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Chronic Kidney Disease, Cardiovascular Events, and the Effects of Perindopril-Based Blood Pressure Lowering: Data from the PROGRESS Study

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ABSTRACT

Chronic kidney disease (CKD) is associated with a high risk of cardiovascular disease, but evidence regarding the effectiveness of interventions to reduce that risk is lacking. The Perindopril Protection against Recurrent Stroke Study (PROGRESS) study enrolled 6105 participants with cerebrovascular disease and randomly allocated them to perindopril-based blood pressure–lowering therapy or placebo. Individuals with CKD were at approximately 1.5-fold greater risk of major vascular events, stroke, and coronary heart disease, and were more than twice as likely to die (all $P \leq 0.002$). Perindopril-based treatment reduced the risk of major vascular events by 30% and stroke by 35% among subjects with CKD, and the absolute effects of treatment were 1.7-fold greater for those with CKD than for those without. Considering patients with CKD and a history of cerebrovascular disease, perindopril prevented one stroke or other cardiovascular event among every 11 patients treated over five years. In conclusion, kidney function should be considered when determining the need for blood pressure lowering therapy in patients with cerebrovascular disease.

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Chronic kidney disease (CKD) is being increasingly recognized as a leading public health problem. CKD, most commonly defined by a reduction in GFR or the presence of proteinuria, affects 10 to 15% of the adult population in Western countries and a much higher proportion of individuals who are older than 65 yr.[1,2]

Individuals with CKD are at significantly increased risk for cardiovascular events as well as progression to end-stage kidney disease. This relationship has been confirmed in a large number of observational analyses[3] and persists after adjustment for other known risk factors. There is, however, a lack of data regarding the effects of interventions such as BP lowering on cardiovascular risk in the CKD population.

BP is an important determinant of cardiovascular risk in the general population,[4] in which interventions that lower BP have been clearly shown to prevent cardiovascular events.[5] BP levels are commonly elevated in people with CKD, raising the possibility that BP lowering may offer significant benefit in this group. BP-lowering agents acting *via* the renin-angiotensin system have been demonstrated to have renoprotective effects in the proteinuric subgroup of people with CKD.[6,7] The few BP-lowering trials that have been conducted in a broader range of participants with CKD[8–10] have not demonstrated clear benefits for either cardiovascular events or kidney function overall. Subsidiary analyses of one large clinical trial[11] suggested

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that angiotensin-converting enzyme inhibitors may produce greater benefits in the presence of CKD. However, a number of other studies that used agents acting *via* the RAS and were performed specifically in participants with CKD, all with limited statistical power, failed to demonstrate clear cardiovascular benefits.[10,12–14]

In this report, we describe the results of new analyses from the Perindopril Protection against Recurrent Stroke Study (PROGRESS), a large, placebo-controlled trial of a perindopril-based BP-lowering regimen in people with previous cerebrovascular disease. The aims of this analysis were to examine the relationship between CKD and cardiovascular events in participants with cerebrovascular disease and to assess the effects of the BP-lowering regimen on cardiovascular events in the subgroup of participants with CKD at baseline.

RESULTS

A total of 6105 participants were recruited from 172 centers in 10 countries, and baseline kidney function was available for 6071 (99.4%). A total of 1757 (28.9%) participants had CKD at entry to the study. A total of 1058 participants experienced major vascular events (some participants experienced more than one event) during an average of 4 yr of follow up, including 724 strokes, 268 major coronary heart disease events, and a total of 621 deaths.

The baseline characteristics of participants overall and according to the presence of CKD at baseline are shown in Table 1. Overall, the participants with CKD at entry were older, more likely to be female and have preexisting coronary disease, but less likely to have diabetes, with lower body mass index and diastolic BP but higher systolic BP. Participants with CKD received single-drug therapy (perindopril *versus* single placebo) more frequently than those without CKD (60 *versus* 54%; $P < 0.0001$).

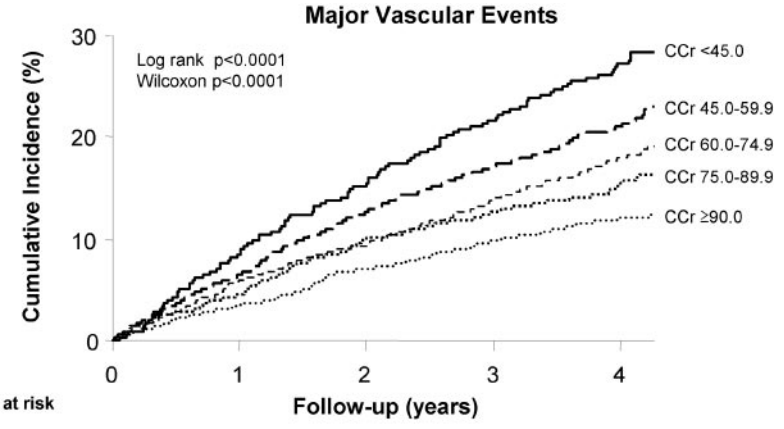
Effects of Kidney Function on the Risk for Cardiovascular Events

An increased risk for cardiovascular events was observed in the participants with CKD at baseline (Figure 1), with an overall hazard ratio (HR) of 1.58 for major cardiovascular events (95% confidence interval [CI] 1.34 to 1.79; $P < 0.0001$). After adjustment for a number of relevant covariates (age, gender, smoking, diabetes, systolic BP, body mass

Table 1. Baseline characteristics of participants overall and according to kidney function at study entry[a]

Characteristic	Overall (n = 6071)	CrCl <60 ml/min (n = 1757)	CrCl ≥60 ml/min (n = 4314)	P[b]
Age (yr; mean ± SD)	64 ± 10	70 ± 8	61 ± 9	<0.0001
Women (%)	30	45	25	<0.0001
Asian (%)[c]	38	37	39	0.4
Creatinine (μmol/L; median [IQR])	88 (75 to 100)	102 (88 to 120)	83 (71 to 95)	<0.0001
Creatinine clearance (ml/min; median [IQR])	72 (58 to 89)	50 (45 to 56)	81 (70 to 96)	<0.0001
Body mass index (kg/m^2; mean ± SD)	26 ± 4	24 ± 3	26 ± 4	<0.0001
Systolic BP (mmHg; mean ± SD)	147 ± 19	149 ± 20	146 ± 19	<0.0001
Diastolic BP (mmHg; mean ± SD)	86 ± 11	84 ± 11	86 ± 11	<0.0001
Medical history (%)				
ischemic stroke	70	71	70	0.6
hemorrhagic stoke	11	10	11	0.04
stroke of unknown type	5	7	4	<0.0001
transient ischemic attack	22	22	23	0.5
coronary heart disease[d]	16	20	15	0.01
diabetes	13	11	13	0.01
current smoker	20	16	22	<0.0001
Medication (%)				
antihypertensive therapy[e]	50	53	49	0.002
antiplatelet therapy	72	73	72	0.3
oral anticoagulants	9	10	9	0.4
lipid-lowering therapy	14	12	15	0.006
Study treatment regimen (%)				
active therapy	50	51	50	0.3
combination therapy or double placebos	58	54	60	<0.0001

[a]IQR, interquartile range.
[b]Differences between patients with and without CKD.
[c]Participants recruited from People's Republic of China or Japan.
[d]History of myocardial infarction or coronary revascularization or of angina (supported by documented electrocardiographic or angiographic evidence).
[e]Current treated hypertension.



Number at risk					
CCr <45.0 ml/min	511	461	416	381	242
CCr 45.0-59.9 ml/min	1,246	1,158	1,067	984	583
CCr 60.0-74.9 ml/min	1,603	1,497	1,428	1,335	786
CCr 75.0-89.9 ml/min	1,302	1,240	1,165	1,122	647
CCr ≥90.0 ml/min	1,409	1,357	1,296	1,245	783
Overall	6,071	5,713	5,372	5,067	3,041

Figure 1. Proportion of participants who experienced major vascular events during follow-up according to baseline kidney function.

index, active *versus* placebo therapy, and single- *versus* dual-agent therapy), CKD was associated with an HR of 1.29 for major cardiovascular events (95% CI 1.11 to 1.49; $P = 0.001$). The risk for stroke was similarly increased, with a crude HR of 1.49 (95% CI 1.28 to 1.73; $P < 0.0001$) and an adjusted HR of 1.21 (95% CI 1.01 to 1.45; $P = 0.04$). For coronary heart disease, a crude HR of 1.48 (95% CI 1.15 to 1.90; $P = 0.002$) and an adjusted HR of 1.42 (95% CI 1.05 to 1.91; $P = 0.02$) were observed. The risk for both total mortality (crude HR 2.27 [95% CI 1.94 to 2.66; $P < 0.0001$]; adjusted HR 1.43 [95% CI 1.18 to 1.73; $P = 0.0003$]) and cardiovascular mortality (crude HR 2.13 [95% CI 1.74 to 2.61; $P = 0.006$]; adjusted HR 1.48 [95% CI 1.16 to 1.90; $P = 0.002$]) were also increased in the presence of CKD. A more detailed breakdown in the relationship between kidney function at baseline and subsequent cardiovascular events and death is shown in Figure 2, demonstrating a progressive increase in the risk for each end point with decreasing levels of kidney function.

Effects of Perindopril-Based Therapy on Cardiovascular Events According to Kidney Function

The administration of a perindopril-based BP-lowering regimen produced similar reductions in the risk for major cardiovascular events at all levels of baseline kidney function (Figures 3 and 4). The hazard ratio (HR) for major cardiovascular events was reduced by 30% (95% CI 14 to 42%) in participants with CKD at baseline, compared with 26% in people without CKD (95% CI 14 to 37%; $P = 0.9$ for homogeneity). Individuals with CKD also had similar reductions in the HR for stroke and coronary heart disease (Figure 4) as participants with better kidney function. No clear effect on

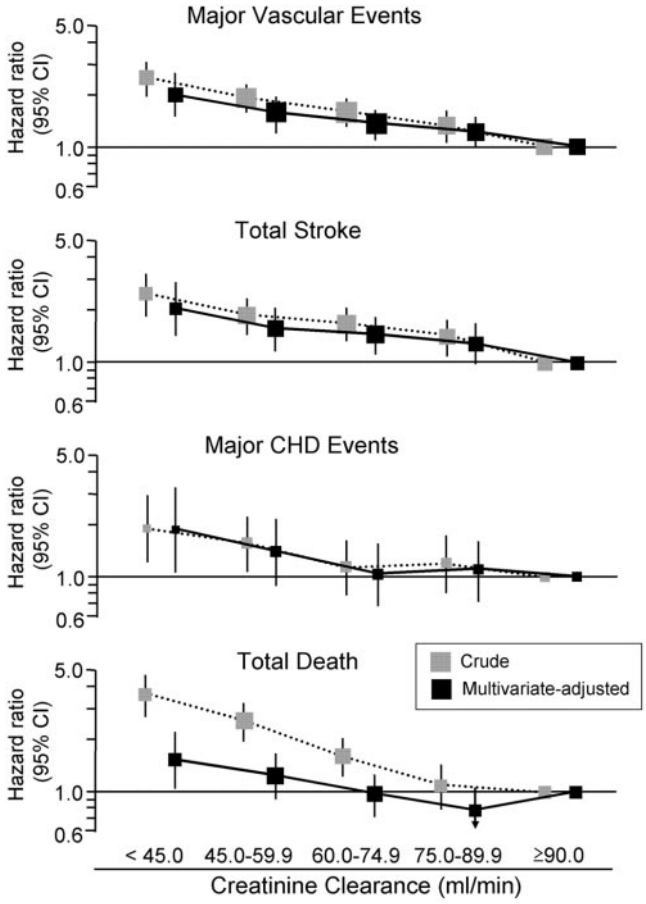


Figure 2. Crude and adjusted (adjusted for baseline age, gender, smoking, diabetes, systolic BP, study treatment, and combination therapy) risk for major cardiovascular events, stroke, coronary heart disease, and death by baseline kidney function.

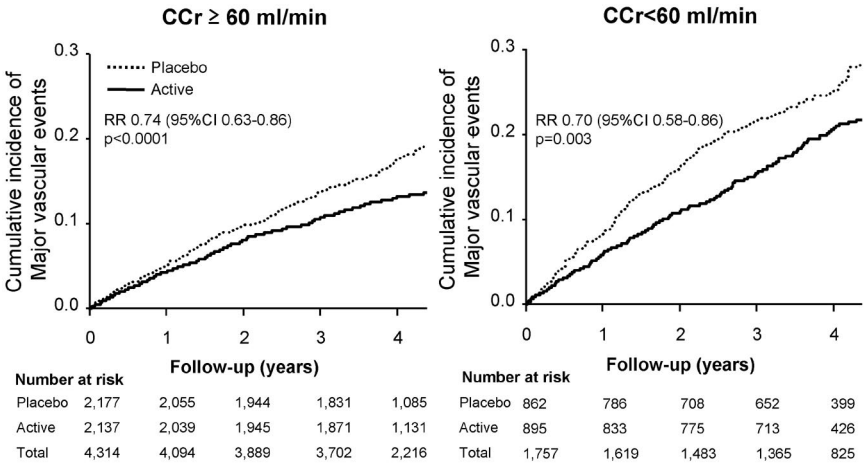


Figure 3. Effects of active therapy on the cumulative incidence of major cardiovascular events according to baseline kidney function. CCr, creatinine clearance.

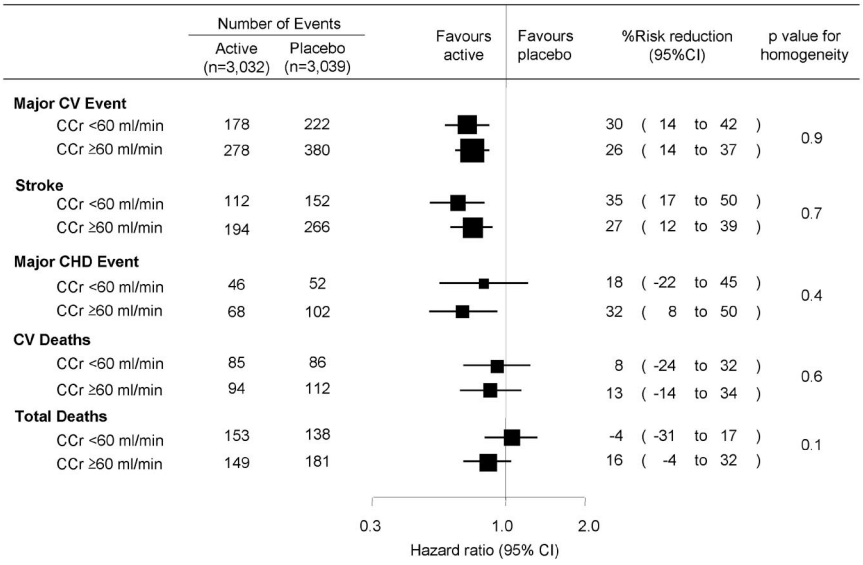


Figure 4. Effects of perindopril-based therapy compared with placebo on the risk for cardiovascular events and death according to baseline kidney function. Treatment effects in subgroups are standardized for the proportions of the study population receiving combination (58%) or single-drug therapy (42%). CV, cardiovascular; CHD, coronary heart disease.

the risk for death could be identified in participants with or without CKD at baseline.

The absolute risk reductions for both major cardiovascular events and stroke (Table 2) were greater in participants with CKD compared with those without. The number needed to treat per 5 yr of therapy (calculated by dividing the difference in absolute event rates over 5 yr into 100) was correspondingly smaller in people with CKD.

Table 2. Comparisons of the RRR and ARR and the NNT for 5 yr to prevent one event, for stroke and cardiovascular events by baseline kidney function[a]

Parameter	Incidence Rate (per 100 person-years)	RRR (95% CI)	ARR over 5 yr (95% CI)	NNT for 5 yr
Major vascular events				
CrCl <60 ml/min	6.5	30 (14 to 42)	8.8 (4.2 to 12.5)	11
CrCl ≥60 ml/min	4.1	26 (14 to 37)	5.3 (2.8 to 7.4)	19
Stroke				
CrCl <60 ml/min	4.2	35 (17 to 50)	7.1 (3.5 to 9.9)	14
CrCl ≥60 ml/min	2.8	27 (12 to 39)	4.1 (1.8 to 6.0)	25

[a]ARR, absolute risk reduction; NNT, number needed to treat; RRR, relative risk reduction

DISCUSSION

Despite widespread recognition of the increased risk for cardiovascular disease (CVD) in people with even mild reductions in kidney function,[3] the benefits of potential therapeutic interventions have not been clearly delineated in this population. This study, conducted among participants at high cardiovascular risk as a result of the presence of cerebrovascular disease at entry, has demonstrated that BP lowering substantially reduces the risk for subsequent cardiovascular events when used in people with CKD, highlighting the public health importance of identifying people with CKD. In light of the fact that people with CKD are at substantially increased risk for cardiovascular events, compared with people with more normal levels of kidney function, fewer individuals with CKD need to be treated to prevent a cardiovascular event. These findings therefore have substantial public health implications, because they suggest that kidney function should be considered when making decisions about the use of BP lowering for the prevention of CVD.

We have demonstrated a clear independent association between kidney function at baseline and the risk for subsequent major cardiovascular events, stroke, and coronary heart disease in people with cerebrovascular disease. Although the increased risk for CVD associated with the presence of CKD has been known for some time, this report provides clear definition of the increased risk for stroke in this population. These data are consistent with other studies that included participants with and without established CVD.[16–18] We have also demonstrated a clear graded increase in the risk for stroke with reducing kidney function that seems to be independent of other known risk factors. This was not clearly shown previously but is consistent with a recent study that found that individuals who undergo dialysis for ESRD have a several-fold higher risk for stroke compared with the general population.[19] Similar relationships between kidney function and the risk for coronary heart disease and death were also found. The importance of the increased risk for stroke is highlighted by data suggesting that outcomes after stroke are particularly poor in people with early[20] or advanced CKD.[21]

The use of a perindopril-based BP-lowering regimen produced a separately statistically significant 30% (95% CI 14 to 42%; $P = 0.002$) reduction in the risk for major cardiovascular events among the 1757 participants in the PROGRESS who had CKD at baseline. The clear nature of these results is in contrast to the African American Study of Kidney Disease (AASK)[12] and the Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND-IT),[9] both of which described the cardiovascular effects of BP lowering using different agents or targets in participants with CKD. Neither study was able to demonstrate a beneficial effect of BP lowering on cardiovascular events. This may simply reflect a difference in statistical power, because the population in the PROGRESS was at particularly high risk for cardiovascular events as all participants had established cerebrovascular disease. A report from the Heart Outcomes Protection Evaluation (HOPE)[11] similarly suggested that participants with a substantially elevated creatinine may derive greater cardiovascular benefit from BP lowering than those with lower creatinine levels but did not use definitions of kidney function that are in routine use today. We used the standard, widely accepted definitions of kidney function and CKD[15] and identified significant reductions in the RR for major cardiovascular events and stroke when the perindopril-based regimen was used in people with CKD that were very similar in relative magnitude to the effects in participants without CKD.

It is important to note that because the background risk for major cardiovascular events is higher in people with CKD, the absolute benefits of BP-lowering therapy will in general be greater (Table 2). This was clearly apparent in PROGRESS, in which the magnitude of the absolute risk reduction achieved with active therapy was approximately 1.7 times greater in participants with CKD than in others and the number needed to treat to prevent a single stroke or cardiovascular event was correspondingly almost halved. Although the absolute risk reductions and numbers needed to treat calculated from the PROGRESS are only directly generalizable to individuals with established cerebrovascular disease, the RR reductions achieved are likely to be similar in the broader range of individuals with CKD. The proportional reduction in the number needed to treat to prevent an event in people with CKD compared with those with normal kidney function is also likely to be similar in the broader CKD population. These results therefore highlight the importance of considering kidney function when identifying high-risk groups that are most likely to benefit from treatment, as well as the importance of BP reduction as a means to reduce the risks for major CVD that are associated with CKD.

This study had some other important limitations. The absence of data on proteinuria makes it impossible to assess the impact of earlier stage CKD on the risk for stroke and other cardiovascular events or whether the effects of therapy are different in this group. The creatinine measurements were conducted locally rather than at a central laboratory, introducing a source of variability that may reduce the ability of the study to identify any true effects. The majority of participants with CKD in this study had relatively mild reductions in creatinine clearance (CrCl), and very few participants had a CrCl of $\leq$30 ml/min. The applicability of these results to populations with advanced CKD is therefore uncertain. Conversely, the strengths of this study include the large sample size and number of events (particularly strokes), providing excellent power for these types of subgroup analyses, with resultant precision in the results obtained, as well as the detailed data collection, validation, and analysis.

These results should help to improve outcomes among people with CKD by highlighting the key role of BP lowering in cardiovascular risk reduction in this population. The incorporation of kidney function into cardiovascular risk assessment and management decisions will improve our ability to target

this intervention to the individuals who are most likely to obtain the greatest benefits.

CONCISE METHODS

Main Study

The design of the PROGRESS has been described in detail previously.[22] In summary, 6105 individuals with a history of cerebrovascular disease (ischemic stroke, hemorrhagic stroke, or transient ischemic attack but not subarachnoid hemorrhage) within the previous 5 yr and no clear indication for or contraindication to treatment with an angiotensin-converting enzyme inhibitor were recruited to the study from 172 centers in 10 countries. There were no BP or kidney function criteria for entry. Informed consent was obtained from all participants, and the study was conducted according to the Declaration of Helsinki.

Eligible participants received perindopril (2 mg for 2 wk, followed by 4 mg for 2 wk) during a 4-wk open-label, active run-in period. Participants who tolerated and adhered to this treatment were subsequently randomly allocated to active therapy or matching placebo. Active treatment comprised a flexible treatment regimen based on perindopril (4 mg/d) in all participants, with the addition of indapamide (2.5 mg/d; 2 mg/d in Japan) in those for whom the responsible study physician believed that there was no specific indication for or contraindication to the use of a diuretic. Participants who were assigned placebo received one or two tablets that were identical in appearance to the active agent(s). Combination therapy (perindopril and indapamide or double placebo), rather than single-drug therapy (perindopril or single placebo), was used whenever possible to maximize the reduction in BP; however, because many investigators had concerns about the safety of BP lowering in patients with stroke (particularly in those with average or below-average levels of BP), it was necessary to provide some flexibility with respect to the intensity of treatment. All other aspects of medical care of the patients were left to the discretion of the responsible physician.

Kidney Function

Serum creatinine was measured at local laboratories during the study period, including at entry to the run-in period, randomization, 3 and 6 mo after randomization, and then annually throughout the duration of the study. Demographic and physical variables allowing the estimation of GFR from serum creatinine were also collected. Urinary protein excretion levels were not collected as part of the study.

GFR was estimated using the Cockroft Gault[23] equation based on previous work[24] suggesting that it is a better predictor of major clinical events in this population than raw serum creatinine or the simplified Modification of Diet in Renal Disease (MDRD)[25] formula. The Cockroft Gault formula is CrCl = (140 − age)/creatinine × weight/72 (× 0.85 for women), where age is in years, serum creatinine is in mg/dl, and weight is in kilograms.

Participants with CKD were defined as those with an estimated CrCl <60 ml/min as recommended by the Kidney Disease Outcomes Quality Initiative (KDOQI)[15] and other guidelines. For better definition of the relationship between levels of kidney function and cardiovascular risk, subsidiary analyses were also performed using further subcategorization of CrCl into 30 to 44.9, 45 to 59.9, 60 to 74.9, and 75 to 89.9 ml/min groups.

Outcomes

The predefined primary outcome for this analysis was "major cardiovascular events," defined as the composite of nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death. Secondary outcomes were stroke, major coronary heart disease, and death. Stroke was defined as a neurologic deficit that lasted at least 24 h and was thought to be due to cerebral ischemia or hemorrhage, and major coronary heart disease was defined as nonfatal myocardial infarction or death ascribed to coronary heart disease. The effects of treatment on kidney function are of great interest and will be analyzed and reported separately.

Statistical Analyses

The SAS software package (SAS Institute, Cary, NC) was used to perform all statistical analyses. Serum creatinine and CrCl are expressed as median and interquartile range, and the statistical significance of differences was examined using Wilcoxon signed-rank test. The values of other variables are expressed as means with SD or percentages unless otherwise indicated. The statistical significance of differences in mean values of continuous variables and frequencies of categorical variables was examined using the students *t*-test and χ^2 test as appropriate. The cumulative event curves were estimated with the Kaplan-Meier procedure. The incidence of events was calculated using the person-year method. The crude- or multivariate-adjusted HR and 95% CI for the development of events were estimated using Cox proportional hazards model.

All analyses of treatment effect were performed on an intention-to-treat basis. The effects of randomized treatment on events were calculated using univariate Cox proportional hazards model. Tests of homogeneity of treatment effects in subgroups were performed by addition of an interaction term to the statistical model. Because the overall effect of treatment was greater among participants who were treated with combination therapy (perindopril and indapamide *versus* double placebo) than those who were treated with single-drug therapy (perindopril *versus* single placebo), treatment effects in subgroups were standardized for the proportions of the study population for whom combination (58%) or single-drug therapy (42%) was prescribed by taking weighted averages of the estimates obtained for the two therapies.[26] Percentage risk reductions were calculated as $[(1 - \text{HR}) \times 100]$. $P < 0.05$ was considered statistically significant in all analyses

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DISCLOSURES

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