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Treatment with triple combination of atorvastatin, perindopril, and amlodipine in patients with stable coronary artery disease: A subgroup analysis from the PAPA-CAD study

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Abstract

Background: In patients with stable coronary artery disease, aspirin, a statin, and an angiotensin-converting enzyme inhibitor are recommended as first-line agents for secondary prevention. Subgroup analyses of the previously published Hungarian Perindopril plus Amlodipine in PAtients with Coronary Artery Disease (PAPA-CAD) non-interventional trial demonstrated that the addition of the metabolically beneficial, fixed combination of perindopril + amlodipine to atorvastatin further improves the patient's lipid profile.

Methods: The PAPA-CAD study, a 6-month open-label, prospective, multicenter, observational/non-interventional survey evaluated data accumulated from patients with hypertensive patients with stable coronary artery disease. The herein-reported subgroup analysis was conducted using the findings from those 1130 patients, who were taking atorvastatin in addition to the fixed combination of perindopril + amlodipine at the time of all four study visits (i.e., at baseline and 1, 3, and 6 months later).

Results: In the subgroup of patients taking atorvastatin as an add-on agent, 82.5% reached the target blood pressure of 140/90 mmHg compared with 78.8% of those not taking a statin. The addition of atorvastatin to the fixed combination of perindopril + amlodipine resulted in further significant improvements of key metabolic parameters.

Conclusion: This subgroup analysis confirmed that favorable synergism exists among perindopril, amlodipine, and atorvastatin.

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Introduction

Key risk factors for stable coronary artery disease

Hypertension and hypercholesterolemia are the two most important, modifiable, and treatable risk factors for ischemic heart disease and thus define the strategy for its primary and secondary prevention. Aspirin, a statin, and an angiotensin-converting enzyme inhibitor (ACEI) are recommended as first-choice agents In patients with stable coronary artery disease (SCAD), whereas beta-blockers and calcium channel blockers (CCBs) are suggested as anti-anginal medications.[1]

ACEIs are the mainstay of pharmacotherapy for SCAD and acute coronary syndrome. By reducing the serum concentration of angiotensin II, the central effector molecule of the renin-angiotensin-aldosterone system, these agents exert a variety of beneficial effects in addition to lowering blood pressure. In particular, ACEIs have been shown to mitigate endothelial dysfunction, reduce vascular inflammation, moderate prothrombotic activity, and normalize the fibrinolytic response.[2,3]

Most hypertensive patients with SCAD require combination therapy with two to three antihypertensive agents to reach their target blood pressure. In view of the demonstrated efficacy of these agents in reducing cardiovascular morbidity and mortality, recent therapeutic guidelines (European Society of Cardiology 2013)[1] recommend the use of ACEIs and CCBs, which have confirmed anti-atherosclerotic activity. Based on the latest recommendations (European Atherosclerosis Society/European Society of Cardiology 2016),[4] patients with dyslipidemia (i.e., hypercholesterolemia or mixed hyperlipidemia) and those with ischemic heart disease should receive statin therapy regardless of their cholesterol level. The target low-density lipoprotein (LDL)-cholesterol level should be <1.8 mmol/L, and/or a $\geq 50\%$ reduction of the baseline LDL-cholesterol concentration must be achieved.[4]

Combination therapy with perindopril, amlodipine, and atorvastatin

The benefits of the combination of an ACEI, CCB, and statin, as well as the synergism among these active substances, were confirmed by the *post hoc* analyses of the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA) study.[5] The beneficial impact of these agents on clinical events may be attributed largely to the synergistic, vascular protective, and metabolic effects common to perindopril, amlodipine, and atorvastatin.[6,7]

The present subgroup analysis of the Hungarian Perindopril plus Amlodipine in PAtients with Coronary Artery Disease (PAPA-CAD) non-interventional trial was undertaken to ascertain whether addition of the fixed combination of perindopril + amlodipine (with favorable or neutral metabolic effects) to atorvastatin could

further improve patients' lipid profiles. The analyzed subgroup comprised patients with SCAD who had received atorvastatin in addition to the fixed combination of perindopril + amlodipine during the period of data acquisition or who had taken some other statin before their inclusion in the study.

Patients and methods

The PAPA-CAD study—a 6-month open-label, prospective, multicenter, observational/non-interventional survey—was performed to evaluate data from hypertensive patients with SCAD.[8] The present subgroup analysis of the PAPA-CAD study was performed using the data of patients who were receiving atorvastatin in addition to the fixed combination of perindopril + amlodipine at the time of all four study visits (i.e., at baseline and 1, 3, and 6 months later). We also evaluated the data of patients who had not been taking a statin along with the fixed combination of perindopril + amlodipine before or during the study.

The data were recorded during the routine follow-up of the patients, during which the investigators did not administer any further supplementary tests or additional therapies for the purposes of the study. The therapy was decided at the professional discretion of the investigator before inclusion of the patients in the study. The patients received written and verbal briefings about the study and then provided written informed consent. The study protocol was drafted in conformity with applicable law and with the principles of the Declaration of Helsinki. The study has been licensed by the MRC-NS&EC under N°21938-1/2011-EKU (698/PI/11.).

The study data were analyzed in compliance with EU-GCP/ICH standards. All data are summarized and presented by descriptive statistics. Repeated-measures analysis of variance was performed to evaluate continuous variables, whereas the Friedman test or McNemar test was applied to categorical variables. A two-tailed significance level of 0.05 was used.

Results

Baseline data

The PAPA-CAD study included data from 3,472 hypertensive patients with SCAD, and the present subgroup analysis included the data of 1130 patients (493 female, 637 male; mean age, 63.5 ± 8.8 years; mean body mass index, 29.1 ± 4.8 kg/m^2). The mean office blood pressure was $156.8 \pm 12.9/93.0 \pm 8.6$ mmHg [systolic blood pressure (SBP)/diastolic blood pressure (DBP)] and the mean duration of hypertension was 12.7 ± 7.9 years. The incidences of the individual risk factors and concomitant disorders differed significantly between the subsets of patients receiving *vs.* not receiving atorvastatin therapy (Table 1). We also evaluated the data of 514 patients who had not been taking a statin along with the fixed combination of perindopril + amlodipine before or during the study.

The diagnosis of SCAD was established by the presence of the following events or diagnostic interventions: angina pectoris, myocardial infarction, coronary angiography, balloon dilatation, stent placement (percutaneous coronary intervention), exercise tolerance testing, stress echocardiography, and stress perfusion scintigraphy (Table 2).

Office blood pressure and heart rate

Of the patients treated with the triple combination of atorvastatin, perindopril, and amlodipine, 44.1% had mild, 46.5% had moderate, and 9.5% had severe hypertension (i.e., Stage I: $140/90 < \text{SBP}/\text{DBP} < 159/99$ mmHg, Stage II: $160/100 < \text{SBP}/\text{DBP} < 179/109$ mmHg, and

Stage III: SBP/DBP > 179/109 mmHg, respectively).

By the end of Month 6, the mean office blood pressure had decreased from $156.8 \pm 12.4/93.0 \pm 8.4$ to $130.6 \pm 7.9/79.6 \pm 5.8$ mmHg; that is, by $26.3 \pm 12.30/13.4 \pm 9.1$ mmHg ($p < 0.0001$). The reductions in the blood pressure and heart rate were proportional to the baseline values. In the subgroup of patients taking atorvastatin as an add-on agent, 82.5% reached the target blood pressure of 140/90 mmHg compared with 78.8% of those not taking a statin. The higher control rates achieved with the perindopril, amlodipine, and atorvastatin combination were clinically relevant and significant in patients with moderate hypertension ($p < 0.01$) (Figure 1). The latter result suggests the ability of statins to reduce blood pressure independently of their lipid-lowering activity, especially in combination with CCBs.[9]

Table 1. Risk factors and concomitant disorders in atorvastatin-treated *vs.* untreated subgroups of the PAPA-CAD study

	Atorvastatin		No statin	
	n	%	n	%
Risk factors				
Dyslipidemia	869	76.9%	84	16.34%
Obesity	434	38.4%	162	31.52%
Smoking	448	39.6%	260	50.58%
Positive family history	449	39.7%	214	41.63%
IFG	187	16.5%	61	11.87%
IGT	59	5.2%	11	2.14%
Co-morbidities				
Diabetes mellitus	349	30.9%	105	20.43%
TIA/stroke	183	16.2%	52	10.12%
Renal disease	76	6.7%	28	5.45%
Peripheral vascular disease	247	21.9%	48	9.34%
Retinopathy	77	6.8%	31	6.03%
COPD	137	12.1%	57	11.09%

COPD, chronic obstructive pulmonary disease; IFG, impaired fasting glucose level; IGT, impaired glucose tolerance; TIA, transient ischemic attack.

Results of electrocardiographic evaluation

Electrocardiographic exercise tolerance testing was performed at Visits 1 and 4 in 64 patients of the subgroup. Testing was performed using a treadmill in 38% patients and a bicycle ergometer in 62%. Exercise tolerance increased significantly after 6 months of treatment. In particular, the mean maximum workload increased from 90.1 ± 37.4 to 107.1 ± 38.8 W (i.e., by 18.8%; $p < 0.001$), or from 8.38 ± 3.00 to 8.77 ± 3.33 METs (i.e., by 4.6%; $p < 0.001$). The mean maximum ST depression decreased from 0.75 ± 0.91 to 0.52 ± 0.68 mm (i.e., by 30.7%; $p < 0.0001$).

Table 2. Rates of symptoms, clinical events, or diagnostic interventions in patients with stable coronary artery disease enrolled in the PAPA-CAD study

	Atorvastatin		No statin	
Coronary artery disease	n	%	n	%
Angina pectoris	769	68.1%	419	81.52%
Myocardial infarction	317	28.1%	45	8.75%
Positive coronary angiography (stenosis)	140	12.4%	13	2.53%
PCI (balloon dilation or stent placement)	120	10.6%	12	2.33%
Positive ECG exercise tolerance testing	174	15.4%	83	16.15%
Positive stress echocardiography	1	0.1%	1	0.19%
Positive stress scintigraphy	21	1.9%	13	2.53%

ECG, electrocardiographic; PCI, percutaneous coronary intervention.

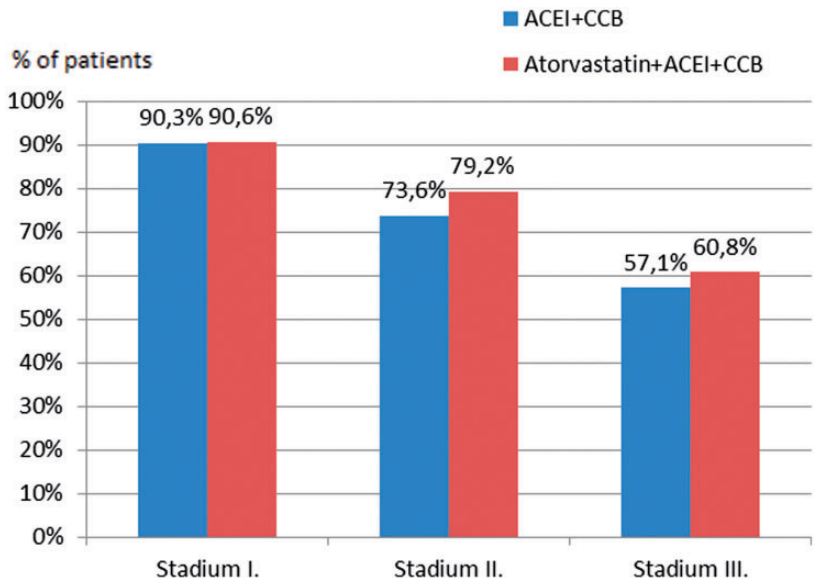

Figure 1. Proportions of patients reaching target blood pressure in the subgroups of the PAPA-CAD study (baseline blood pressure: 160–179/100–109 mmHg).

Changes in metabolic parameters

The following statistically significant changes in metabolic parameters were observed in patients taking atorvastatin: the total cholesterol concentration decreased from 5.53 ± 1.04 to 4.90 ± 0.79 mmol/L, the LDL-cholesterol concentration decreased from 3.09 ± 0.91 to 2.65 ± 0.82 mmol/L, the triglyceride concentration decreased from 2.11 ± 0.76 to 1.80 ± 0.53 mmol/L, the fasting blood glucose concentration decreased from 6.12 ± 1.44 to 5.80 ± 1.10 mmol/L, the HgA1c level decreased from $6.99\% \pm 3.87\%$ to $6.46\% \pm 1.05\%$, the serum uric acid concentration decreased from 330.35 ± 72.68 to 310.04 ± 57.65 μmol/L, and the serum high-density lipoprotein cholesterol level increased from 1.30 ± 0.36 to 1.35 ± 0.34 mmol/L (all $p < 0.0001$). The other monitored parameters (potassium, sodium, and serum creatinine) did not change significantly (Table 3).

This analysis was performed exclusively on the data of patients who had been taking a statin at the time of their inclusion in the trial and received atorvastatin therapy during the 6-month study period. Therefore, any additional favorable changes observed in their metabolic parameters may be attributed to the following three factors:

1. Antihypertensive agents with unfavorable metabolic effects (such as conventional thiazides or second-generation beta-blockers) were discontinued in a large proportion of these patients.
2. At baseline, a small proportion (8%) of the patients on pre-existing therapy with simvastatin or fluvastatin was switched to atorvastatin.
3. Patients' adherence to atorvastatin treatment administered as an add-on to the perindopril + amlodipine fixed combination was greater; thus, the favorable changes in metabolic parameters may

Table 3. Changes in metabolic parameters in the analyzed subgroup of the PAPA-CAD study

	Atorvastatin					No statin				
Parameter	n	Visit 1	Visit 4	Change	%	n	Visit 1	Visit 4	Change	%
Total cholesterol (mmol/L)	316	5.53	4.9	−0.63*	−11.4%	102	5.13	4.92	−0.21*	−4.1%
HDL-cholesterol (mmol/L)	164	1.3	1.35	0.05*	3.8%	45	1.29	1.32	0.03	2.3%
LDL-cholesterol (mmol/L)	135	3.09	2.65	−0.44*	−14.2%	35	2.8	2.72	−0.08	−2.9%
Potassium (mmol/L)	280	4.38	4.34	−0.04	−0.9%	93	4.3	4.26	−0.04	−0.9%
Glucose (mmol/L)	354	6.12	5.8	−0.32*	−5.2%	121	5.84	5.32	−0.52*	−8.9%
HbA_{1c} (%)	137	6.99	6.46	−0.53*	−7.6%	36	5.94	5.64	−0.3	−5.1%
Triglycerides (mmol/L)	299	2.11	1.8	−0.31*	−14.7%	94	1.87	1.67	−0.2*	−10.7%
Uric acid (μmol/L)	223	330.35	310.04	−20.3*	−6.1%	82	324.59	302.13	−22.46*	−6.9%
Sodium (mmol/L)	268	140.12	140.52	0.4	0.3%	90	141.68	141.46	−0.22	−0.2%
eGFR (ml/min/1.73 m^2)	151	61.31	62.01	0.7	1.1%	33	65.73	66.21	0.48	0.7%
Serum creatinine (mmol/L)	257	90.34	87.25	−3.09	−3.4%	79	85.42	83.18	−2.24	−2.6%

*$p < 0.0001$.
eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

be related to the higher persistence of patients on this therapy.

Discussion

Combination therapy with an ACEI, a CCB, and a statin is common in the routine management of SCAD. The favorable clinical effects of these active substances are possibly attributable to the anti-atherosclerotic activity shared by all three agents. These agents prevent the onset of endothelial dysfunction and inhibit the oxidation of LDL-cholesterol, proliferation and migration of smooth muscle cells, and disruption of the fibrous cap of atherosclerotic plaques. All of these actions contribute to halting plaque formation and stabilizing existing plaques.[6]

Experimental studies have shown that smooth muscle cells have two types (phenotypes). Normally, the state of the cell is influenced by the activity of voltage-gated L-type receptors (i.e., extracellular calcium influx) and by the functioning of ryanodine receptors in the sarcoplasmic reticulum (i.e., release of intracellular calcium ion reserves). The activation of these receptors induces vascular contraction, while their inhibition causes vasodilatation. As a result of toxic or mechanical damage to the cell membrane provoked by cholesterol accumulation in the membrane or the shear stress resulting from high blood pressure, the cell transitions from the resting state to a proliferative, synthesizing state, or a de-differentiated phenotype. This in turn leads to a decrease in the expression of L-type receptors and the activation of low-voltage-activated T-type receptors. The practical implication is that in this condition, the cell does not contract and relax and is susceptible to proliferation and migration. CCBs are not able to induce vasorelaxation in this scenario; therefore, they do not reduce blood pressure. If atherosclerotic factors are present in the background of this pathology, atorvastatin may regenerate the cell membrane, and the function of the voltage-gated L-type calcium channels may be restored as well. Consequently, the efficacy of CCBs will also return, and amlodipine will be able to induce vasorelaxation.[10–12]

The benefits of add-on therapy with the combination of an ACEI and a CCB,

as well as the synergism between these active substances, were primarily confirmed by the lipid-lowering arm of the ASCOT study. In particular, the *post hoc* analyses of the ASCOT-LLA data showed a significant reduction of cardiovascular risk regardless of the baseline total cholesterol level in hypertensive patients treated even with a low 10-mg dose of atorvastatin. When atorvastatin was added to the combination of amlodipine administered with or without perindopril, the relative risk of nonfatal myocardial infarction and fatal coronary heart disease decreased by 53% ($p < 0.001$) after 3.3 years of treatment. In contrast, adding atorvastatin to an alternative antihypertensive combination (atenolol ± bendroflumethiazide) failed to achieve a significant reduction of any of these endpoints.[5]

An inverse relationship has been demonstrated between therapy with HMG-CoA-reductase inhibitor statins and the incidence of acute cardiac events caused by atherosclerosis and ischemic heart disease.[13]

During the last few years, however, several biased analyses and misinterpreted findings have been published, among other findings on issues related to statin treatment in senile patients and the possible induction of new-onset diabetes. These reports have raised concerns among medical practitioners regarding the usefulness of statins. Moreover, rumors about the magnitude of the risks associated with the use of these agents has begun to spread on a large scale among laypeople, leading some to reject statins altogether.[14,15]

Considering the aging of the population and the impressive progress achieved in the diagnostics of coronary artery disease, one would expect an increasing trend of statin use. In reality, however, the expansion of the therapeutic administration of statins has slowed in the last 2 to 3 years and even decreased somewhat in 2016.[16] All of these developments may be perceived as the possible aftermath of the negative views published in both professional journals and the lay media.

The difficulty of initiating statin therapy is further aggravated by rather poor patient persistence, which is characteristic of this group of medicines. Similarly low patient compliance and adherence are common with all medicinal products intended for the management of cardiovascular risk factors (such as hypertension, hypercholesterolemia, and hyperuricemia). Conversely, patient persistence can be as high as 75% during the administration of an original, fixed combination of an ACEI + CCB.[17]

Conclusions

According to the subgroup analysis from the PAPA-CAD study, the clinical benefits of the studied agents were evident as early as after the brief 6-month study period.

Notwithstanding the confirmed reductions in morbidity and mortality by statins, the statistics describing the persistence of patients on statin therapy have been showing progressive worsening over the last several years. One viable means of rectifying this situation is integrating the statin into a fixed antihypertensive combination characterized by better persistence indices. The triple fixed combination of the ACEI perindopril, the CCB amlodipine, and atorvastatin might be a suitable candidate for this purpose. Because of improved patient adherence and persistence as well as the proven synergistic actions of its components, this fixed triple combination of active substances might enhance primary and secondary prevention of SCAD.

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Declaration of conflicting interests

The author declares that there is no conflict of interest.

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