Rate of Change in Renal Function and Mortality in Elderly Treated Hypertensive Patients

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Abstract

Background and objectives Evidence relating the rate of change in renal function, measured as eGFR, after antihypertensive treatment in elderly patients to clinical outcome is sparse. This study characterized the rate of change in eGFR after commencement of antihypertensive treatment in an elderly population, the factors associated with eGFR rate change, and the rate's association with all-cause and cardiovascular mortality.

Design, setting, participants, & measurements Data from the Second Australian National Blood Pressure study were used, where 6083 hypertensive participants aged ≥65 years were enrolled during 1995–1997 and followed for a median of 4.1 years (in-trial). Following the Second Australian National Blood Pressure study, participants were followed-up for a further median 6.9 years (post-trial). The annual rate of change in the eGFR was calculated in 4940 participants using creatinine measurements during the in-trial period and classified into quintiles (Q) on the basis of the following eGFR changes: rapid decline (Q1), decline (Q2), stable (Q3), increase (Q4), and rapid increase (Q5).

Results A rapid decline in eGFR in comparison with those with stable eGFRs during the in-trial period was associated with older age, living in a rural area, wider pulse pressure at baseline, receiving diuretic-based therapy, taking multiple antihypertensive drugs, and having blood pressure <140/90 mmHg during the study. However, a rapid increase in eGFR was observed in younger women and those with a higher cholesterol level. After adjustment for baseline and in-trial covariates, Cox-proportional hazard models showed a significantly greater risk for both all-cause (hazard ratio, 1.28; 95% confidence interval, 1.09 to 1.52; P=0.003) and cardiovascular (hazard ratio, 1.40; 95% confidence interval, 1.11 to 1.76; P=0.004) mortality in the rapid decline group compared with the stable group over a median of 7.2 years after the last eGFR measure. No significant association with mortality was observed for a rapid increase in eGFR.

Conclusions In elderly persons with treated hypertension, a rapid decline in eGFR is associated with a higher risk of mortality.

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Introduction

Elevated BP is one of the leading risk factors for the development of CKD (1,2). CKD is a global health burden with an annual growth rate of 8% (3) and is an independent risk factor for the development of cardiovascular diseases (4–6). This risk for cardiovascular events substantially increases when elevated BP accompanies CKD, particularly in older adults (7,8). Evidence suggests that a rapid decline in renal function is associated with an increased risk of cardiovascular and all-cause mortality (9,10). Recent studies also have reported a higher risk of mortality with a rapid improvement in renal function (11,12). However, there is inadequate evidence on the relationship between a rapid rate of change in renal function and the risk of fatal events in elderly patients treated for hypertension.

The association between lowering of BP to a target level and the rate of change in renal function is still unclear, and in particular, it is not well documented in older adults. Although some observational studies have shown a protective effect of BP lowering on hypertension-related deterioration of renal function (13–15), some randomized controlled trials have shown no such effect (16–18). In addition, there is limited information in older adults with hypertension regarding the prognostic significance of rates of change in renal function using different antihypertensive drug regimens. Some studies have evaluated the renoprotective effect of angiotensin-converting enzyme inhibitors (ACEIs) compared with other antihypertensive agents, but results are mixed (19).

We conducted a *post hoc* analysis in older adults treated for hypertension to identify the rate of change in renal function, the factors associated with rapid change in renal function, and the rate's association with mortality.

Materials and Methods

Study Design

Data from the Second Australian National Blood Pressure (ANBP2) study were used. The ANBP2 study was a prospective randomized open-label study with blinded assessment of end points conducted in 1594 family practices in five states of Australia. There were 6083 participants who were hypertensive, mostly white, and aged 65–84 years who were enrolled during 1995–1997 and randomized to receive either an ACEI- or thiazide diuretic–based BP lowering regimen. Participants were followed for a median of 4.1 years (interquartile range [IQR], 3.9–4.6). Details relating to the ANBP2 clinical trial and the main findings have been previously published (20). Following the ANBP2 study, post-trial information on participants' survival was collected over a median of a further 6.9 years (IQR, 6.1–6.9) until data were censored on October 31, 2009 (Figure 1). The ANBP2 study was approved by the Ethics Committee of the Royal Australian College of General Practitioners and conducted according to the Helsinki Declaration of the World Medical Association.

Renal Function Measurement and Definition of on-Trial Deterioration

The current recommendation for measuring renal function and for early recognition of CKD is the eGFR (21,22). Information on renal function (serum creatinine concentration) was collected from the ANBP2 study participants at baseline (prerandomization) and during the follow-up period (in-trial postrandomization) as part of routine clinical assessment (Figure 1). No information was available on renal function throughout the post-trial period. The CKD Epidemiology Collaboration (CKD-EPI) equation that is specified for the white race was used for the eGFR (expressed as milliliters per minute per 1.73 m^2) from the serum creatinine measurements (23). The CKD-EPI equation is on the basis of standardized serum creatinine values. The serum creatinine values that were available in the ANBP2 study were not standardized to those obtained by isotope dilution mass spectrometry. Therefore, the serum creatinine concentrations were reduced by 5% using the calibration process that has been used in other epidemiologic studies (24,25). We used the CKD-EPI equation rather than other estimates of GFR because it is more accurate in risk prediction across a broad spectrum of population cohorts (25).

On the basis of the eGFR information, we classified the ANBP2 cohort into having no CKD (eGFR≥60 ml/min per 1.73 m^2) and CKD (eGFR<60 ml/min per 1.73 m^2) at baseline and at the end of the ANBP2 study, using the last available serum creatinine measurement to assess change in renal function status (CKD or no CKD) during the trial. In addition, the rate of change in renal function over the trial period from study entry for an individual was calculated from the slope of the regression line of annual eGFR measurements against time. We divided the participants' into quintiles (Q1–5) on the basis of the annual rate of change in eGFR, where Q1 represents those with the highest decline in eGFR and Q5 represents the highest increase in eGFR. We labeled Q1–5 as follows: rapid decline, decline, stable, increase, and rapid increase in eGFR.

Outcome

The primary outcomes of interest were all-cause and cardiovascular mortality. The outcomes were determined during the ANBP2 trial period by an end point committee blinded to randomization allocation and during the post-trial period by linkage of data to the Australian Institute of Health and Welfare National Death Index (death registry) using the *International Classification of Diseases Version 10* coding for cause of death.

Statistical Analyses

We compared the baseline characteristics of participants across the Q on the basis of the rate of change in renal function during the ANBP2 in-trial period. Differences in results for continuous variables were compared using ANOVA and for categorical variables by the chi-squared test in relation to those whose renal function was stable. We also performed a nonparametric test to analyze the trend for the ranks across ordered groups of Q for different continuous and categorical variables of baseline characteristics. We used multinomial logistic regression to identify the predictors of rapid change in eGFR (Q1 and Q5), including the effect of BP control (<140/90 mmHg) and the specific antihypertensive drugs prescribed in comparison with the stable renal function group. Thereafter, we used Cox-regression proportional hazard models to assess the effect of in-trial change in eGFRs in comparison with stable eGFRs on cardiovascular and all-cause mortality after the last creatinine measurement to the

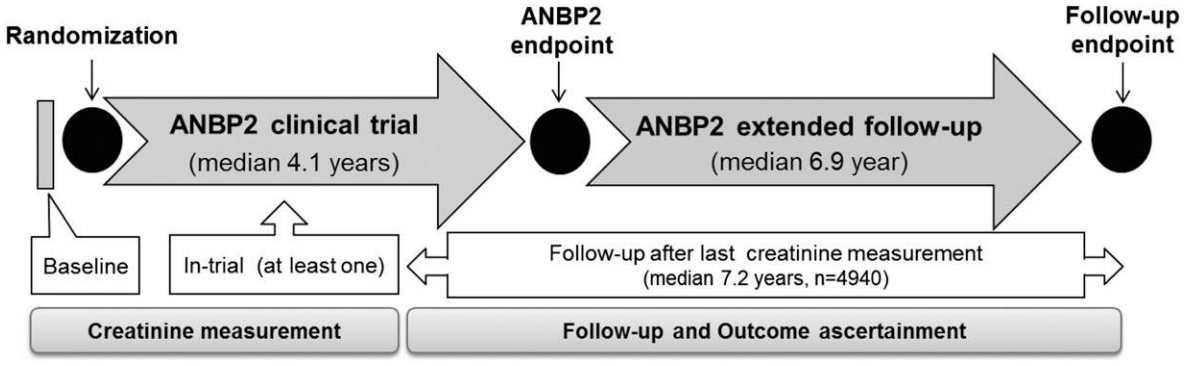

Figure 1. | Overview of the ANBP2 study and long-term follow-up, creatinine measurement, clinical outcome ascertainment, and analysis time period. ANBP2, Second Australian National Blood Pressure.

end of the post-trial follow-up. These analyses were adjusted for clustering of participants within family practices and for potential baseline and in-trial risk factors that were associated with a rapid change in eGFRs identified in the previous step. We conducted sensitivity analyses to compare results between those with more versus fewer repeated creatinine values during the in-trial period, and we adjusted the analysis using the last eGFR instead of the baseline eGFR. All analyses were performed using Stata version 11.2 for Windows (26).

Results

Information on baseline renal function was available for all 6083 participants, whereas 4940 participants had available serum creatinine measurements (median, 2; range, 1–5) during the postrandomization in-trial period. The reason for unavailability of serum creatinine values for the rest of the participants is unknown. We observed no differences in baseline eGFRs between those who have or did not have serum creatinine values during follow-up. However, participants with no serum creatinine values during the in-trial period were older (36% versus 29% aged ≥75 years, $P<0.001$), more likely to be women (54% versus 50%, $P=0.01$), and experienced more fatal events (18% versus 4%, $P<0.001$) than those with available information. Therefore, we only considered the 4940 participants in the current analysis (Figure 1). Among these 4940 older adults with hypertension, 28% had CKD (eGFR<60 ml/min per 1.73 m^2) at baseline, and 34% had CKD at the end of the study (on the basis of the last available serum creatinine measurement). Overall, 77% of the participants retained a similar level of renal function to that at baseline (58% with no CKD and 19% with CKD at baseline), 8% had reversion of renal function status from CKD to no CKD (eGFR≥60 ml/min per 1.73 m^2), and 15% of participants progressed from no CKD to CKD. During the ANBP2 trial period, 29% of the participants achieved on-treatment target for both systolic BP and diastolic BP <140/90 mmHg.

Annual Rate of Change in Renal Function

The demographic and clinical characteristics of participants according to quintiles of the annual rate of change in eGFR are summarized in Table 1. Compared with baseline values, we observed an average±SD annual rate of change in eGFR of –0.55±4.6 ml/min per 1.73 m^2, with a median of –0.51 (IQR, –2.76 to 1.82) ml/min per 1.73 m^2 over the in-trial study period. The mean (range) changes in annual eGFR for different groups (Q1–5) are shown in Table 1. Among those who experienced a rapid decline in eGFRs, 37% (n=367/988) had renal function that was still classified as no CKD at study closure.

Predictors' of Rapid Decline or Rapid Increase in eGFRs during Trial Period

The results of the simple logistic regression analysis for the baseline and in-trial period variables that possibly could have an association with the rapid decline or rapid increase in eGFR in relation to those with stable eGFRs are presented in Supplemental Table 1. Those variables that showed an association ($P<0.10$) with rapid change in eGFRs were included in the multinomial logistic regression model (Table 2). After adjustment for clustering of participants within family practice, the following predictors were associated with rapid decline in eGFRs compared with those in the stable eGFR group: older age (≥75 years at study entry), living in a rural area, having a wider pulse pressure, having a higher eGFR at baseline, randomized to receive diuretic-based therapy, achieving target BP (<140/90 mmHg), and requiring multiple antihypertensive drugs during the in-trial study period (Table 2). A rapid increase in eGFRs was observed in those who were younger, women, having higher total and HDL cholesterol concentrations, and having a lower eGFR at baseline (Table 2).

Effect of Rate of Change in Renal Function on Mortality

During the period after the last eGFR measure, including the ANBP2 post-trial phase, there were 1334 deaths (39.9/1000 patient years) from all causes. Among these, 696 deaths (20.8/1000 patient years) were caused by cardiovascular causes. We observed a significantly higher risk for all-cause and cardiovascular mortality over a median 7.2 years in those who experienced rapid decline in eGFRs during the in-trial period (Table 3). However, those who experienced a rapid increase in eGFRs showed a trend to a protective effect (statistically not significant) from subsequent all-cause and cardiovascular mortality compared with those whose eGFRs remained stable (Table 3). Kaplan–Meier survival curves for both all-cause and cardiovascular mortality by rapid decline, stable, and rapid increase in eGFR groups are illustrated in Figure 2.

We observed similar results in the sensitivity analyses that compared the effect of change in eGFRs on the basis of more versus fewer repeated serum creatinine values on mortality (Supplemental Figure 1). On sensitivity analysis, by controlling for the last eGFR measure instead of the baseline measure, the relationship with mortality was attenuated and no longer significant (Supplemental Table 2).

Discussion

Our findings in older adults treated for hypertension, aged ≥65 years at study entry, have demonstrated that a change in annual eGFR, particularly a rapid decline, compared with eGFR remaining stable were associated with a higher risk of all-cause and cardiovascular mortality over a median 7.2 years after the last eGFR measure. In-trial target BP (<140/90 mmHg) achievement and being randomized to the thiazide diuretic arm were associated with a rapid decline in eGFR during the study period. This study has also identified a number of baseline and in-trial demographic and clinical characteristics associated with an annual rapid change in eGFR.

During the in-trial period of our study, over a median of 4 years, we observed an average 0.55 ml/min per 1.73 m^2 decline in eGFR annually among the study participants. Despite this change, at study closure, overall renal function status (CKD or no CKD) remained unchanged from baseline status in 77% of participants. In those who remained classified as no CKD at study closure, approximately 13% observed a rapid decline in eGFR annually. These findings highlighted the importance of observing the rate of change in renal function rather than absolute renal function status because the adjusted results in our study showed that a rapid annual decline in eGFR independently predicted a higher risk of all-cause and cardiovascular mortality, whereas using

Table 1. Baseline characteristics of the Second Australian National Blood Pressure study patients (with available in-study renal function information) overall and categorized by annual change in renal function (quintile) during the study

Characteristic	Overall	Rapid Decline[a]	Decline[c]	Stable[d]	Increase[e]	Rapid Increase[f]	*P* Value for Trend[g]
Age (y)	71.7±4.9	72.3±4.9[b]	71.9±4.9	71.7±4.9	71.5±4.8	71.2±4.8[b]	<0.001
≥75 y	28.8	33.1[b]	29.1	28.9	27.4	25.4	<0.001
Men	49.6	52.9	51.4	51.4	52.1	40.2[b]	<0.001
Education							0.002
Primary	22.9	26.0[b]	23.3	21.9	21.3	21.9	
Some high school	43.9	44.7[b]	43.5	44.4	44.2	42.9	
Completed high school/university	33.2	29.3[b]	33.2	33.7	34.5	35.3	
Rural location	19.0	22.6[b]	19.8	17.3	17.4	17.9	0.003
BMI (kg/m^2)	27±4	27±4	27±4	27±4	27±4	27±4	0.26
Obese (BMI≥30 kg/m^2)	21.6	21.6	20.8	20.7	21.8	23.1	0.34
Current smoker	6.7	8.4	6.4	6.2	5.5	7.2	0.19
Current drinker	74.2	74.1	74.3	75.0	75.3	72.5	0.63
Pulse pressure quartile							<0.001
1 (31–66 mmHg)	26.7	21.7[b]	26.4	28.4	29.9	26.8	
2 (67–77 mmHg)	26.9	25.7[b]	25.2	27.4	26.1	30.0	
3 (78–87 mmHg)	24.5	25.9[b]	27.4	22.7	23.1	23.7	
4 (88–137 mmHg)	21.9	26.7[b]	21.0	21.5	21.0	19.5	
Systolic BP (mmHg)	167±13	169±13[b]	167±12	167±12	167±13	167±12	<0.001
Diastolic BP (mmHg)	91±8	91±8	91±8	91±8	92±8	91±8	0.01
Previously treated with antihypertensive	63.1	63.1	63.2	61.2	62.8	65.1	0.45
Previous coronary heart disease	8.0	9.0	8.1	7.9	8.4	6.8	0.13
Previous cerebrovascular heart disease	4.4	4.4	4.0	5.4	3.7	4.6	0.96
Diabetes	6.9	9.1[b]	7.3	6.7	6.9	4.8	<0.001
Elevated total cholesterol (>251 mg/dl)	21.6	20.3	21.5	19.4	20.6	26.0[b]	0.01
Low HDL (<40 mg/dl)	13.4	13.1	14.7	15.6	13.3	10.1[b]	0.03
eGFR (ml/min per 1.73 m^2)	68.7±13.7	72.6±13.8[b]	69.1±14.5	69.3±14.1	68.6±13.4	63.8±11.0[b]	<0.001
eGFR<60 ml/min per 1.73 m^2 (CKD at baseline)	27.7	20.1[b]	27.5	26.2	28.8	35.6[b]	<0.001
Physical activities in previous 2 wk							0.47
No exercise	32.5	33.2	32.3	31.6	31.9	33.8	
1–6 h	29.4	27.1	30.8	29.1	30.5	29.5	
≥7 h	38.1	39.7	36.9	39.3	37.6	36.7	
Randomized to receive ACEI	50.0	47.5[b]	48.3[b]	52.7	51.4	50.2	0.09

Values are means±SDs, percentages, or as otherwise indicated. BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitor.

[a]Quintile 1: mean annual change in eGFR: –6.62 (range, –51.8 to –3.43 ml/min per 1.73 m^2; *n*=988).

[b]Significant differences ($P<0.05$) with those observed as having a stable change in eGFR.

[c]Quintile 2: mean annual change in eGFR: –2.18 (range, –3.42 to –1.10 ml/min per 1.73 m^2; *n*=988).

[d]Quintile 3: mean annual change in eGFR: –0.45 (range, –1.10 to 0.33 ml/min per 1.73 m^2; *n*=988).

[e]Quintile 4: mean annual change in eGFR: 1.33 (range, 0.34 to 2.49 ml/min per 1.73 m^2; *n*=988).

[f]Quintile 5: mean annual change in eGFR: 5.16 (range, 2.50 to 56.04 ml/min per 1.73 m^2; *n*=988).

[g]Trend for ranks across ordered groups of quintiles analyzed using nonparametric test (nptrend command in Stata software was used to perform the test, which is an extension of the Wilcoxon rank-sum test).

Table 2. Predictors of a rapid decline and rapid increase in annual eGFR in relation to those with stable change in annual eGFR among the Second Australian National Blood Pressure study older adults with hypertension cohort

Characteristic	Rapid Decline		Rapid Increase	
	RR Ratio (95% CI)	*P* Value	RR Ratio (95% CI)	*P* Value
Baseline characteristics				
Age ≥75 y	1.41 (1.14 to 1.74)	0.002	0.60 (0.48 to 0.77)	<0.001
Men	1.09 (0.90 to 1.31)	0.37	0.72 (0.59 to 0.88)	0.001
Education				
Primary	1.00		1.00	
Some high school	0.84 (0.66 to 1.08)	0.18	0.86 (0.66 to 1.13)	0.29
Completed high school/university	0.76 (0.58 to 0.99)	0.05	1.00 (0.76 to 1.32)	0.98
Rural location (versus major cities)	1.29 (1.03 to 1.60)	0.02	1.02 (0.78 to 1.35)	0.87
Pulse pressure (in quartile)				
1 (31–66 mmHg)	1.00		1.00	
2 (67–77 mmHg)	1.23 (0.93 to 1.62)	0.15	1.12 (0.88 to 1.44)	0.36
3 (78–87 mmHg)	1.57 (1.19 to 2.07)	0.002	0.96 (0.74 to 1.26)	0.79
4 (88–137 mmHg)	1.54 (1.14 to 2.07)	0.01	0.82 (0.61 to 1.10)	0.19
Previously treated with antihypertensive	1.04 (0.85 to 1.27)	0.73	1.17 (0.95 to 1.45)	0.14
Elevated total cholesterol (>251 mg/dl)	1.15 (0.92 to 1.45)	0.22	1.28 (1.02 to 1.60)	0.03
Low HDL cholesterol (<40 mg/dl)	0.84 (0.64 to 1.11)	0.22	0.65 (0.49 to 0.87)	0.004
Base eGFR (per 1 ml/min per 1.73 m^2 higher)	1.02 (1.02 to 1.03)	<0.001	0.97 (0.96 to 0.97)	<0.001
Diabetes	1.27 (0.88 to 1.83)	0.20	0.80 (0.53 to 1.21)	0.30
Current smoker	1.44 (0.97 to 2.14)	0.07	1.17 (0.81 to 1.68)	0.41
In-study characteristics				
ACEI (versus diuretics)	0.79 (0.65 to 0.96)	0.02	0.88 (0.73 to 1.07)	0.22
Number of antihypertensive drug				
1	1.00		1.00	
2	1.21 (0.99 to 1.48)	0.06	0.99 (0.81 to 1.22)	0.95
≥3	1.94 (1.24 to 3.03)	0.004	1.09 (0.67 to 1.75)	0.74
No drug	0.50 (0.27 to 0.93)	0.03	1.42 (0.91 to 2.22)	0.12
BP control (<140/90 mmHg)	1.44 (1.17 to 1.76)	0.001	0.86 (0.69 to 1.07)	0.18

ACEI, angiotensin-converting enzyme inhibitor; RR, relative risk; 95% CI, 95% confidence interval.

Table 3. Effect of annual change in renal function on all-cause and cardiovascular mortality in relation to those with stable renal function

Annual Change in Renal Function	All-Cause Mortality		Cardiovascular Mortality	
	Hazard Ratio[a] (95% CI; *P* Value)	Event rate per 1000	Hazard Ratio[a] (95% CI; *P* Value)	Event rate per 1000
Rapid decline	1.28 (1.09 to 1.52; 0.003)	53.6	1.40 (1.11 to 1.76; 0.004)	28.9
Decline	0.97 (0.82 to 1.16; 0.75)	39.2	1.14 (0.90 to 1.45; 0.28)	22.8
Stable	1.00	37.9	1.00	18.3
Increase	0.94 (0.78 to 1.13; 0.49)	35.2	1.07 (0.84 to 1.36; 0.60)	19.5
Rapid increase	0.92 (0.76 to 1.11; 0.38)	33.8	0.83 (0.63 to 1.10; 0.20)	15.0

95% CI, 95% confidence interval.
[a]Hazard ratio adjusted for age, sex, education level, remoteness, smoking, diabetes, pulse pressure, total cholesterol, HDL cholesterol, and eGFR at baseline and BP control status, use of either angiotensin-converting enzyme inhibitors/diuretics, number of antihypertensive drugs, and clustering by family practitioner during the Second Australian National Blood Pressure trial period.

just the last eGFR measure during the in-trial period showed no such relationship. The most likely reason for a weaker relationship when adjusting for the last eGFR is that those who were observed having rapid decline in eGFR over time might have had a lower level of eGFR at the end, even though previously at baseline many of them had better renal

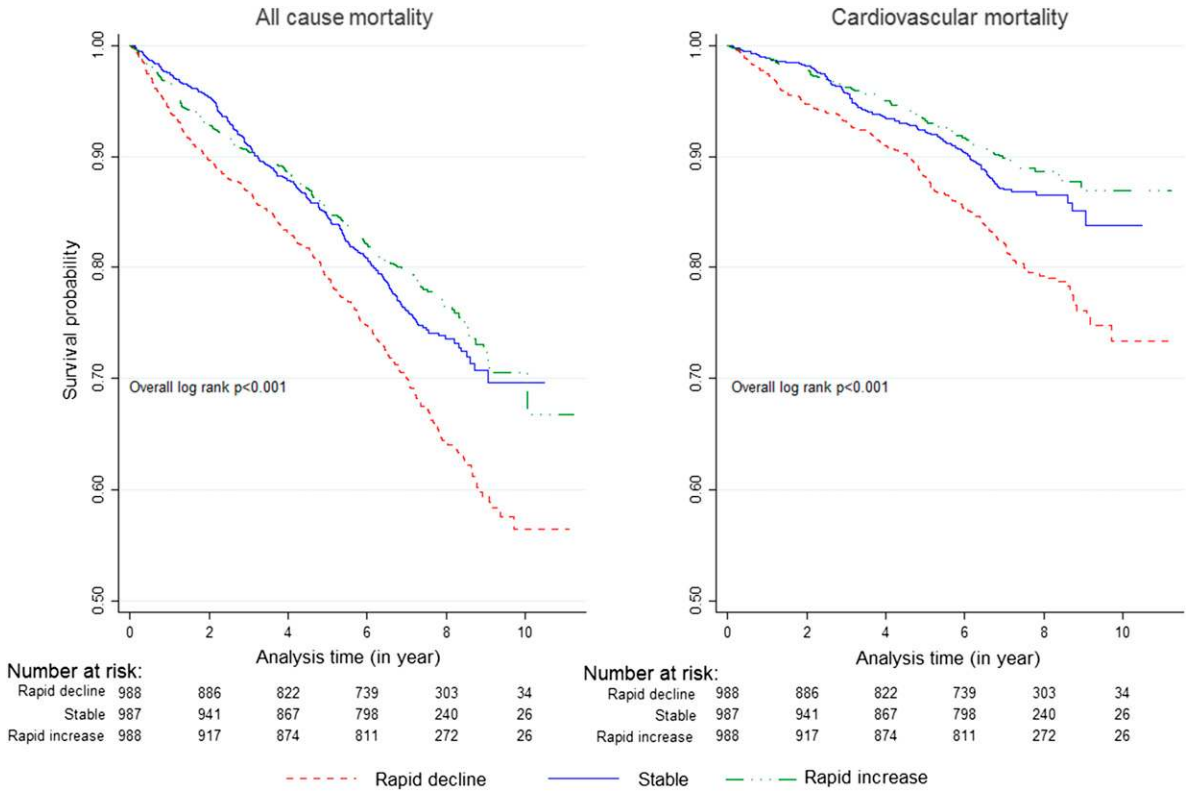

Figure 2. | Kaplan–Meier survival curves in the patients with treated hypertension on the basis of annual renal function change (rapid decline, stable, and rapid increase) for all-cause and cardiovascular mortality after the last eGFR measure.

function. Earlier research has reported renal impairment is associated with vascular damage, endothelial dysfunction, and increased activation of the renin-angiotensin system, which increases risk of cardiovascular disease (27). Our findings in older adults treated for hypertension support earlier findings on the association of a higher decline in renal function (defined as eGFR reduction >3 ml/min per 1.73 m^2) and higher risk of mortality among older adults (9,10). We did not observe any higher risk of mortality with a rapid increase in eGFR as reported in previous studies (11,12,28).

This study has observed a number of factors associated with a rapid annual change in eGFR. We observed that being older (≥75 years at study entry) was associated with a rapid decline, whereas being younger (65–74 years at study entry) and a woman was associated with a rapid increase in eGFR. Decline in renal function with advancing age occurs because of aging-related nephron dropout (8,29). Moreover, organ function impairment associated with aging and chronic diseases, such as diabetes, hypertension, and atherosclerotic vascular disease, can enhance the aging-related impairment in renal function (30,31). We also observed that higher pulse pressure at baseline was associated with a decline in renal function. Higher pulse pressure in older adults is associated with advancing age and with worse outcome (32). In addition, older participants residing in a rural area compared with major cities had a rapid decline in renal function in the ANBP2 study. One possible reason could be a more limited access to health care services in rural areas (33). These factors may well explain the more likely rapid reduction in GFR in the older subgroup.

The observed increase in eGFR in the younger elderly group with a predominance of women may not represent an improvement in renal function but rather may be because of the reduction in muscle mass over time as part of the aging process opposing any aging-related increases in serum creatinine values caused by renal impairment (7). We observed a rapid increase in eGFR associated with elevated total cholesterol and HDL cholesterol. The reasons for these associations are unclear. However, such lipid abnormalities have been reported among patients with normal and elevated eGFRs who suffered from chronic disease and particularly had microalbuminuria (34).

The available evidence on the association between BP and renal function progression is contradictory. A number of studies have shown that intensive BP control had no associated benefit on improving renal outcomes (17,18,35). On the other hand, a reduced risk of renal failure was reported over a long-term follow-up in participants with better BP control who had moderate to severe decreased eGFR at study entry (13). We observed that achieving an in-trial average target BP <140/90 mmHg was associated with a rapid decline in renal function. The underlying pathophysiology could be caused by reduced renal perfusion and therefore overall renal function because of lower BP, which has been observed in animal studies (36). Multiple antihypertensive drug use, which tends to be associated with lower BP (37,38), was also associated with a rapid decline in eGFR in these elderly participants. However, the findings from our study should not be taken as a clinical message to avoid achieving a target BP of <140/90 mmHg in older

patients because BP control has a number of beneficial effects (39,40), which may outweigh any observed deleterious effect on renal function.

In our study, people who were receiving ACEI-based treatment compared with thiazide diuretic–based treatment were less likely to have a rapid decline in eGFR. There is no clear evidence on which BP-lowering drug class has a greater protective effect on the rate of change of renal function or CKD progression (41); however, some studies suggest that ACEI might delay the progression of CKD in low-risk hypertensive patients (15,19). It is possible that the mechanisms by which ACEI reduce systemic vascular resistance in patients with hypertension may have a renoprotective effect over the long term because with a diminished renal perfusion pressure, the kidney is able to maintain both blood flow and glomerular filtration (42,43).

Our study has several limitations. First, renal function was only assessed indirectly from serum creatinine measurements. There was no information on other markers of kidney damage, such as albuminuria or proteinuria. Moreover, we did not have any information on whether any participant experienced AKI during the in-trial or post-trial period. Second, the serum creatinine measurements that we used for calculating eGFR using the CKD-EPI equation were not standardized to isotope dilution mass spectrometry values and therefore needed calibration. This might have introduced some systematic bias in estimation. However, this method of calibration is widely accepted (25,44). Third, we could not incorporate treatment adherence information in the analysis because we had limited information on self-reported treatment adherence. However, from the available data we did not observe any differences in treatment adherence between the ACEI-based and thiazide diuretic–based treatment group. Finally, we did not consider the effect of add-on antihypertensive drugs over time because the family physicians were responsible for these occasional changes. However, the add-on drugs were similar in both treatment groups (20).

Despite these limitations, the results of our large prospective study are likely to be valid and are generalizable in similar contexts. The long-term survival information in the older adults with hypertension has provided a unique opportunity to determine the association of outcome in our participants with the rates of change in their renal function. The findings from this study may have implications for clinicians making decisions about the management of hypertension in older patients and taking protective measures to reduce cardiovascular risk.

In conclusion, renal function decline with advancing age is well established. Our findings in older adults with hypertension indicate that a more rapid decline is independently associated with a greater chance of both all-cause and cardiovascular mortality. Our findings also suggest possible demographic and clinical characteristics to target for limiting the rate of change in renal function in older adults treated for hypertension.

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Disclosures

None.

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