Post hoc analysis of the EUROPA study: The clinical synergy of perindopril and any calcium channel blocker (CCB) in the prevention of cardiac events and mortality in patients with coronary artery disease (CAD)[3]

EUROPA STUDY BACKGROUND

— Evaluate the outcomes in a subset population of EUROPA clinical trial patients who were on both perindopril and any CCB vs. those on placebo and any calcium channel blocker in the long-term treatment of coronary artery disease
— Demonstrate the clinical synergy between perindopril and any CCB in secondary prevention

METHODS

— Identified participants receiving any CCB at every visit during 4.2-year follow-up
— Analyzed the effect of perindopril (n=1022 perindopril/CCB vs. n=1100 placebo/CCB)

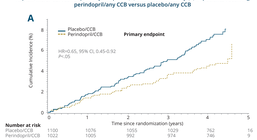
RESULTS

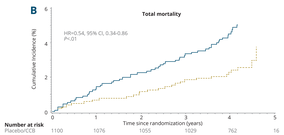
— The combination of perindopril and any CCB significantly reduced total mortality by 46% (*P*<.01 vs. placebo)
— Perindopril with CCB also reduced the primary endpoint—a composite of cardiovascular mortality, nonfatal myocardial infarction, and resuscitated cardiac arrest—by 35% (*P*<.05 vs. placebo)
— There were 41%, 54%, and 28% reductions in cardiovascular mortality, hospitalization for heart failure, and myocardial infarction, respectively
— Comparison of hazard ratios suggests the presence of a clinical synergy between perindopril and any CCB, with a greater effect than addition of individual effects

CONCLUSION

The combination of perindopril and any CCB in stable CAD patients had a significant supplementary impact on cardiac outcomes and mortality.

Kaplan-Meier curves for *primary endpoint* (A) and *total mortality* (B) in patients receiving perindopril/any CCB versus placebo/any CCB





Effect of study treatments in patients receiving CCB on primary and secondary endpoints.

	Event rate (%) Perindopril/CCB (n=1022)	Placebo/CCB (n=1100)	Relative risk reduction	95% CI
Primary endpoint	4.9	7.5	35%	0.45-0.92
Total mortality	2.65	4.85	46%	0.34-0.86
Cardiovascular mortality	1.6	2.6	41%	0.32-1.06
Fatal and nonfatal MI	3.9	5.4	28%	0.48-1.07
Hospitalization for HF	0.3	0.6	54%	0.12-1.76

Favors perindopril/CCB — Favors placebo/CCB

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[2]

Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J; ASCOT Investigators

ASCOT STUDY BACKGROUND

— Apparent shortfalls in prevention of coronary heart disease (CHD) noted in early hypertension trials have been attributed to disadvantages of the diuretics and beta blockers used
— It has been suggested that newer agents would confer advantages over diuretics and beta blockers
— The aim of the ASCOT study was to compare the effect of combinations of atenolol with a thiazide versus amlodipine with perindopril on nonfatal myocardial infarction and nonfatal CHD

METHODS

— Conducted a multicenter, prospective, randomized, controlled trial in 19,257 patients, aged 40 to 79 years, with hypertension and at least 3 other CV risk factors
— Patients assigned either amlodipine 5 mg to 10 mg adding perindopril 4 mg to 8 mg as required (amlodipine-based regimen; n=9639) or atenolol 50 mg to 100 mg adding bendroflumethiazide 1.25 mg to 2.5 mg and potassium as required (atenolol-based regimen; n=9618)
— The primary endpoint was nonfatal MI (including silent MI) and fatal CHD

RESULTS

Compared with the atenolol-based regimen, patients on the amlodipine-based regimen had:
— A nonfatal MI (429 vs 474; unadjusted HR 0.90; 95% CI, 0.79-1.02; *P*=0.1052)
— Fatal and nonfatal stroke (327 vs 422; unadjusted HR 0.77; 95% CI, 0.66-0.89; *P*=0.0003)
— Total cardiovascular events and procedures (1362 vs 1602; unadjusted HR 0.84; 95% CI, 0.78-0.90; *P*<0.0001)
— All-cause mortality (738 vs 820; unadjusted HR 0.89; 95% CI, 0.81-0.99; *P*=0.025)

CONCLUSION

The amlodipine-based regimen—adding perindopril as required—prevented more major cardiovascular events than the atenolol-based regimen. These results have implications with respect to optimum combinations of antihypertensive agents.

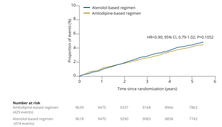


Figure 1: Kaplan-Meier curves of cumulative incidence of nonfatal MI, including silent MI, and fatal CHD.

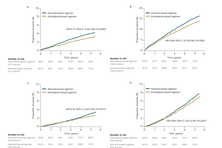


Figure 2: Kaplan-Meier curves of cumulative incidence of fatal and nonfatal stroke (A), total cardiovascular events and procedures (B), cardiovascular mortality (C), and all-cause mortality (D).

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OUTSIDE

PRESTALIA® is available as the following 3 combinations:
3.5/2.5 mg, 7/5 mg, or 14/10 mg.

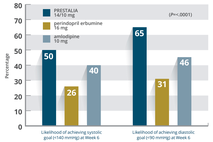
PRESTALIA is available for $0 commercial co-pay, $6 for all state- or government-subsidized programs, and $8.95 for uninsured patients. Free, direct shipping and a free Omron® blood pressure monitor included.

prestalia®
perindopril arginine/
amlodipine besylate tablets

References:

1. PRESTALIA® (perindopril arginine and amlodipine besylate) tablets Summary of Product Characteristics. 2016.2. Dahlof B, Sever PS, Poulter NR, et al; ASCOT Investigators. 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(9489):895-906. 3. Bertrand ME, Ferrari R, Remme W, et al; EUROPA Investigators. Clinical synergy of perindopril and calcium-channel blocker in the prevention of cardiac events and mortality in patients with coronary artery disease. Post hoc analysis of the EUROPA study. Am Heart J. 2010;159(5):795-802.

Likelihood of Achieving Target Systolic and Diastolic Blood Pressure Goals*†



*Patient with a baseline blood pressure of 170/105 mm Hg. The curve for each treatment group was estimated by logistic regression modeling.

SAFETY

Adverse Event	PRESTALIA 14/10 mg (N=279) / n (%)	perindopril erbumine 16 mg (N=278) / n (%)	amlodipine 10 mg (N=280) / n (%)
Edema peripheral	20 / (7.2)	1 / (0.4)	37 / (13.2)
Cough	9 / (3.2)	8 / (2.9)	2 / (0.7)
Headache	7 / (2.5)	8 / (2.9)	8 / (2.9)
Dizziness	7 / (2.5)	4 / (1.4)	3 / (1.1)

The safety of the maximum dose of PRESTALIA (14/10mg) was evaluated in a 6-week clinical trial 279 patients with hypertension and compared with perindopril erbumine 16 mg and amlodipine 10 mg. Adverse reactions were generally mild and transient in nature.[1]

WARNING: FETAL TOXICITY
- **When pregnancy is detected, discontinue PRESTALIA as soon as possible**
- **Drugs that act directly on the renin-angiotensin system, can cause injury and death to the developing fetus**

Fixed-dose combinations (FDCs): A strong offense in chronic disease management[2]

According to *The American Journal of Medicine*[2]:
- Noncompliance to medication regimens is reduced by 24% to 26% with FDC regimens
- FDCs should be considered in patients with chronic conditions like hypertension
- FDCs improve medication compliance, which can translate into better clinical outcomes

For more information about PRESTALIA® (perindopril arginine and amlodipine):

Call: 888-552-9769 e-mail: info@symplmed.com

Rx: Submit to ***Condo Pharmacy*** or fax to **(518) 563-5946** for **$0 commercial co-pay, $6** for all state- or government-subsidized programs, and $8.95 for uninsured patients. Free, direct shipping and a free Omron® blood pressure monitor included.

Visit: **www.prestalia-us.com** or **www.bpcareconnect.com**

INDICATIONS AND USAGE

PRESTALIA® (perindopril arginine and amlodipine) is a combination of perindopril, an angiotensin converting enzyme inhibitor, and amlodipine, a dihydropyridine calcium channel blocker, indicated for the treatment of hypertension to lower blood pressure:

- In patients not adequately controlled with monotherapy.
- As initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals.

Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.

IMPORTANT SAFETY INFORMATION

When pregnancy is detected, discontinue PRESTALIA® as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

PRESTALIA is contraindicated in patients with hereditary or idiopathic angioedema, with or without previous angiotensin converting enzyme (ACE) inhibitor treatment, and in patients who are hypersensitive to perindopril, to ACE inhibitors, or to amlodipine. Rare cases of angioedema, including intestinal angioedema, have been reported in patients treated with ACE inhibitors. Do not co-administer aliskiren with ACE inhibitors, including PRESTALIA, in patients with diabetes.

Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of PRESTALIA, particularly in patients with severe obstructive coronary artery disease. In patients at risk of excessive hypotension, start PRESTALIA therapy under close medical supervision. Follow patients closely for the first 2 weeks of treatment and whenever the dose of PRESTALIA is increased or a diuretic is added or its dose increased. Monitor renal function periodically in patients treated with PRESTALIA. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function.

The most common adverse events associated with PRESTALIA include peripheral edema, cough, headache, and dizziness.

PLEASE SEE ACCOMPANYING FULL PRESCRIBING

prestalia®
perindopril arginine/
amlodipine besylate tablets

symplmed™
THE PRESCRIPTION FOR BETTER CARE

When monotherapy is inadequate or multiple drugs are likely needed to control high blood pressure...

PRESCRIBE **PRESTALIA®**, THE SIMPLICITY OF A PROVEN SINGLE-PILL COMBINATION (SPC)

prestalia®
perindopril arginine/
amlodipine besylate tablets

PRESTALIA® is the first SPC of perindopril arginine and amlodipine (an ACE inhibitor and the most widely used calcium channel blocker [CCB]) indicated for first-line treatment of hypertension besylate for the treatment of hypertension.[1]

3 approved combinations of PRESTALIA®:
3.5/2.5mg, 7/5 mg, 14/10 mg

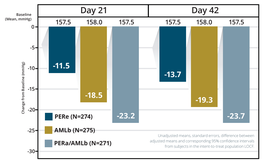
WARNING: FETAL TOXICITY
- **When pregnancy is detected, discontinue PRESTALIA as soon as possible**
- **Drugs that act directly on the renin-angiotensin system, can cause injury and death to the developing fetus**

EFFICACY AND DOSING

Rapid and sustained BP control

The antihypertensive effects of PRESTALIA (perindopril arginine and amlodipine) tablets were studied in the PATH (Perindopril and Amlodipine in Treatment of Hypertension) trial.[1] Peak efficacy was achieved by Week 3 and sustained to Week 6.

Mean Change from Baseline in Sitting SBP



PRESTALIA 14/10 mg

The highest strength of PRESTALIA (14/10) mg was studied in 837 patients in a 6-week, double-blind, active controlled clinical trial. Patients with a seated diastolic pressure of 95 mm to 115 mm Hg received treatments of PRESTALIA 14/10 mg, perindopril erbumine 16 mg, or amlodipine 10 pg once daily for 6 weeks.

Reduction of CV events

Any reduction in blood pressure may reduce the incidence of heart attack, stroke and death. Both perindopril and amlodipine have proven in both placebo controlled trials and event trials to have an effect beyond just blood pressure reduction when compared to similar agents.[1]

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