

ARTICLE

The effect of age on blood pressure response by 4-week treatment perindopril: A pooled sex-specific analysis of the EUROPA, PROGRESS, and ADVANCE trials

Michelle M. Schreuder¹ | Katrina M. Mirabito Colafella² | Eric Boersma³ |
Jasper J. Brugts³ | Jeanine E. Roeters van Lennep¹ | Jorie Versmissen^{1,4}

¹Department of Internal Medicine, Erasmus MC University Medical Centre, Rotterdam, The Netherlands

²Cardiovascular Disease Program, Biomedicine Discovery Institute and Department of Physiology, Monash University, Melbourne, Australia

³Department of Cardiology, Erasmus MC University Medical Centre, Rotterdam, The Netherlands

⁴Department of Hospital Pharmacy, Erasmus MC University Medical Centre, Rotterdam, The Netherlands

Correspondence

Jorie Versmissen, Erasmus Medical Centre, Department of Internal Medicine, PO Box 2040, 3000 CA Rotterdam, The Netherlands.
Email: j.versmissen@erasmusmc.nl

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Abstract

Previous studies showed that postmenopausal women are more likely to have poorly controlled hypertension than men of the same age. Whether this is caused by inadequate treatment or poor response to antihypertensive agents remains unknown. The aim of this study is to analyze treatment response to the most potent renin angiotensin aldosterone system (RAAS) inhibitor perindopril in different age categories in women and men. Individual patient data were used from the combined European Trial on Reduction of Cardiac Events With Perindopril (EUROPA), Perindopril Protection Against Recurrent Stroke Study (PROGRESS), and Action in Diabetes and Vascular disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) trials, which include patients with vascular disease ($n = 29,463$). We studied the relative and absolute changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) during a 4-week run-in phase in which all patients were treated with the perindopril-based treatment in different age categories. In total, 8366 women and 21,097 men were included in the analysis. Women greater than 65 years of age showed a significantly smaller blood pressure reduction after perindopril treatment (2.8 mmHg [95% confidence interval {CI} = 0.1–5.5] less reduction compared to women ≤ 45 years, $p = 0.039$). In men, the SBP reduction after perindopril in patients greater than 55–65 and greater than 65 years was lower compared to the age category less than or equal to 45 years (adjusted mean difference >55 –65: 2.8 mmHg [95% CI = 1.8–3.7], $p < 0.001$, >65 : 3.7 mmHg [95% CI = 2.7–4.7], $p < 0.001$). A trend of less blood pressure reduction was seen with ageing in both men and women ($p < 0.001$). To conclude, we observed that in both women and men the perindopril leads to less SBP reduction with increasing age, whereas the DBP reduction increases with age. More research is needed to determine whether it would be beneficial to use age-adjusted perindopril dosages.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Previous animal studies have shown that the response to antihypertensive treatment targeting the renin angiotensin aldosterone system (RAAS) might be different after reproductive senescence.

WHAT QUESTION DID THIS STUDY ADDRESS?

Are there differences in perindopril-based treatment response to RAAS inhibitor perindopril in different age categories in women and men?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

In both women and men, the effects of perindopril on systolic blood pressure decrease and on diastolic blood pressure increase with age.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

More research is needed to find out whether it would be beneficial to use age-adjusted perindopril dosages in isolated systolic hypertension.

INTRODUCTION

Premenopausal women typically have lower blood pressure than age-matched men.¹ Studies have shown that aging in men and women is accompanied by an increase in blood pressure, and that this age-related increase is more prominent in women after menopause.² As a result, the prevalence of hypertension in postmenopausal women is higher than in age-matched men.³ Moreover, postmenopausal women are more likely to have poorly controlled hypertension than men.³ Whether this is caused by inadequate treatment or poor response to antihypertensive agents remains unknown.

Renin angiotensin aldosterone system (RAAS) inhibitors, such as angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) are a mainstay treatment for hypertension. In recent years, animal studies have provided strong evidence that sex- and age-related differences exist in the RAAS.⁴ For example, sex chromosomes and sex hormones are known to modulate the depressor/pressor balance of the RAAS with female mice having greater expression of the depressor components of the RAAS (e.g., angiotensin type 2 receptor and angiotensin converting enzyme 2). Consequently, women of reproductive age are less sensitive to the vasopressor effects of angiotensin II than age-matched men⁵ and aging reproductively senescent women.⁴ In humans, the acute infusion of angiotensin II has similar effects on blood pressure between women and men. However, when given an ARB, the depressor response is more rapid in premenopausal women as compared to men.⁶ Therefore, the response to antihypertensive treatment targeting the RAAS might be different after menopause. Earlier sex-specific analyses of RAAS inhibitors compared men and women and did not take menopausal status into account.⁷

As a result of the above-described differences in RAAS, the short-term response of ACEi on blood pressure might differ between women and men in relation to age. To evaluate

this hypothesis, we performed a proof-of-principal study based on the 4-week run-in phase of three large randomized controlled trials of the ACEi perindopril in cardiovascular (CV) patients: the European Trial on Reduction of Cardiac Events With Perindopril (EUROPA), Perindopril Protection Against Recurrent Stroke Study (PROGRESS), and Action in Diabetes and Vascular disease: Preterax and Diamicon-MR Controlled Evaluation (ADVANCE).^{8–10}

METHODS

Patients and material

EUROPA, PROGRESS, and ADVANCE studied the effectiveness of perindopril to reduce CV outcomes in patients with established CV disease (CVD).^{8–10} ADVANCE enrolled patients with type 2 diabetes, EUROPA included patients with stable coronary heart disease, and PROGRESS studied patients with a history of stroke or transient ischemic attack (TIA). In all three trials, potentially eligible patients entered a pre-randomization run-in phase of 4–6 weeks, during which they received open-label perindopril. For the current study, we only used the blood pressure data that were obtained during this run-in. The dosage of perindopril and the comedication varied between the trials: EUROPA studied perindopril 4 mg/day for 2 days followed by 8 mg/day for 2 weeks; PROGRESS studied perindopril 2 mg/day for 2 weeks followed by 4 mg/day for 2 weeks, ADVANCE studied a fixed dose combination of perindopril 2 mg/day plus indapamide 0.625 mg/day. The combined dataset has been used previously and confirmed the consistency of the treatment benefit of perindopril within patients at different level of risk but with the same underlying disease (vascular disease). Heterogeneity of the treatment effect of perindopril has been studied previously within these cohorts as well as on

pharmacological levels, where perindopril is one of the more potent ACE-inhibitors in terms of bradykinin release,^{11–13} which makes it the most relevant to study.

Data analysis and presentation

Continuous baseline characteristics are presented as mean values \pm one SD, whereas categorical characteristics are presented as numbers and percentages. Differences between women and men, as well as differences between age categories were studied by Student's *t*-tests and linear trend tests for continuous data, and by χ^2 tests for categorical data.

Information on menopausal (hormonal) status in women was not systematically collected. Alternatively, we used the women's (baseline) age to estimate menopausal (hormonal) status. We considered the following age-strata: less than or equal to 45 years, greater than 45–55 years, 56–65 years, and greater than 65 years. According to the US National Institute of Health,¹⁴ these thresholds correspond with the most common start (45 years) and end (55 years) of the menopausal transition, and with a definite (late) postmenopausal status (65 years). Univariable and multivariable linear regression analyses were applied to study changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) during the run-in phase in relation to sex and age. In multivariable analyses, we adjusted for trial of origin and CV risk factors, including diabetes, stroke/TIA and history of CVD (among other factors). We report crude and adjusted mean changes with corresponding 95% confidence interval (CI).

IBM SPSS statistics 25 was used for the analyses. A two-sided *p* value less than 0.05 was considered as significant.

RESULTS

In total, 8366 women and 21,097 men were included in the analysis. We observed significant differences in baseline characteristics in relation to age with respect to blood pressure, CV risk factors, CV history, and medication in both sexes (Table S1). In women and men, the prevalence of hypertension and diabetes increased with age, whereas the prevalence of smoking and previous CVD was not age-related. Platelet inhibitors, beta blockers, and lipid lowering agents were more often used by younger patients, whereas calcium blockers were more frequently used by the elderly (Table S1).

Women

In women, pretreatment SBP showed a significant increasing trend with age, from a mean of 134.7 mmHg in patients less than or equal to 45 years to 137.7, 143.3 and 148.5 mmHg

in those aged greater than 45–55, greater than 55–65, and greater than 65, respectively (*p* value for trend <0.001; Table 1). An inverse trend with age was observed for pretreatment DBP (Table 1).

In unadjusted analyses, a significant SBP reduction after the run-in period with perindopril was observed in all age categories, which was numerically smallest in patients less than or equal to 45 years (mean change -6.1 mmHg, -5.3%) and largest in those greater than 45–55 years (mean change -8.5 mmHg -7.3%), however, the differences between the age categories were not significant. In addition, we found no consistent, significant (linear) trend for SBP reduction after perindopril treatment in relation to age (*p* value trend test = 0.425; Table 1). After multivariable adjustment for potential confounders, we observed a significant positive linear trend for both absolute and relative SBP reduction in relation to age (*p* value trend test <0.001) meaning that the perindopril response on SBP decreases with age.

In unadjusted analyses, the DBP response to perindopril showed a similar pattern to SBP, with numerically smallest change in patients less than or equal to 45 years (mean change -2.7 mmHg, -2.3%) compared to patients greater than 45–55 years (-4.3 mmHg -3.6%), patients greater than 55–65 years (-3.6 mmHg, -3.0%), and greater than 65 years (-3.4 mmHg, -2.8%), but without significant intergroup differences. After multivariable adjustment, we observed a negative significant (linear) trend (*p* for trend <0.001) meaning that the response on DBP increases with age (Table 1).

Men

In men, pretreatment SBP and DBP showed a similar trend as in women, with a significant increasing trend for SBP with age, from a mean of 130.7 mmHg in patients less than or equal to 45 years to 134.9 and 145.2 mmHg in those greater than 45–55 and greater than 65, respectively (*p* value for trend <0.001) and pretreatment DBP showing an inverse trend with age (Table 1).

In unadjusted analyses, a significant SBP reduction after the run-in period with perindopril was observed in all age categories, which was numerically smallest in patients greater than 55–65 years (-8.0 mmHg, -6.7%) and largest in those greater than 45–55 years (-8.6 mmHg, -7.5%) with no significant intergroup differences (Table 1). After multivariable adjustment, we observed a positive significant (linear) trend for SBP reduction in relation to age (*p* < 0.001), meaning that the response on SBP decreases with age (Table 1).

The DBP response to perindopril in the univariate analyses showed a linear pattern over age, with numerically smallest change in patients greater than 55–65 years (-3.7 mmHg, -3.1%) and largest in patients less than or equal to 45 years (-4.6 mmHg, -4.0% , *p* value for trend 0.002; Table 1). The

TABLE 1 SBP and DBP response after 4-week perindopril-based treatment in women and men in different age categories

Metric	Age groups, years	Women					
		Mean (SD) baseline value	Unadjusted mean (95% CI) difference	<i>p</i> value trend test	<i>p</i> value for comparison with the reference	Adjusted mean difference (95% CI) ^a	<i>p</i> value adjusted trend test
SBP pretreatment, mmHg	≤45	134.7(17.8)	-ref-	<0.001	-ref-	-ref-	<0.001
	>45–55	137.7(19.3)	3.0 (−0.6, 6.7)		0.105	2.6 (−0.6, 6.2)	
	>55–65	143.3(19.8)	8.6 (5.1, 12.1)		<0.001	7.6 (4.3, 10.8)	
	>65	148.5(21.3)	13.9 (10.4, 17.3)		<0.001	12.2 (8.9, 15.5)	
DBP pretreatment, mmHg	≤45	84.5 (11.4)	-ref-	<0.001	-ref-	-ref-	<0.001
	>45–55	83.8 (10.3)	−0.8 (−2.7, 1.1)		0.427	0.2 (−1.6, 1.9)	
	>55–65	81.9 (10.3)	−2.6 (−4.4, −0.8)		0.004	−1.0 (−2.7, 0.7)	
	>65	80.3 (10.7)	−4.2 (−6.0, −2.4)		<0.001	−3.0 (−4.7, −1.3)	
Delta SBP, mmHg	≤45	−6.1 (13.7)	-ref-	0.425	-ref-	-ref-	<0.001
	>45–55	−8.5 (16.2)	−2.4 (−5.6, 0.8)		0.139	−1.5 (−4.3, 1.2)	
	>55–65	−8.2 (17.1)	−2.1 (−5.2, 0.9)		0.169	0.7 (−1.9, 3.4)	
	>65	−8.4 (18.8)	−2.4 (−5.4, 0.7)		0.127	2.8 (0.1, 5.5)	
Delta SBP (%)	≤45	−5.3 (10.8)	-ref-	0.958	-ref-	-ref-	<0.001
	>45–55	−7.3 (12.8)	−2.0 (−4.4, 0.4)		0.098	−1.5 (−3.6, 0.7)	
	>55–65	−6.9 (13.0)	−1.6 (−3.9, 0.7)		0.166	0.2 (−1.8, 2.3)	
	>65	−6.9 (13.9)	−1.6 (−3.9, 0.7)		0.163	1.7 (−0.3, 3.8)	
Delta DBP, mmHg	≤45	−2.7 (10.0)	-ref-	0.145	-ref-	-ref-	<0.001
	>45–55	−4.3 (8.9)	−1.6 (−3.3, 0.1)		0.065	−2.1 (−3.5, −0.6)	
	>55–65	−3.6 (9.5)	−1.0 (−2.6, 0.7)		0.245	−2.5 (−3.9, −1.1)	
	>65	−3.4 (9.7)	−0.8 (−2.4, 0.8)		0.343	−3.2 (−4.6, −1.8)	
Delta DBP, %	≤45	−2.3 (8.0)	-ref-	0.018	-ref-	-ref-	<0.001
	>45–55	−3.6 (7.1)	−1.3 (−2.6, 0.0)		0.056	−1.6 (−2.8, −0.5)	
	>55–65	−3.0 (7.3)	−0.6 (−1.9, 0.6)		0.308	−1.8 (−2.9, −0.8)	
	>65	−2.8 (7.2)	−0.4 (−1.6, 0.8)		0.513	−2.4 (−3.5, −1.3)	

Abbreviations: DBP, diastolic blood pressure; CI, confidence interval; SBP, systolic blood pressure.

^aAdjusted for hypertension, diabetes mellitus, smoking, previous myocardial infarction, previous revascularization, previous stroke, previous transient ischemic attack/stroke, mean SBP, mean DBP, platelet inhibitors, betablockers, calcium blockers, lipid lowering agents, type of study (European Trial on Reduction of Cardiac Events With Perindopril [EUROPA]; Perindopril Protection Against Recurrent Stroke Study [PROGRESS]; Action in Diabetes and Vascular disease: Preterax and Diamicon-MR Controlled Evaluation [ADVANCE]).

multivariate analyses showed a significant negative (linear) trend over age (*p* for trend <0.001) meaning that DBP response increases with age (Table 1).

DISCUSSION

This study of 29,459 patients with CVD treated with perindopril for 4–6 weeks is the largest study so far studying the blood pressure response over age for women and men. Elderly patients had higher pretreatment SBP, whereas perindopril-induced SBP reductions declined with age. In contrast, elderly patients had lower pretreatment DBP, whereas DBP

reductions increased with age. After adjustment for potential confounders, we found no relevant differences in blood pressure response between women and men.

Previous research has shown that SBP increases linearly with age, due to arterial and arteriole stiffness, which is also seen in our study population.¹⁵ DBP is known to have a varying pattern with aging: a systematic rise is seen from until the age of ~ 50 years, whereas thereafter DBP slowly declines with age, which we also observed in our study population.¹⁶

In women, the menopausal transition leads to additional significant increases in arterial pressure.¹⁷ Genetic factors affecting RAAS and endothelial nitric oxide synthase (eNOS), environmental factors, such as body mass index (BMI),

Men							
<i>p</i> value for comparison with the reference	Mean (SD) baseline value	Unadjusted mean (95% CI) difference	<i>p</i> value trend test	<i>p</i> value for comparison with the reference	Adjusted mean difference (95% CI) ^a	<i>p</i> value adjusted trend test	<i>p</i> value for comparison with the reference
	130.7 (14.3)	-ref-	<0.001	-ref-	-ref-	<0.001	-ref-
0.104	134.9 (15.8)	4.2 (2.9, 5.5)		<0.001	2.4 (1.2, 3.6)		<0.001
<0.001	140.5 (18.0)	9.9 (8.6, -11.1)		<0.001	6.2 (5.0, 7.3)		<0.001
<0.001	145.2 (19.0)	14.6 (13.3, 15.8)		<0.001	9.8 (8.6, 11.0)		<0.001
	83.1 (9.0)	-ref-	<0.001	-ref-	-ref-	<0.001	-ref-
0.848	84.0 (9.4)	0.9 (0.2, 1.6)		0.013	0.4 (-0.3, 1.0)		0.268
0.240	83.1 (9.7)	0.1 (-0.6, 0.7)		0.874	-0.7 (-1.4, -0.1)		0.024
0.001	81.1 (10.0)	-2.0 (-2.7, -1.3)		<0.001	-3.2 (-3.9, -2.6)		<0.001
	-8.4 (12.5)	-ref-	0.601	-ref-	-ref-	<0.001	-ref-
0.275	-8.6 (14.2)	-0.2 (-1.4, 0.9)		0.697	0.8 (-0.2, 1.8)		0.129
0.594	-8.0 (15.6)	0.4 (-0.7, 1.5)		0.451	2.8 (1.8, 3.7)		<0.001
0.039	-8.6 (16.5)	-0.2 (-1.3, 0.9)		0.704	3.7 (2.7, 4.7)		<0.001
	-7.4 (10.4)	-ref-	0.218	-ref-	-ref-	<0.001	-ref-
0.175	-7.5 (11.6)	-0.1 (-1.0, -0.8)		0.834	0.5 (-0.3, 1.3)		0.205
0.842	-6.7 (12.0)	0.7 (-0.2, 1.5)		0.128	2.1 (1.3, 2.8)		<0.001
0.101	-7.1 (12.5)	0.3 (-0.6, 1.1)		0.495	2.7 (1.9, 3.5)		<0.001
-ref-	-4.6 (8.6)	-ref-	0.002	-ref-	-ref-	<0.001	-ref-
0.006	-4.4 (9.0)	0.2 (-0.4, 0.9)		0.500	0.3 (-0.2, 0.9)		0.239
0.001	-3.7 (8.9)	0.9 (0.2, 1.5)		0.006	0.2 (-0.4, 0.7)		0.522
<0.001	-3.9 (9.2)	0.7 (0.1, 1.4)		0.022	-1.3 (-1.9, -0.7)		<0.001
-ref-	-4.0 (7.2)	-ref-	<0.001	-ref-	-ref-	<0.001	-ref-
0.005	-3.8 (7.4)	0.3 (-0.3, 0.8)		0.314	0.3 (-0.2, 0.7)		0.226
0.001	-3.1 (6.9)	1.0 (0.5, 1.5)		<0.001	0.3 (-0.2, 0.7)		0.255
<0.001	-3.1 (7.0)	0.9 (0.4, 1.4)		<0.001	-0.9 (-1.3, -0.4)		<0.001

cholesterol and obesity, and hormonal changes are thought to contribute to the increase in blood pressure in menopause.¹⁸ The drop in estrogen during menopause leads to vascular changes, which has been shown before to occur during the menstrual cycle as well: in the luteal phase, when estradiol levels are highest, blood pressure is lower compared to the follicular phase.¹⁹

In addition, previous animal studies have shown that estrogen causes increased expression of angiotensinogen and renin and downregulates angiotensinogen converting enzyme (ACE). This leads to a decrease in plasma angiotensin II, which has a decrease in blood pressure as a result.²⁰⁻²²

This hypothesis has been proven in human studies as well. Serum ACE activity was lower in normotensive pregnant women, who have increased estrogen levels, as compared to nonpregnant women.²³ In addition, hormone replacement therapy (HRT) in postmenopausal women is correlated to higher ACE activity compared to postmenopausal women not using HRT.²⁴

However, our study shows that these differences in ACE activity in women at an older age do not lead to a different response to the 4-6 week treatment of perindopril compared to premenopausal women. We showed, that, women and men less than or equal to 45 years have lower SBP before treatment and higher the absolute SBP reduction compared to the age

group greater than 65 years. In women, this could imply that physiological differences are subtle and overcome by pharmacological intervention. In men, more research is needed to find out the less responsiveness to perindopril above the age of 55 years. However, it has to be taken into account that the absolute and relative differences found in the different age categories were small and might not be of clinical relevance for the individual. Nevertheless, even small changes in blood pressure (response) can be relevant on population level.

In general, menopausal status should be taken into account when studying drug effects in women, considering major differences regarding pharmacokinetics (for instance, body composition) and pharmacodynamics (for instance, RAAS activity). Previous evidence suggested that age affects ACE-inhibitor response in female mice,⁴ however, we observed that the 4-week perindopril response in SBP declines with age in women and the DBP response increases with age in both men and women. In addition, decreasing testosterone levels are known to reduce ACE-activity as well,²⁵ so more research is needed in this field to find out whether this could be the leading cause of older men showing less SBP reduction after treatment with ACEi.

Limitations

The findings of this study have to be seen in light of some limitations. First, EUROPA, PROGRESS, and ADVANCE enrolled different types of patients, whereas various doses of perindopril were studied, whether or not in combination with other agents that influence blood pressure, including thiazide diuretics. These between-trial variations might somewhat complicate the interpretation of our findings. However, noteworthy, differences in clinical phenotypes and treatment regimens were the same in all age categories and do, therefore, most likely, not explain the differences we found. Indeed, accounting for the trial of origin in the multivariable regression models did not alter our findings and conclusions.

Second, our analysis included a total of 8366 women, which, although substantial, was lower than the number of men ($N = 21,097$). It is a well-known phenomenon that fewer women than men are enrolled in CV trials. Without going into detail, the clinical phenotype studied is one of the reasons why. Indeed, we found variations in the percentage of women that were enrolled in the EUROPA (15%), PROGRESS (30%), and ADVANCE (43%) trials. Because our findings were homogeneous across the trials, we feel justified to obtain pooled estimates, also in the various age-strata in women. Nevertheless, the obtained estimates in women are less certain than in men, because of the smaller numbers.

Third, information on pre-, peri-, and postmenopausal state was not systematically collected at the study entry visits. Alternatively, for our analyses, we used the women's

(baseline) age to estimate menopausal (hormonal) status. Although, most likely, most women less than or equal to 45 years were premenopausal than those greater than 55 years postmenopausal, we acknowledge the lack of precision of our definition; however, this is a common issue because the exact transition can be difficult to define and depends on the remembrance of the patients. In addition, most women that we studied had established vascular disease. In view of the relation between menopausal status and (cardio)vascular disease, we appreciate that the label "premenopausal" for all women less than or equal to 45 years can be questioned.²⁶

CONCLUSION

To conclude, we observed that in both women and men the perindopril response on SBP decreases with age and DBP response increases with age. More research is needed to determine whether this is caused by changing levels of sex hormones in women and men and whether it would be beneficial to use age-adjusted perindopril dosages especially in isolated systolic hypertension as commonly seen in the elderly.

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CONFLICTS OF INTEREST

All authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

M.M.S., K.M.M.C., J.V., E.B., and J.R.v.L. wrote the manuscript. J.V. designed the research. M.M.S. and J.B. performed the research and analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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