for CV symptom-free high CV risk patients, LDL-C ≥3.0 mmol/l; with high CV risk (diabetes mellitus, coronary and peripheral artery disease), LDL-C ≥2.5 mmol/l; in the very high-risk group, LDL-C ≥1.8 mmol/l.

Exclusion criteria included contraindications listed in the prescribing information for lisinopril–amlodipine (10/5, 20/5, 20/10 mg) and rosuvastatin (10 and 20 mg). Patients were excluded if they had known allergy or hypersensitivity to ACE inhibitors, calcium channel blockers, statins, or had severe kidney diseases, malignant diseases, unreliable contraception, or were pregnant and/or breastfeeding.

Trial end points

Primary end points were: systolic and diastolic blood pressure values, serum LDL-C levels, ambulatory blood pressure monitoring (ABPM) examination parameters (subgroup analysis) at baseline and month 6 (measurements were made at the same frequency, every 20 min, during the day and night); and Clinician Global Impression of Change (CGIC; measuring global functioning at all follow-up visits compared with baseline).

Target values for blood pressure and LDL-C were below those values listed in the inclusion criteria for each risk group (described above). It is important to note that we started this trial using 2007 ESH/ESC and 2011 Hungarian hypertension guidelines [7,24], but the 2013 ESC/ESH guidelines [8] set new target values (<140/90 mmHg and <140/85 mmHg for diabetes mellitus) that negated the 130/80 mmHg value we used in this study for high- and very high-risk patients.

Drug therapy was deemed 'effective' if blood pressure after lisinopril–amlodipine therapy and LDL-C levels after rosuvatatin treatment were below target values for these risk groups at month 6.

Secondary end points were adverse reactions and other safety parameters. Incidence, severity and rate of treatment discontinuation due to adverse events were recorded by the physicians.

Pulse and blood pressure measurements were performed after 5 min rest, on both arms, in a sitting position, on two consecutive occasions, with at least 2 min between the two measurements. Blood pressure was taken using electric devices and upper-arm cuffs.

Laboratory tests, performed in accordance with professional guidelines, were carried out as follows:

Baseline (patient enrollment): blood glucose, LDL-C, serum urea, serum creatinine, glomerular filtration rate, aspartate aminotransferase (AST), alanine aminotransferase, creatine kinase (CK) total cholesterol, HDL-C, triglycerides, serum sodium, serum potassium, uric acid, microalbumin, C-reactive protein (CRP), carbamide. At visits 2, 3 and 4 (months 1, 3 and 6), repeated laboratory tests were performed after a fast of at least 10 h. BMI was also assessed. ABPM testing was not mandatory and data for only nine patients were documented. Statistical evaluation of ABPM data was therefore not carried out. CGIC was measured at months 1, 3 and 6 and patients' actual status was compared with baseline. The extent of change was determined (0–7 scale) by the physicians.

The 10-year risk of fatal CV disease was calculated according to the recent SCORE chart. The model includes the following risk factors: age, sex, smoking, systolic blood pressure, total cholesterol and HDL-C [35].

Drug therapy

Lisinopril–amolidipine combination therapy was started at doses of 10/5, 20/5 or 20/10 mg/day. The initial dose was determined by the physicians; the preferred dose for grade I hypertension was 10/5 mg, and for grade II hypertension 20/5 or 20/10 mg. Rosuvastatin was initiated at doses of 10 or 20 mg/day according to risk stratification; for very high-risk group and/or for previous statin receivers, the initial dose was 20 mg/day. Doses could be stepped up if necessary to achieve blood pressure or LDL-C targets [7,22]. At each time point, doses could be modified in accordance with professional protocols and drug prescribing information for reasons of efficacy and tolerability. Additional concomitant therapy was prescribed in compliance with the guidelines of the Hungarian Society of Hypertension and other professional protocols, if blood pressure and LDL-C levels failed to reach target values at maximum drug doses. At study end patients continued to receive drug therapy according to professional guidelines [7,24].

Record keeping

Patients' data were recorded on information sheets according to protocol. Editing of the sheets was performed in accordance with data protection and handling regulations. The method of patient identification ensured patient confidentiality. The study was approved by the national ethics and review committees (reference number ETT TUKEB 9273/2013/EKU).

Statistical evaluation

Data were analyzed according to EU-GCP/ICH guidelines. Apart from standard methods of analysis (mean, standard deviation [SD], median, t-test), statistical analysis of all clinical and laboratory data was performed using correlation and variance analysis. Differences in data obtained between the first and last visits were characterized by the 95% CI: $p < 0.05$ probability levels were considered significant when using statistical methods.

Results

Of the 2452 patients enrolled in the trial, 2241 patients were evaluable and were included in the analysis. Data from 211 patients were excluded due to deviation from protocols (mostly incomplete documentation).

Table 1 summarizes patients' demographic data. Mean age was 63.2 ± 11.4 years, mean BMI was 29.1 ± 4.1 kg/m^2 and 45.2% were male. According to the risk assessment recommended by the 5th Hungarian Therapeutic Consensus Conference [24], 6.8% of patients fell into the very high CV risk category. 48% of patients had mild (grade I) hypertension and 52% had moderate (grade II) hypertension. 32% of patients had not received prior antihypertensive therapy and 68% had received drug therapy as listed in Table 1. Of these, 65% received monotherapy and 35% combination therapy.

Initial metabolic panel, lipid profile and blood pressure values of diabetic patients (34% of total) were compared with those of nondiabetics. There were higher levels of triglycerides and uric acid, lower

Table 1. Descriptive parameters of evaluable patients.

Parameter	Patients (n = 2241)
Age (years), mean ± standard deviation;	63.2 ± 11.4
Male (%)	45.2
Bodyweight (kg); mean ± standard deviation	82.4 ± 16.0
Height (cm); mean ± standard deviation	168.3 ± 8.6
BMI (kg/m^2); mean ± standard deviation	29.1 ± 4.1
Current smoker (%)	29
Coronary artery disease (%)	27
Peripheral artery disease (%)	35
Diabetes mellitus (%)	34
Metabolic syndrome (%)	38
Very high cardiovascular risk (%)	6.8
High cardiovascular risk (%)	93.2
High cardiovascular risk, no symptoms (%)	47
Grade I hypertension (%)	48
Grade II hypertension (%)	52
Antihypertensive agents (%)	68
ACE inhibitor (%)	56
β-blocker (%)	22
Calcium channel blocker (%)	20
Diuretic (%)	23
Statin (%)	48
Aspirin and/or clopidogrel (%)	44

ACE: Angiotensin-converting enzyme.

HDL-C and higher blood pressure and BMI values in Type 2 diabetic patients than in the nondiabetic population (Table 2).

Effects of lisinopril–amlodipine therapy on blood pressure

Table 3 demonstrates systolic and diastolic blood pressure changes during lisinopril–amlodipine plus rosuvasatin therapy. Both systolic and diastolic blood pressure values decreased significantly by visit 2 (month 1) compared with baseline and continued to decrease to the study end (visit 4; month 6).

Decreases in heart rate were not considered clinically important but were statistically significant over the 6 months of treatment when compared with baseline (75.3 ± 8.0 beats per min [bpm] vs 73.3 ± 5.9 bpm; $p < 0.05$). Lisinopril–amlodipine therapy was effective regardless of prior drug therapy: systolic and diastolic blood pressure decreases in patients receiving prior antihypertensive drug therapy responded to treatment similarly to naive patients ($p = 0.25$ and $p = 0.33$, respectively, for reductions in systolic and diastolic values). In patients with diabetes mellitus, metabolic syndrome or peripheral arterial disease, there were no significant differences in blood pressure reductions, compared with the group without comorbidities.

Figure 1A illustrates the distribution of lisinopril–amlodipine doses (10/5, 20/5, 20/10 mg). Higher doses were required to achieve target values in a greater proportion of patients at each study visit.

Efficacy of lisinopril–amlodipine therapy

Target blood pressure values below 140/90 mmHg were achieved in 68% of asymptomatic, high CV risk patients with hypertension by month 1 and in 91% by month 6. A target value below 130/80 mmHg was attained in 30% of patients with diabetes mellitus, metabolic syndrome, coronary or peripheral artery disease by month 1 and nearly doubled (to 57%) by month 6. Of patients with hypertension who were aged 79 years or older, 94% achieved target blood pressure values of <150/90 mmHg by study end (n = 176).

Effect of rosuvastatin therapy on lipid levels

As shown in Table 4, total and LDL-C levels decreased significantly by month 1, compared with baseline, and continued to decrease to study end (month 6). Serum triglycerides markedly decreased while serum HDL-C levels significantly increased ($p < 0.05$; Table 4). Reductions in lipid levels were similar in patients with diabetes mellitus and metabolic syndrome compared with the nondiabetic population (data not shown).

Table 2. Baseline metabolic profile, lipid profile and blood pressure values in diabetic and nondiabetic patients (mean ± standard deviation).

Parameter	T2DM	No T2DM	p-value
BMI (kg/m^2)	30.9 ± 4.6	28.1 ± 4.0	<0.05
Triglycerides (mmol/l)	2.6 ± 1.3	2.0 ± 1.1	<0.05
Uric acid (μmol/l)	335.2 ± 89.8	310.2 ± 80.3	<0.05
HDL-C (mmol/l)	1.28 ± 0.9	1.49 ± 0.7	<0.05
Diastolic blood pressure (mmHg)	92.1 ± 9.0	89.0 ± 8.4	<0.05

HDL-C: High-density lipoprotein cholesterol; T2DM: Type 2 diabetes mellitus.

Table 3. Changes in systolic and diastolic blood pressure over 6 months of lisinopril–amlodipine therapy (mean ± standard deviation).

Parameter	Month	Patients (n = 2241)	p-value
Systolic blood pressure (mmHg)	0	159.9 ± 13.3	
	1	136.9 ± 10.9	<0.05
	3	132.9 ± 10.4	<0.05
	6	129.5 ± 9.1	<0.05
Diastolic blood pressure (mmHg)	0	90.0 ± 8.6	
	1	81.5 ± 6.9	<0.05
	3	79.6 ± 6.8	<0.05
	6	78.1 ± 6.1	<0.05

Figure 1B displays the distribution of rosuvastatin doses (10 mg/day, 20 mg/day) and demonstrates an increase in dose over time.

Efficacy of rosuvastatin therapy

59% of patients achieved a target LDL-C value <3 mmol/l by month 3 and 67% by month 6 in the group who were CV symptom-free with high CV risk. After 6 months of rosuvastatin therapy, the percentage of patients reaching a target <2.5 mmol/l was 49% (those with high CV risk, i.e., diabetes mellitus, coronary or peripheral artery disease, n = 1543), whereas the proportion of patients having achieved a target <1.8 mmol/l was 40% (in the very high-risk group, n = 152). In patients who had received prior statin therapy without meeting lipid targets, switching to rosuvastatin increased the proportion of patients with LDL-C <3 mmol/l to 51%, the proportion of those <2.5 mmol/l to 42% and those <1.8 mmol/l to 28%.

Effect of treatment on SCORE risk classification

The calculated 10-year risk of fatal CV disease was improved significantly by an average of 6.2% in males and 2.7% in females after receiving lisinopril–amlodipine plus rosuvastatin therapy ($p < 0.05$, Table 4).

Effect of treatment on the CGIC

According to the CGIC questionnaire assessed by physicians, patients were deemed to be very much

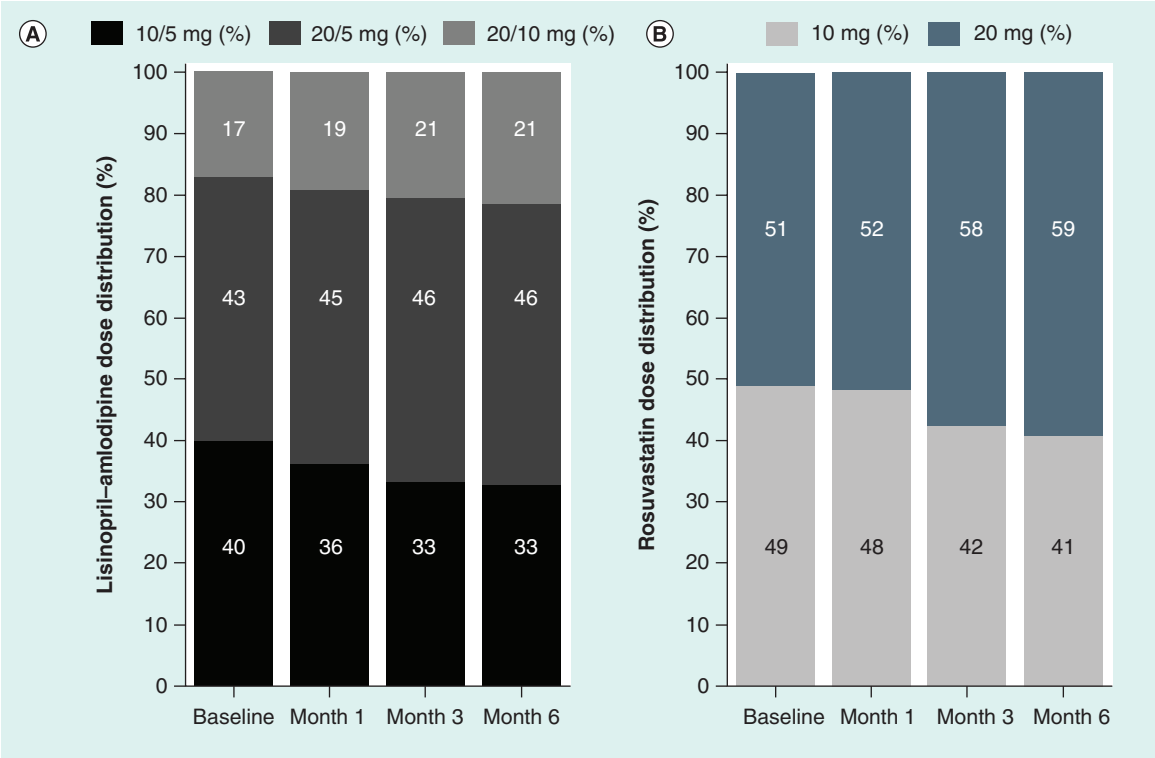

Figure 1. Lisinopril–amlodipine and rosuvastatin dose distributions over 6 months.

Table 4. Changes in laboratory parameters and SCORE risk over 6 months of lisinopril–amlodipine/rosuvastatin therapy (mean ± standard deviation).

Parameter	Baseline (n = 2241)	Month 1 (n = 2201)	Month 3 (n = 2213)	Month 6 (n = 2241)
Blood glucose (mmol/l)	6.3 ± 1.9	6.0 ± 1.6*	5.9 ± 1.5*	5.7 ± 1.3*
Total cholesterol (mmol/l)	6.4 ± 1.1		5.0 ± 1.0*	4.8 ± 0.9*
LDL-C (mmol/l)	3.8 ± 1.1		2.8 ± 0.9*	2.6 ± 0.8*
HDL-C (mmol/l)	1.42 ± 0.7		1.48 ± 0.4*	1.5 ± 0.4*
Triglyceride (mmol/l)	2.2 ± 1.1		1.8 ± 0.8*	1.7 ± 0.7*
Aspartate aminotransferase (U/l)	26.3 ± 11.7	26.9 ± 11.6*	27.0 ± 11.7*	27.1 ± 11.5*
Alanine aminotransferase (U/l)	27.6 ± 15.7	27.8 ± 10.8	27.7 ± 12.8	27.8 ± 11.8
Carbamide (mmol/l)	6.4 ± 1.9	6.3 ± 1.7	6.4 ± 1.8	6.4 ± 1.7
Creatinine (μmol/l)	82.3 ± 20.8	82.4 ± 17.0	82.2 ± 19.0	82.1 ± 18.3
Sodium (mmol/l)	139.7 ± 3.7	139.8 ± 3.5	139.5 ± 3.8	139.6 ± 3.6
Potassium (mmol/l)	4.37 ± 0.43	4.37 ± 0.41	4.35 ± 0.44	4.33 ± 0.44*
Creatine kinase (U/l)	99.5 ± 60.7	107.1 ± 91.0*	106.1 ± 98.0*	104.6 ± 60.3*
C-reactive protein (mg/l)	3.86 ± 2.40			3.43 ± 2.14*
Uric acid (μmol/l)	318.2 ± 84.3			299.9 ± 71.9*
Microalbumin (mg/l)	25.4 ± 60.3			20.4 ± 43.1*
SCORE risk for males (%)	11.3 ± 5.8			5.1 ± 3.9*
SCORE risk for females (%)	5.9 ± 3.1			3.2 ± 2.8*

*Significant ($p < 0.05$) changes from baseline.
LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol.

improved (63.2%), much improved (20.8%), minimally improved (8.7%), had no change from baseline (6.7%) or were minimally worse (0.58%) after receiving lisinopril–amlodipine plus rosuvastatin therapy.

Change in laboratory parameters during treatment

During lisinopril–amlodipine plus rosuvastatin therapy there were both statistically and clinically significant decreases in total cholesterol, LDL-C, triglyceride, uric acid, microalbumin, CRP and blood glucose levels (Table 4). A clinically unimportant but significant reduction in potassium levels ($p < 0.05$) was detected, but there were no significant changes in alanine aminotransferase, carbamide, creatinine and sodium levels (Table 4). Elevations in AST, CK and HDL-C were statistically but not clinically significant. Our results showed that a CK level higher than 200 IU was present in 0.92% and an AST level higher than 60 IU in 0.9% of patients. Clinically important AST elevations (<3 times the upper limit of normal [ULN] at two consecutive visits) and CK elevations (<10 times the ULN with associated muscle symptoms) were not observed.

Adverse events & treatment discontinuation

4.4% (98 patients) of the 2241 patients enrolled in the trial experienced adverse events associated with therapy during the 6 months of treatment. The majority of the 148 adverse events in total were mild and four were moderate in intensity. The events did not necessitate hospital care. Dry cough (3.1%), leg swelling (2.2%), muscle ache (1.1%) and vertigo (0.2%) were the most common adverse events. Lisinopril–amlodipine therapy was discontinued in nine patients and rosuvastatin treatment was discontinued in ten patients. This was due to missing scheduled checkups in two patients, dry cough (five patients), swelling of legs (two patients) and muscle aches (eight patients).

Discussion

The most important tool in reducing atherosclerotic events is the amelioration of CV risk factors. The most relevant factors are smoking, diabetes mellitus, hypertension and hyperlipidemia. Recently published European and American guidelines (ESC, American College of Cardiology [ACC]/American Heart Association [AHA], American Society of Hypertension [ASH]) have significantly altered CV risk assessment and the definition of target values needed in antihypertensive and dyslipidemia therapy [8,9,25,36]. It is important to note that these guidelines still consider statin-based therapy to be a cornerstone of antihyperlipidemic treatment. All statins reduce LDL-C

levels; however, their lipid-lowering effects differ. Of all the statins (pravastatin, simvastatin, atorvastatin, rosuvastatin), rosuvastatin is the most effective agent in reducing LDL-C levels: rosuvastatin 40 mg/day resulted in a 56% reduction [37].

In the recently published European hypertension guidelines, none of the five main drug classes (β-blockers, ACE inhibitors, angiotensin II receptor blockers, calcium channel blockers, diuretics) was highlighted as a drug of choice in monotherapy [8]. It was noted, however, that combination therapy is preferred in order to improve patients' compliance, especially in those with hypertension in whom compliance with treatment is low [8,38]. Of the drug combinations, a renin–angiotensin–aldosterone system inhibitor (ACE inhibitor, angiotensin II receptor blocker) is recommended in combination with either a diuretic or a calcium channel blocker. The combination of an ACE inhibitor and a long-acting calcium channel blocker allows effective blood pressure control, target organ protection and a decreased rate of CV events [6,14,15].

We analyzed the safety and efficacy of fixed-combination lisinopril–amlodipine antihypertensive drug therapy and free-combination cholesterol-lowering rosuvastatin therapy in patients with mild or moderate hypertension and hypercholesterolemia who fell into high or very high CV risk categories. The strength of our 6-month, prospective, observational trial lies in its large number of evaluable patients and the enrollment of high-risk patients with comorbidities in whom the coexistence of multiple risk factors was known. The long-term amelioration of risk factors with multiple medications often presents a problem for patients and worsens compliance. Lisinopril–amlodipine fixed-combination preparations with their wide range of doses (10/5, 20/5, 20/10 mg) provide an opportunity to personalize therapy and achieve target blood pressure without the addition of more drugs to the regimen. This would be expected to significantly improve compliance in the long term and reduce CV morbidity and mortality.

Lisinopril–amlodipine-based therapy has proven to be effective in most high or very high-risk patients, according to our results. In symptom-free, high CV risk patients with hypertension, blood pressure values decreased below target (140/90 mmHg) in 68% of patients during the first 3 months of therapy and in 91% by the end of the sixth month of treatment. In the presence of comorbidities (diabetes mellitus, coronary and peripheral artery disease), our target value of <130/80 mmHg was achieved by 57% of patients by the end of the trial. It is important to note that, in the middle of our trial, the 2013 ESC/ESH hypertension guidelines [8] set new target blood pressure values (<140/90 mmHg, and <140/85 mmHg for diabetes mellitus) that negated the 130/80 mmHg target level we used in this study.

At the time of enrollment of patients with high and very high CV risks in our trial, their blood pressure was not in target range despite more than two-thirds of patients having received prior antihypertensive therapy. Achieving target values in this group is of paramount importance from a clinical perspective. According to our results, effective blood pressure control can be achieved with fixed-combination lisinopril–amlodipine-based therapy in previously treated patients who had failed to achieve target blood pressure. We found that lisinopril–amlodipine therapy was effective in reducing systolic and diastolic blood pressure to a similar extent in *de novo* patients and in those receiving prior antihypertensive drug therapy.

Concomitant rosuvastatin therapy significantly decreased LDL-C levels: a target of <3.0 mmol/l was achieved by 67% of patients during the 6 months of treatment in the trial. The proportion of patients achieving <2.5 mmol/l was 49%, while a target of 1.8 mmol/l was reached by 40%. Decreases in total cholesterol and triglyceride levels (25 and 23%), and increases in HDL-C values (6%) were also significant. Emphasis must be placed on the significant improvement in the lipid profile of the high CV risk population, in whom 48% of patients had received prior statin therapy yet their LDL-C levels were not in the target range. Switching to rosuvastatin in this high-risk population resulted in an increase in the proportion of patients (42%) achieving the <2.5 mmol/l target value. In the very high-risk patient group, 28% reached the target value (<1.8 mmol/l) by switching to rosuvastatin-based therapy. It is especially important to control blood pressure and lipid levels in patients with Type 2 diabetes mellitus and metabolic syndrome, as both conditions are associated with increased CV morbidity and mortality [39,40]. According to our observations, higher initial triglyceride, uric acid and BMI values and lower HDL-C values were present in patients with hypertension and dyslipidemic Type 2 diabetes than in the nondiabetic population. In patients with Type 2 diabetes mellitus and metabolic syndrome, the changes observed in blood pressure and lipid values were significant and were similar to those in nondiabetic patients in our trial. Thus, there were no significant differences between the diabetic and nondiabetic populations in the antihypertensive and antihyperlipidemic efficacy of the lisinopril–amlodipine plus rosuvasatin combination.

Lisinopril–amlodipine plus rosuvastatin therapy resulted in a significant drop in CRP values. Our results are in harmony with those of the JUPITER trial [30]; however, we observed a smaller decrease (12 vs 37%). This disparity is probably due to the different clinical characteristics of patients enrolled in the trials: the CRP reduction and subsequent reduction in CV events in the JUPITER trial were documented in patients with normal baseline LDL-C and elevated CRP levels. It deserves mentioning that during lisinopril–amlodipine plus rosuvastatin therapy a clinically moderate but statistically significant decrease was seen in independent laboratory parameters such as uric acid, microalbumin and blood glucose.

The increases in AST and CK were minimal in a clinical sense but were statistically significant. These findings were supported by those from the JUPITER trial where there was no difference in the rosuvastatin compared with the placebo group in these two parameters [30]. A previous study also found that elevations in CK were the lowest with rosuvastatin [31].

Lisinopril–amlodipine plus rosuvastatin treatment was well tolerated in most patients. Severe adverse events did not occur over the course of the trial. Dry cough (3.1%), leg swelling (2.2%), muscle aches (1.1%) and vertigo (0.2%) were the most common adverse events. Lisinopril–amlodipine plus rosuvastatin therapy was discontinued in 19 patients, primarily due to a dry cough and muscle aches. Global functioning as measured by CGIC showed that most patients were rated 'very much improved' (63.2%) or 'much improved' (20.8%).

The long-term amelioration of risk factors with fixed-combination preparations provides an opportunity to personalize therapy and achieve target blood pressure and LDL-C levels. This would be expected to significantly improve compliance in the long term and reduce CV morbidity and mortality as shown by the improvement in our SCORE risk data. Our study was performed in a large, general population with a high attendance rate. The limitation of our 6-month, prospective, observational trial lies in its short observation period. Future studies are also expected to allow conclusions regarding CV events.

Conclusion

Based on the results of this trial, fixed-combination lisinopril–amlodipine antihypertensive therapy and free-combination rosuvastatin treatment can be effectively and safely used in high and very high CV risk patients with mild or moderate hypertension and hypercholesterolemia.

Financial & competing interests disclosure

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

- Control of cardiovascular (CV) risk factors, particularly hypertension and hyperlipidemia, is the most important tool in reducing atherosclerotic events.
- This large 6-month, prospective observational trial assessed the safety and effectiveness of fixed-combination lisinopril–amlodipine (10/5, 20/5 or 20/10 mg/day) plus rosuvastatin (10 or 20 mg/day) in patients with mild or moderate hypertension and hypercholesterolemia who were at high and very high CV risk.
- At 6 months, 91% of patients achieved target blood pressure levels (<140/90 mmHg) with lisinopril–amlodipine-based therapy.
- Rosuvastatin effectively reduced LDL-cholesterol levels: after 6 months, a target of <3 mmol/l was reached by 67% of patients, while 49% achieved <2.5 mmol/l and 40% achieved the 1.8 mmol/l target. Reductions in blood pressure and low-density lipoprotein cholesterol were similar for patients with Type 2 diabetes mellitus versus nondiabetic patients, and for previously treated versus *de novo* patients.
- Significant decreases in C-reactive protein, uric acid, microalbumin and blood glucose levels were observed at study end.
- The incidence of adverse events was low (4.4%) and most events were mild.
- In this large observational study, lisinopril–amlodipine plus rosuvastatin was well tolerated and effective in patients with mild or moderate hypertension and hypercholesterolemia at high and very high CV risk.

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