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The Cardioprotective Effects of the Angiotensin-Converting Enzyme Inhibitor Perindopril in Patients With Stable Coronary Artery Disease Are Not Modified by Mild to Moderate Renal Insufficiency

Insights From the EUROPA Trial

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Objectives This study sought to examine whether the cardioprotective effects of angiotensin-converting enzyme (ACE) inhibitor therapy by perindopril are modified by renal function in patients with stable coronary artery disease.

Background A recent study reported that an impaired renal function identified a subgroup of patients with stable coronary artery disease more likely to benefit from ACE inhibition therapy. In light of the growing interest in tailored therapy for targeting medications to specific subgroups, remarks on the consistency of the treatment effect by ACE inhibitors are highly important.

Methods The present study involved 12,056 patients with stable coronary artery disease without heart failure randomized to perindopril or placebo. Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease equation. Cox regression analysis was used to estimate multivariable-adjusted hazard ratios.

Results The mean eGFR was 76.2 (±18.1) ml/min/1.73 m^2. During follow-up, the primary end point (cardiovascular death, nonfatal myocardial infarction, or resuscitated cardiac arrest) occurred in 454 of 5,761 patients (7.9%) with eGFR ≥75 and in 631 of 6,295 patients (10.0%) with eGFR <75. Treatment benefits of perindopril were apparent in both patient groups either with eGFR ≥75 (hazard ratio 0.77; 95% confidence interval 0.64 to 0.93) or eGFR <75 (hazard ratio 0.84; 95% confidence interval 0.72 to 0.98). We observed no significant interaction between renal function and treatment benefit ($p = 0.47$). Using different cutoff points of eGFR at the level of 60 or 90 resulted in similar trends.

Conclusions The treatment benefit of perindopril is consistent and not modified by mild to moderate renal insufficiency.
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Several clinical trials in patients with stable coronary artery disease (CAD) have shown that inhibitors of the angiotensin-converting enzyme (ACE) reduce the incidence of cardiovascular events during long-term follow-up (1–4). Because these effects are apparent in both low- and high-risk populations, as well as in those with and without preserved left ventricular function, clinical treatment guidelines argue that ACE inhibitors should be used as routine secondary prevention for the broad group of patients with known CAD (5). Still, it should be realized that absolute treatment effects in low-risk patients are modest. Because the cost effectiveness of medications is of increasing importance, there is a rapidly growing interest in tailored therapy. In cardiovascular disease, targeting ACE inhibitor therapy to specific patient groups that are most likely to benefit is of high clinical relevance. Patients with impaired renal function are a potential target because renal function is indepen-

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dently associated with adverse clinical outcome in cardiovascular disease (6,7).

In a recent substudy of the PEACE (Prevention of Events With ACE Inhibition) trial, a significant heterogeneity in treatment effect with trandolapril was observed in relation to renal function (8). In patients with poor renal function, defined as an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m^2, trandolapril was associated with a significant reduction in all-cause mortality (27% relative risk reduction) as compared with placebo. In contrast, no risk reduction was observed in patients with higher eGFR levels. The PEACE Investigators concluded that, in a stable CAD population, ACE inhibition offered the best cardiovascular protection in patients with poor renal function, which could be used as a subgroup to target therapy (8,9). As the treatment effect of trandolapril in the entire PEACE study was neutral (10), retrospective analyses to define patient populations with positive ACE inhibitor effects should be regarded cautiously and verified in comparable patient populations.

The EUROPA (European Trial on Reduction of Cardiac Events With Perindopril) study examined the preventive effects of ACE inhibition in a large population of patients with stable CAD and preserved left ventricular function. In light of the growing interest in tailored therapy and the recent results of the PEACE trial, we examined whether renal function modified the cardioprotective benefits of ACE inhibition therapy by perindopril in the EUROPA study.

Methods

Study population. The design and principal results of the EUROPA study have been reported elsewhere (2,11). In short, the EUROPA study was a randomized, double-blind, multicenter study of 12,218 patients with stable CAD without overt heart failure designed to assess the effect of 8 mg perindopril (n = 6,110) versus placebo (n = 6,108) on the combined end point of cardiovascular death, nonfatal myocardial infarction (MI), and resuscitated cardiac arrest. After a mean follow-up of 4.2 years, 8.0% of patients randomized to perindopril and 9.9% of those randomized to placebo reached the primary end point, which yields a 20% relative risk reduction with perindopril (hazard ratio [HR] 0.80; 95% confidence interval [CI] 0.71 to 0.91). In the EUROPA study, a serum creatinine level >1.7 mg/dl was an exclusion criteria; however, 30 patients (0.02%) enrolled with serum creatinine between 1.7 and 2.2 mg/dl. Baseline blood samples with standardized measurements of serum creatinine levels according to protocol were available in 12,056 patients. Written informed consent was obtained from all patients.

Assessment of renal function. Renal function was assessed by eGFR using the abbreviated 4-variable Modification of Diet in Renal Disease equation (12). The dimension of all mentioned eGFR levels is in ml/min/1.73 m^2.

Outcome measures. The primary end point was a composite of cardiovascular death, nonfatal MI, and resuscitated cardiac arrest. Secondary end points were the composite of total mortality, nonfatal MI, hospital admission for unstable angina, and cardiac arrest with successful resuscitation; cardiovascular mortality, nonfatal MI, and stroke or unstable angina; fatal and nonfatal MI and unstable angina; stroke; and admission for heart failure. In addition, we assessed total mortality and cardiovascular mortality as individual end points. The diagnosis of MI was based on the recommendations of the European Society of Cardiology and the American College of Cardiology (13).

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
CAD = coronary artery disease
CI = confidence interval
eGFR = estimated glomerular filtration rate
HR = hazard ratio
MI = myocardial infarction

Statistical analysis. Summary statistics for continuous variables are presented as mean ± 1 standard deviation. Categorical data are summarized as frequencies and percentages. One-way analysis of variance and Pearson chi-square tests were used to calculate p values. We examined eGFR as a categorical variable for the association of renal function and clinical outcome (<45, 45 to 59.9, 60 to 74.9, 75 to 89.9, and ≥90 ml/min/1.73 m^2). In our initial analyses for the relation between renal function and clinical outcome, we confined ourselves to this clinically relevant classification. Still, we realize that dichotomization of a continuous measure may result in loss of information. Therefore, all analyses were repeated with eGFR as a continuous variable. Because both approaches showed similar results (we found no evidence of heterogeneity in treatment effect in relation to renal function), we present our findings of the analysis of renal function and treatment benefit by perindopril according to a binary classification. To systematically test the consistency of perindopril in relation to renal function, we have chosen 2 approaches. First, because there is a continuous relation between eGFR and cardiovascular risk, we divided the study population according to the median eGFR in our study. This resulted in 2 groups of comparable size, which we defined as relatively preserved (eGFR ≥75) versus impaired (eGFR <75) renal function. Second, from a clinical point of view, we have chosen a cutoff (also dichotomous) at an eGFR ≥60 or an eGFR <60 and at an eGFR ≥90 or an eGFR <90, corresponding to the presence of chronic kidney disease or a normal renal function at baseline, respectively. In the literature, there is an ongoing debate regarding which cutoff point to use. For completeness and comparability, we present all treatment effects on all cardiovascular end points at different cutoff points of eGFR, namely 60, 75, and 90 ml/min/1.73 m^2. Because of numerous studies reporting that the increased risk of cardiovascular events is already apparent at the earliest stages of renal insufficiency, well above 60 ml/min/1.73 m^2, we confined ourselves to the cutoff at 75 ml/min/1.73 m^2 for our main analyses (14–16).

The incidence of the primary and secondary end points over time was studied using the Kaplan-Meier method. Differences in incidence according to renal function were evaluated by log-rank tests. Absolute risk differences were calculated until 4 years of follow-up; after that Kaplan-Meier estimates became increasingly unstable because of the small number of patients at risk.

Univariable and multivariable Cox proportional hazards regression analyses were applied to examine the association between renal function and study end points. In multivariable analysis, we adjusted for the following (potentially) confounding baseline characteristics: age, gender, systolic blood pressure, diastolic blood pressure, presence of diabetes mellitus, hypercholesterolemia, current smoking, history of CAD (MI, percutaneous coronary intervention, coronary artery bypass graft surgery). Interaction between renal function and treatment effect was analyzed in a continuous as well as a categorical model for eGFR. Each model was tested for interaction and included an [renal function × treatment group] interaction term. The assumption of proportional hazards was assessed by visual judgment of the log-minus-log survival plots. All measures of association are presented as multivariable-adjusted HRs together with 95% CIs. All analyses were based on intention to treat. Statistical tests were 2-sided, and a value of $p < 0.05$ was considered significant. We used SPSS statistical software (version 12.01 for Windows, SPSS Inc., Chicago, Illinois) for our calculations.

Results

Patients. The distribution of eGFR in the EUROPA trial is presented in Figure 1. The mean eGFR in our study population was 76.2 ± 18.1 (median 74.2, interquartile range 64.6 to 85.2) ml/min/1.73 m^2, corresponding to a mean serum creatinine of 1.1 ± 0.2 mg/dl. A total of 6,295 (52.1%) patients had impaired renal function (eGFR <75). Baseline characteristics are shown in Table 1. Patients with lower eGFR were older and more often were female. Furthermore, patients with impaired renal function were more likely to have a higher frequency of comorbidities including hypertension and diabetes mellitus, but less often reported current smoking. Baseline characteristics for patients randomized for treatment with perindopril or placebo were in balance in the subjects considered in the analysis of treatment benefits and yielded no clinically relevant differences.

Renal function and clinical outcome. Regardless of allocated treatment, renal function was significantly associated with clinical outcome. In patients allocated to perindopril, each 10 ml/min/1.73 m^2 decrease in eGFR was related to an 8.7% (HR 1.09, 95% CI 1.03 to 1.15, p = 0.005) increased risk in the primary end point. A similar increased risk was found in those allocated to placebo: 6.5% (HR 1.06, 95% CI 1.02% to 1.12%, p = 0.015). With worsening eGFR categories, the associated HRs increased considerably for all end points in both treatment groups (Table 2).

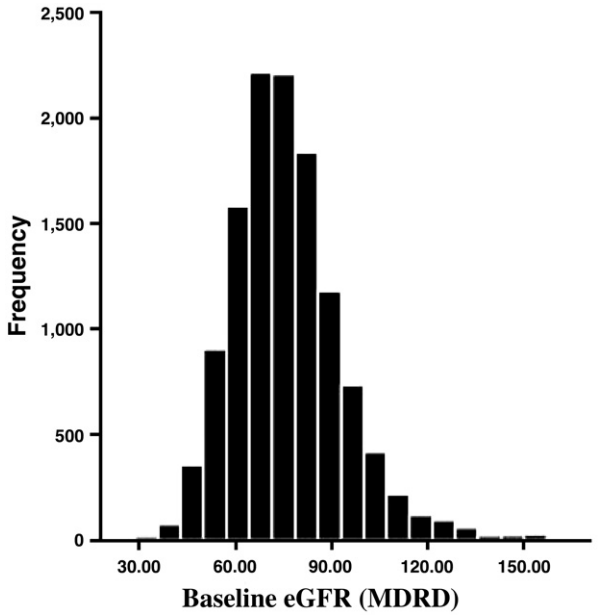

Figure 1 Distribution of eGFR in the EUROPA Trial

Distribution of estimated glomerular filtration rate (eGFR) in the EUROPA trial (n = 12,056). MDRD = Modification of Diet in Renal Disease equation.

Kaplan-Meier estimates of the primary end point with perindopril and placebo for the 2 different categories of eGFR are presented in Figure 2. Log-rank tests were performed for perindopril versus placebo in patients with eGFR ≥75 and <75, which resulted in p values of 0.005 and 0.023, respectively.

Renal function and treatment effects by perindopril. In patients with a relatively preserved renal function, perindopril was associated with a 23% (HR 0.77, 95% CI 0.64 to 0.93) relative reduction in the incidence of the primary end point as compared with placebo. For patients with impaired renal function, perindopril was associated with a 16% reduction (HR 0.84, 95% CI 0.72 to 0.98). There was no evidence of heterogeneity in the cardioprotective effect of perindopril in relation to eGFR, when assessed as a categorical (p = 0.47) or as a continuous variable (p = 0.37). Similar consistencies were found for all other end points considered.

The treatment effects of perindopril at the other cutoff levels of 60 and 90 ml/min/1.73 m^2 are presented in Table 3. The results were similar, and no significant heterogeneity in treatment effect of perindopril was observed over the whole range of eGFR on all cardiovascular end points.

Absolute risks during follow-up. The absolute risk of the primary end point was highest in patients with impaired renal function using placebo (10.3%). The absolute risk reduction of the primary end point by perindopril at 4 years of follow-up was 1.90% in patients with an eGFR ≥75 and 1.77% in patients with eGFR <75 (Table 4).

Table 1 Baseline Characteristics of Study Population (n = 12,056)

Characteristic	eGFR (ml/min/1.73 m^2) ≥90 (n = 2,131)	75–89.9 (n = 3,630)	60–74.9 (n = 4,378)	45.0–59.9 (n = 1,756)	<45 (n = 161)	p Value
Mean (SD) age, yrs	55.2 (9.3)	58.3 (9.1)	61.5 (8.5)	65.1 (7.9)	69.1 (6.7)	<0.01
Gender, female	155 (7.3)	322 (8.9)	678 (15.5)	516 (29.4)	94 (58.4)	<0.01
Hypertension*	472 (22.1)	926 (25.5)	1218 (27.8)	610 (34.7)	64 (39.8)	<0.01
Hypercholesterolemia†	1,288 (60.4)	2,312 (63.6)	2,815 (64.2)	1,134 (64.5)	94 (58.4)	0.02
Diabetes mellitus	232 (10.9)	411 (11.3)	529 (12.1)	277 (15.8)	31 (19.3)	<0.01
Current smoking	469 (22.0)	626 (17.2)	538 (12.3)	180 (10.2)	17 (10.6)	<0.01
Peripheral vessel disease	130 (6.1)	236 (6.5)	328 (7.5)	161 (9.2)	18 (11.2)	<0.01
Previous stroke/TIA	47 (2.2)	91 (2.5)	165 (3.8)	96 (5.5)	10 (6.2)	<0.01
History of CAD						
MI	1,444 (67.8)	2,359 (64.9)	2,771 (63.3)	1,130 (64.3)	113 (70.2)	0.01
PCI	637 (29.9)	1,107 (30.5)	1,259 (28.8)	475 (27.0)	37 (23.0)	0.03
CABG	514 (24.1)	1,011 (27.8)	1,408 (32.2)	556 (31.6)	55 (34.2)	<0.01
Medication						
Platelet inhibitors	1,965 (92.2)	3,386 (93.2)	4,039 (92.3)	1,589 (90.4)	140 (87.0)	<0.01
Lipid-lowering agents	1,134 (53.2)	2,040 (56.2)	2,492 (56.9)	1,002 (57.0)	79 (49.1)	0.02
Beta-blockers	1,299 (60.9)	2,269 (62.5)	2,781 (63.5)	1,128 (64.2)	96 (59.6)	0.18
Calcium antagonists	624 (29.3)	1,130 (31.1)	1,428 (32.6)	647 (36.8)	73 (45.3)	<0.01
Nitrates	960 (45.0)	1,553 (42.8)	1,917 (43.8)	846 (48.1)	82 (50.9)	<0.01
Diuretics	139 (6.5)	237 (6.5)	467 (10.6)	325 (18.5)	49 (30.4)	<0.01
Mean (SD) systolic blood pressure, mm Hg	134.5 (14.2)	136.3 (15.2)	138.0 (15.8)	139.5 (15.8)	143.5 (17.5)	<0.01
Mean (SD) diastolic blood pressure, mm Hg	82.0 (8.1)	81.8 (8.2)	81.8 (8.1)	81.4 (8.4)	80.5 (9.0)	0.08
Mean (SD) eGFR	104.1 (18.3)	81.7 (4.2)	68.0 (4.2)	54.5 (3.9)	40.9 (4.4)	<0.01
Randomized to perindopril	1,060 (49.7)	1,809 (49.8)	2,189 (50.0)	906 (51.6)	72 (44.7)	0.46

Values are n (%) unless otherwise noted. *Blood pressure >160/95 mm Hg or receiving antihypertensive treatment. †Cholesterol >6.5 mmol/l or receiving lipid-lowering treatment.
CABG = coronary artery bypass grafting; CAD = coronary artery disease; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

For comparability, we present the number of events of total mortality, cardiovascular mortality, and nonfatal MI in the PEACE and EUROPA trials in Table 5.

Discussion

This analysis confirms that perindopril is effective in reducing cardiovascular events in patients with stable CAD irrespective of renal function. Treatment benefit by perindopril is substantial and consistent in patients with and without impaired renal function. Hence, renal function, as measured by eGFR, cannot be used to select a target population that will benefit most from ACE inhibition.

Regarding clinical outcome, we showed a significant relationship with renal function. With worsening eGFR, patients showed higher comorbidity and the associated HRs increased considerably for all end points. On a continuous scale, each 10 ml/min/1.73 m^2 decrease in eGFR was related to a 6.5% increase in risk of the primary end point in the placebo group. The relation between renal function and risk of cardiovascular events has been intensively investigated for several years. It has been suggested that the increased risk can be explained by the co-occurrence of a high prevalence of baseline risk factors (17,18). However, in our study, the observed relationships remained significant after multivariable analysis including these factors. Another explanation may be that renal function is a marker of ongoing or pre-existing atherosclerosis starting in the smallest vessels at the glomerulus, explaining the increased risk of subjects with only mildly decreased renal function (16–18).

Regarding the observed treatment effect, we showed that perindopril reduced events in all patients with stable CAD regardless of the level of renal function. The relative reduction in the incidence of the primary end point by perindopril was somewhat better for patients with relatively preserved renal function. However, CIs were overlapping and we observed no significant interaction between treatment and renal function.

A recent substudy of the PEACE trial investigated the relationship between renal function and the effectiveness of ACE inhibition therapy in stable CAD (8). In that study, patients with an eGFR <60 showed a significant treatment effect of trandolapril on total mortality, but not on the other studied end points nor in patients with better levels of renal function. The investigators observed a significant heterogeneity in treatment effect in relation to renal function. The inconsistency of the treatment effect of trandolapril was mainly related to the lack of benefit in patients with an eGFR >60. Therefore, they concluded that an impaired

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Table 2 Multivariable-Adjusted Hazard Ratios for Baseline Renal Function and Clinical Outcome (n = 12,056)

		Placebo (n = 6,027)		Perindopril (n = 6,029)	
End Points	eGFR	Events/Total	HR (95% CI)	Events/Total	HR (95% CI)
Primary end point (cardiovascular death, nonfatal MI, resuscitated cardiac arrest)	Reference	8.6	1.00	6.7	1.00
	75–89.9	9.1	1.03 (0.80–1.33)	6.9	1.00 (0.74–1.34)
	60–74.9	10.1	1.13 (0.88–1.46)	8.0	1.10 (0.83–1.46)
	45–59.9	12.3	1.31 (0.97–1.76)	11.4	1.53 (1.10–2.11)
	<45	15.7	1.59 (0.88–2.86)	15.3	1.86 (0.96–3.60)
Total mortality, AMI, UAP, or cardiac arrest	Reference	16.0	1.00	12.5	1.00
	75–89.9	15.4	0.92 (0.76–1.11)	13.1	1.00 (0.80–1.23)
	60–74.9	17.3	1.00 (0.83–1.20)	15.1	1.09 (0.88–1.34)
	45–59.9	20.7	1.15 (0.92–1.43)	18.8	1.31 (1.03–1.66)
	<45	29.2	1.57 (1.01–2.42)	29.2	1.86 (1.15–3.01)
Cardiovascular mortality, AMI, and stroke	Reference	9.2	1.00	7.1	1.00
	75–89.9	10.0	1.04 (0.82–1.33)	8.0	1.08 (0.81–1.43)
	60–74.9	11.4	1.18 (0.93–1.50)	9.1	1.16 (0.89–1.53)
	45–59.9	13.3	1.30 (0.98–1.73)	12.9	1.61 (1.18–2.19)
	<45	19.1	1.77 (1.03–3.04)	18.1	1.99 (1.08–3.69)
Cardiovascular mortality, AMI	Reference	8.4	1.00	6.7	1.00
	75−89.9	9.0	1.05 (0.81–1.35)	6.9	0.99 (0.74–1.33)
	60–74.9	10.0	1.15 (0.89–1.48)	8.0	1.10 (0.82–1.46)
	45–59.9	12.1	1.31 (0.97–1.77)	11.2	1.50 (1.09–2.08)
	<45	15.7	1.62 (0.90–2.93)	15.3	1.86 (0.96–3.60)
Cardiovascular mortality, AMI, and UAP	Reference	13.4	1.00	10.5	1.00
	75–89.9	12.9	0.93 (0.76–1.15)	11.2	1.04 (0.83–1.32)
	60–74.9	14.8	1.06 (0.86–1.30)	12.6	1.13 (0.90–1.42)
	45–59.9	18.1	1.26 (0.99–1.60)	15.5	1.38 (1.06–1.80)
	<45	23.6	1.58 (0.98–2.56)	23.6	2.00 (1.18–3.41)
Fatal and nonfatal AMI and UAP	Reference	10.0	1.00	8.2	1.00
	75–89.9	11.1	1.10 (0.87–1.40)	9.8	1.17 (0.90–1.52)
	60–74.9	12.4	1.24 (0.98–1.56)	9.7	1.14 (0.89–1.48)
	45–59.9	13.3	1.33 (1.00–1.76)	11.8	1.42 (1.05–1.91)
	<45	19.2	1.88 (1.10–3.21)	15.3	1.82 (0.95–3.48)
Fatal and nonfatal AMI	Reference	4.9	1.00	4.4	1.00
	75–89.9	7.2	1.47 (1.07–2.03)	5.4	1.20 (0.84–1.70)
	60–74.9	7.3	1.54 (1.12–2.12)	4.7	1.03 (0.72–1.47)
	45–59.9	7.1	1.46 (0.99–2.16)	7.3	1.65 (1.11–2.45)
	<45	9.0	1.82 (0.84–3.94)	6.9	1.56 (0.60–4.03)
Total mortality	Reference	6.6	1.00	4.8	1.00
	75–89.9	5.5	0.74 (0.54–0.99)	4.8	0.86 (0.61–1.22)
	60–74.9	6.7	0.80 (0.59–1.05)	6.5	1.04 (0.75–1.45)
	45–59.9	9.5	0.94 (0.67–1.31)	8.8	1.23 (0.85–1.78)
	<45	14.6	1.28 (0.69–2.40)	16.7	1.72 (0.88–2.33)
Cardiovascular mortality	Reference	4.0	1.00	2.6	1.00
	75–89.9	2.8	0.64 (0.43–0.96)	2.7	0.93 (0.58–1.47)
	60–74.9	4.2	0.86 (0.59–1.24)	3.8	1.22 (0.78–1.89)
	45–59.9	6.2	1.06 (0.69–1.62)	5.3	1.49 (0.91–2.45)
	<45	9.0	1.32 (0.60–2.94)	9.7	2.11 (0.88–5.05)
Stroke	Reference	1.3	1.00	0.7	1.00
	75–89.9	1.2	0.79 (0.40–1.54)	1.4	1.74 (0.75–4.03)
	60–74.9	2.1	1.16 (0.63–2.14)	1.7	1.88 (0.83–4.26)
	45–59.9	1.9	0.87 (0.41–1.85)	2.8	2.45 (1.02–5.87)
	<45	5.6	2.13 (0.71–6.36)	2.8	1.84 (0.36–9.29)
Heart failure	Reference	1.2	1.00	0.6	1.00
	75–89.9	1.1	0.80 (0.40–1.62)	0.9	1.28 (0.50–3.29)
	60–74.9	1.9	1.20 (0.63–2.28)	1.1	1.41 (0.57–3.50)
	45–59.9	2.8	1.43 (0.70–2.91)	1.3	1.29 (0.46–3.57)
	<45	4.5	1.75 (0.53–5.74)	6.9	5.39 (1.52–19.1)

Cox regression multivariable-adjusted hazard ratios (HRs) were adjusted for age, gender, systolic blood pressure, diastolic blood pressure, presence of diabetes mellitus, hypercholesterolemia, current smoking, and history of coronary artery disease (MI, PCI, CABG).

AMI = acute myocardial infarction; CI = confidence interval; UAP = unstable angina pectoris; other abbreviations as in Table 1.

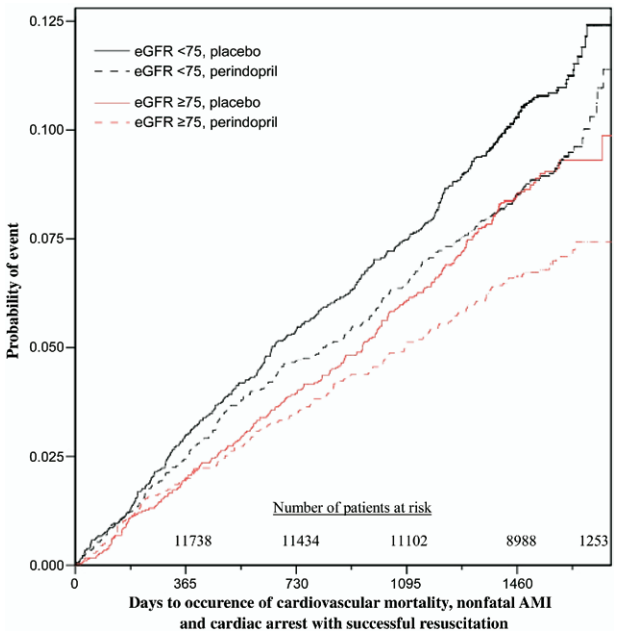

Figure 2 **Kaplan-Meier Estimates of Primary End Point With Perindopril and Placebo According to Baseline eGFR**

Kaplan-Meier estimates of the primary end point with perindopril and placebo for different estimated glomerular filtration rates (eGFR) during follow-up (days). The **black line** corresponds to patients with an eGFR <75 using placebo, and the **dotted black line** corresponds to patients with an eGFR <75 using perindopril. The **red line** corresponds to patients with an eGFR ≥75 using placebo, and the **dotted red line** corresponds to patients with an eGFR ≥75 using perindopril. The X-axis represents the follow-up time in days. The Y-axis represents the risk of the primary end point. AMI = acute myocardial infarction.

renal function defined a subset of CAD patients more likely to benefit from ACE inhibitor therapy for cardiovascular protection (8,9).

The results of the PEACE trial could not be confirmed by our analysis. Both trials studied a population of stable CAD patients with a similar cardiovascular risk profile and a similar eGFR and gender distribution. In contrast to the PEACE trial, we have shown considerable treatment benefits at different levels of renal function and no heterogeneity in the treatment effect of perindopril. In particular, no heterogeneity in the treatment effect was observed on total mortality and cardiovascular mortality in contrast to the PEACE trial analysis. The direction of the treatment benefit by ACE inhibition is different because point estimates were somewhat better at higher eGFR levels, implying that the treatment effect is also present in patients with relatively preserved renal function. The difference in direction must be considered against the background of the overall neutral results of the main PEACE trial. Our analysis confirms that the treatment benefit of ACE inhibition with perindopril is consistent within subgroups, which is in line with our prior subgroup analyses and risk models (2,19). The HOPE (Heart Outcome and Prevention Evaluation) and SAVE (Survival and Ventricular Enlargement) trials studied the relationship between renal function and treatment effect of ACE inhibition, respectively ramipril and captopril, in a high-risk population (20,21). In these patients, no heterogeneity in treatment effect in relation to renal function was shown.

In the main study of the PEACE trial, the overall treatment effect of trandolapril was neutral (10). The investigators performed subgroup analyses for possible explanations for this neutral finding. They stated that their study consisted of relatively few patients with poor renal function (16.3% eGFR <60). Trandolapril reduced the incidence of total mortality only in patients with poor renal function. Because of this low prevalence in the PEACE trial, the investigators stated that this could potentially explain the overall neutral results. However, the distribution of eGFR in the EUROPA trial was similar (15.9% eGFR <60). Still, the overall effect of the main EUROPA study was in favor of ACE inhibition therapy (2). The different result in the PEACE trial may be explained by the fact that the PEACE study potentially had the lowest-risk population. Renal insufficiency could identify a higher risk subgroup and hence explain why the PEACE trial shows a benefit only in this subgroup in an otherwise low-risk population. However, subgroup analyses of the HOPE and EUROPA studies in low-risk groups showed similar event rates compared with those of the PEACE study, and in low-risk groups of the EUROPA study, perindopril reduced the risk of cardiovascular mortality and nonfatal MI by 17%, contrasting with 3% in the PEACE trial. These analyses indicate that the apparent neutral results of the PEACE trial may not be attributable to the lower risk of these patients nor to the background therapies used, but rather are related to the reduced power of the PEACE trial caused by greater crossover and shorter follow-up than in the other studies (1,2,4,10,19). In addition, the different results may be related to substance-specific or (target) dose-dependent differences between ACE inhibitors potentially in relation to the level of renal function, which may have resulted in suboptimal dosages (22). In the EUROPA trial, patients were assigned to receive a relatively high dose of perindopril (8 mg), which was achieved rapidly and in a high proportion of patients, whereas in the PEACE trial, trandolapril was up-titrated to the target dose (4 mg) only 6 months after randomization. At 3 years, target dose was achieved in 57.8% of patients in the PEACE trial and 93.0% of patients in the EUROPA trial. Both agents are in a broadly similar ACE inhibitor subgroup, share chemical moieties, are lipophilic, and are mainly excreted from the kidney and were used in doses that showed important pharmacologic effects. Still, without head-to-head trials it cannot be excluded that there are pharmacologic differences between the agents, possibly in relation to renal insufficiency, that are important to their clinical efficacy to reduce cardiovascular end points (22).

Table 3 Treatment Benefit of Perindopril at Different Levels of Renal Function (n = 12,056)

	eGFR 60		eGFR 75		eGFR 90	
	HR (95% CI)	Testing Interaction	HR (95% CI)	Testing Interaction	HR (95% CI)	Testing Interaction
Primary end point	0.77 (0.68–0.89)	0.19	0.77 (0.64–0.93)	0.47	0.76 (0.56–1.04)	0.71
	0.96 (0.74–1.24)	NS	0.84 (0.72–0.98)	NS	0.82 (0.72–0.93)	NS
Total mortality, AMI, UAP, or cardiac arrest	0.84 (0.76–0.93)	0.48	0.83 (0.72–0.95)	0.44	0.76 (0.61–0.96)	0.30
	0.92 (0.76–1.13)	NS	0.89 (0.79–1.00)	NS	0.88 (0.80–0.97)	NS
Cardiovascular mortality, AMI, and stroke	0.79 (0.69–0.90)	0.12	0.79 (0.66–0.94)	0.48	0.75 (0.55–1.01)	0.51
	1.00 (0.78–1.27)	NS	0.86 (0.74–0.99)	NS	0.84 (0.74–0.95)	NS
Cardiovascular mortality, AMI	0.78 (0.68–0.89)	0.20	0.77 (0.64–0.93)	0.50	0.78 (0.57–1.07)	0.81
	0.96 (0.74–1.24)	NS	0.84 (0.72–0.99)	NS	0.82 (0.72–0.93)	NS
Cardiovascular mortality, AMI, and UAP	0.84 (0.75–0.93)	0.76	0.83 (0.72–0.97)	0.81	0.76 (0.59–0.97)	0.41
	0.88 (0.71–1.09)	NS	0.86 (0.75–0.97)	NS	0.86 (0.77–0.95)	NS
Fatal and nonfatal AMI, UAP	0.82 (0.73–0.93)	0.65	0.86 (0.73–1.01)	0.62	0.80 (0.60–1.06)	0.85
	0.89 (0.69–1.14)	NS	0.82 (0.70–0.94)	NS	0.84 (0.74–0.94)	NS
Fatal and nonfatal AMI	0.71 (0.61–0.84)	0.06	0.79 (0.63–0.98)	0.74	0.88 (0.59–1.30)	0.45
	1.04 (0.75–1.46)	NS	0.75 (0.62–0.92)	NS	0.75 (0.64–0.88)	NS
Total mortality	0.87 (0.74–1.03)	0.72	0.80 (0.64–1.00)	0.25	0.71 (0.49–1.02)	0.24
	0.97 (0.72–1.29)	NS	0.97 (0.81–1.16)	NS	0.93 (0.80–1.08)	NS
Cardiovascular mortality	0.86 (0.69–1.06)	0.94	0.81 (0.60–1.09)	0.70	0.65 (0.59–0.94)	0.32
	0.90 (0.62–1.30)	NS	0.91 (0.72–1.14)	NS	0.91 (0.74–1.11)	NS
Stroke	0.86 (0.62–1.18)	0.28	0.89 (0.55–1.44)	0.79	0.50 (0.20–1.25)	0.51
	1.24 (0.70–2.20)	NS	0.96 (0.68–1.35)	NS	1.00 (0.75–1.35)	NS
Heart failure	0.64 (0.44–0.92)	0.84	0.65 (0.38–1.12)	0.80	0.46 (0.17–1.21)	0.16
	0.59 (0.32–1.08)	NS	0.61 (0.42–0.90)	NS	0.65 (0.47–0.91)	NS

Cox regression multivariable-adjusted HRs adjusted for age, gender, systolic blood pressure, diastolic blood pressure, presence of diabetes mellitus, hypercholesterolemia, current smoking, and history of coronary artery disease (MI, PCI, CABG). Analysis of treatment effect by perindopril at different cutoff levels of eGFR: upper line corresponds to patients with an eGFR above the cutoff level, lower line corresponds to patients with an eGFR below the mentioned cutoff level for each end point (dichotomous ≥60 or <60; ≥75 or <75; ≥90 or <90).

NS = not significant; other abbreviations as in Tables 1 and 2.

In an additional analysis, we investigated whether the treatment effect of perindopril showed any differences between the renal groups in absolute risks during follow-up. Impaired renal function was associated with higher comorbidity, such as hypertension, and worse clinical outcome in our study. This may explain the small difference in absolute risk reduction in the beginning of follow-up, in which this group shows a direct benefit presumably from the blood pressure lowering effects. Still, at longer follow-up the absolute benefits of perindopril were the same in both groups, which may further be related to the additional effects of ACE inhibitors (beyond lowering blood pressure). The ACE inhibitors with high tissue affinity especially improve the angiotensin II–bradykinin balance, reduce remodeling, improve endothelial function, and may have antiatherosclerotic effects (23,24).

Clinical perspective. Remarks on the consistency of the treatment effect of ACE inhibition in patients with stable CAD are clinically relevant. In our study, in contrast to the PEACE trial, also patients with an eGFR >60 ml/min/1.73 m^2 benefited from ACE inhibition by perindopril (eGFR >60: 83.4% in the PEACE trial, 84.1% in the EUROPA trial). In patients with mild renal insufficiency, an increased risk of cardiovascular events was already apparent and perindopril significantly reduced cardiovascular events. Therefore, the earliest stages of renal insufficiency can be considered a key target for preventing the progression of renal disease and to decrease the risk of cardiovascular disease, especially when we also take into account the recent remarks on potential renoprotective effects of ACE inhibitors. We question the conclusion of the PEACE trial to specifically target therapy to patients

Table 4 Absolute Risk Reduction by Perindopril for the Primary End Point (n = 12,056)

	eGFR >75 (%)			eGFR <75 (%)		
Absolute Risk (yrs)	Placebo	Perindopril	Risk Difference	Placebo	Perindopril	Risk Difference
1	2.01	1.96	−0.05	3.01	2.44	−0.57
2	3.95	3.54	−0.41	5.41	4.72	−0.69
3	6.08	5.12	−0.96	7.51	6.49	−1.02
4	8.54	6.64	−1.90	10.29	8.52	−1.77

Absolute risks during follow-up were calculated using Kaplan-Meier analysis.

eGFR= estimated glomerular filtration rate.

Table 5 Data From the EUROPA and PEACE Trials

	No. of Events/No. of Controls (%)	
	EUROPA	PEACE
Total mortality	420/6,108 (6.9)	334/4,132 (8.1)
Cardiovascular mortality	249/6,108 (4.1)	152/4,132 (3.7)
Nonfatal MI	378/6,108 (6.2)	220/4,132 (5.3)

Mean follow-up: EUROPA trial, 4.2 years; PEACE trial, 4.8 years.
MI = myocardial infarction.

with an eGFR <60 as the subgroup more likely to benefit from ACE inhibition.

Some limitations of this study can be noted. The generalizability of these findings to patients with severe renal insufficiency is limited because numbers in the lowest eGFR category were relatively small, which limits our statistical power to detect differences in treatment benefit in these patients. The current analysis mainly addresses patients with mild to moderate renal insufficiency according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines (25). Furthermore, the eGFR levels calculated with the Modification of Diet in Renal Disease equation remain an estimate of the true GFR; however, it is superior to using the serum creatinine level or the Cockcroft-Gault equation (12). Unfortunately, we did not have data on microalbuminuria (26).

Conclusions

The treatment benefit of perindopril is consistent and is not modified by the level of renal function in patients with stable CAD. We observed no heterogeneity in the treatment effect of perindopril in relation to mild or moderate renal insufficiency.

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