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Hypertension Control, Apparent Treatment Resistance, and Outcomes in the Elderly Population With Chronic Kidney Disease

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Introduction: Chronic kidney disease (CKD) is often associated with poor hypertension control and treatment resistance, but whether CKD modifies the effect of hypertension control on outcomes is unknown.

Methods: We studied 10-year mortality and cardiovascular events according to hypertension control status and CKD (glomerular filtration rate <60 ml/min/1.73m^2) in 4262 community-dwelling individuals (40% men) more than 65 years of age.

Results: At baseline, 19% had CKD, and 31.2% had controlled hypertension on $\leq$3 antihypertensive drugs, 62.3% uncontrolled hypertension $\geq$140/90 mm Hg on $\leq$2 drugs, and 6.5% apparent treatment-resistant hypertension (aTRH) $\geq$140/90 mm Hg with $\geq$3 drugs or use of $\geq$4 drugs regardless of level. There were 1115 deaths (305 total cardiovascular deaths) and 274 incident nonfatal or fatal strokes or coronary events. Compared to the reference group (controlled hypertension and no CKD), participants without CKD and with uncontrolled hypertension or aTRH had adjusted hazard ratios for all-cause mortality of 0.86 (0.74−1.01) and 1.09 (0.82−1.46), and those with CKD and controlled or uncontrolled hypertension, or aTRH, of 1.33 (1.06−1.68), 1.14 (0.93−1.39), and 1.34 (0.98−1.85), respectively. Participants with aTRH and CKD had a risk of coronary death more than 3 times higher than that of the reference group; participants with aTHR, with or without CKD, had a risk of stroke more than twice as high, and those with CKD but controlled hypertension a 2 times higher risk for cardiovascular deaths from other causes.

Discussion: CKD does not appear to amplify the risk of stroke and coronary events associated with aTRH in this older population. The reasons for excess cardiovascular mortality from other causes associated with controlled hypertension require further study.

Kidney Int Rep (2017) **2,** 180–191; http://dx.doi.org/10.1016/j.ekir.2016.10.006
KEYWORDS: cardiovascular; chronic kidney disease; hypertension

Uncontrolled hypertension is common in patients with chronic kidney disease (CKD), including a substantial number who have treatment-resistant hypertension.[1–5] Apparent treatment-resistant hypertension (aTRH), defined as uncontrolled blood pressure (BP), that is, $\geq$140/90 mm Hg while treated with 3 different antihypertensive drug classes or using 4 or more drug classes, regardless of BP level, is observed in 20% to 40% of people with CKD and treated for hypertension.[5–9] Uncontrolled hypertension and aTRH have been associated with higher risks of all-cause mortality and major cardiovascular events in both the general population[10–12] and in CKD cohorts.[9,13,14] The optimal level of BP control, however, is still debated, particularly for the older population and for individuals with CKD. Target recommendations have recently risen from $<$130/80 mm 0/80 to $<$140/90 for CKD patients and up to $<$150/90 in the older population.[15,16]

A recent meta-analysis of randomized clinical trials showed clear effects of intensive treatment to lower BP on combined major cardiovascular events, but less consistent findings for all-cause mortality and heart failure.[17] The recent Systolic Blood Pressure Intervention Trial (SPRINT), however, reported a significant

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Received 22 August 2016; revised 15 October 2016; accepted 25 October 2016; published online 31 October 2016

25% risk reduction in major cardiovascular events and 27% reduction in all-cause mortality, with intensive versus standard BP control (systolic BP of <120 vs. <140 mm Hg) in adults with hypertension but without diabetes.[18] Notably, the beneficial role of such strict BP control was seen in middle-aged to elderly people, including those 75 years and older. Neither the meta-analysis nor SPRINT, however, demonstrated that intensive BP control significantly affects outcomes in patients with CKD, although there was a 27% risk reduction for mortality of borderline significance in SPRINT. These results are consistent with observational studies showing no advantage and even higher mortality risk associated with achieving BP control of <130/90 mm Hg in CKD patients,[19–21] particularly those on dialysis,[19,22,23] and in community-dwelling frail elderly people treated with multiple antihypertensive agents.[24] These observations may call into question the recommendation for strict BP control in elderly individuals with CKD. Nevertheless, insufficient data are available about whether CKD modifies the prognosis of uncontrolled and treatment-resistant hypertension in this population.

To test our hypothesis that CKD might modify the relation between hypertension control and outcomes in older populations, we studied the interaction between CKD and uncontrolled hypertension or aTRH in their relations to all-cause mortality and major cardiovascular events among hypertension-treated elderly participants in the population-based Three-City Study.

MATERIALS AND METHODS

Study Design and Participants

The Three-City Study is a population-based prospective cohort that included 9294 noninstitutionalized individuals aged 65 years or older who were randomly selected from electoral rolls of 3 French cities from March 1999 through March 2001: Bordeaux (2104), Dijon (4931), and Montpellier (2259). Details of the study protocol have been published elsewhere.[25] Both BP and kidney function were measured at baseline in 8689 participants, 4262 of whom were then being treated for arterial hypertension (Figure 1).

The institutional review committee of Kremlin-Bicêtre University Hospital approved the study protocol, and all participants provided written informed consent.

Assessment of Hypertension Control

Blood pressure was measured twice (5 minutes separated the 2 measurements), most often at the participant's home (61%), after at least 5 minutes at rest in a seated position by trained nurses using a validated digital electronic sphygmomanometer with an appropriately sized cuff on the right arm (OMRON M4; OMRON Corp., Kyoto, Japan).[26] The mean of these 2 BP measurements was used in the analyses.

Hypertension was defined as controlled if the mean systolic and diastolic BP were <140 mm Hg and <90 mm Hg, respectively, for participants taking 1 to 3 antihypertensive drug classes (cHT), and as uncontrolled, but nonresistant, if it was ≥140 mm Hg and/or ≥90 mm Hg with 2 drugs (ucHT); apparent treatment-resistant hypertension (aTRH) was defined as BP of ≥140 mm Hg and/or ≥90 mm Hg in participants receiving ≥3 antihypertensive drug classes or ≥ 4, regardless of BP level.[27,28] In sensitivity analyses, we defined aTRH including the use of diuretics as a criterion as follows: BP of ≥140/90 mm Hg in participants receiving ≥3 antihypertensive drug classes, 1 of them a diuretic, or ≥4, regardless of BP level; consequently, the definition for uncontrolled hypertension changed for BP of ≥140/90 mm Hg with 2 drugs or with 3 drugs excluding a diuretic, whereas that for controlled hypertension remained unchanged.[27]

Study Outcomes

We studied both all-cause and cardiovascular mortality, overall and by cause: stroke, coronary heart disease, other cardiovascular causes (including heart failure, strict sudden death, myocardiopathy, unlocalized aneurysm, and other cardiovascular deaths) as well as incident fatal and nonfatal stroke and coronary events. In addition, we investigated risk for recurrent strokes and coronary events among participants with a history of these diseases at baseline. All participants were actively followed up to assess 10-year mortality, and only 9 individuals were lost to follow-up. An adjudication committee analyzed and confirmed the causes of death based on all available clinical information collected from hospitalization reports and interviews with the participant's family physician or specialists, nursing home staff (for participants who entered in nursing home during follow-up), or proxy.[29] Detailed definitions of the study endpoints have been published elsewhere.[25] Two adjudication committees, one for coronary events and another for strokes, validated coding of myocardial infarction, sudden death, and stroke and classified each event according to the International Classification of Diseases—10th Edition (ICD-10).[25] Coronary events included definite hospitalized angina, definite myocardial infarction, definite cardiovascular death, coronary balloon dilatation, and coronary artery bypass. Stroke was considered when a new focal neurological deficit of sudden or rapid onset was diagnosed and attributable to a cerebrovascular

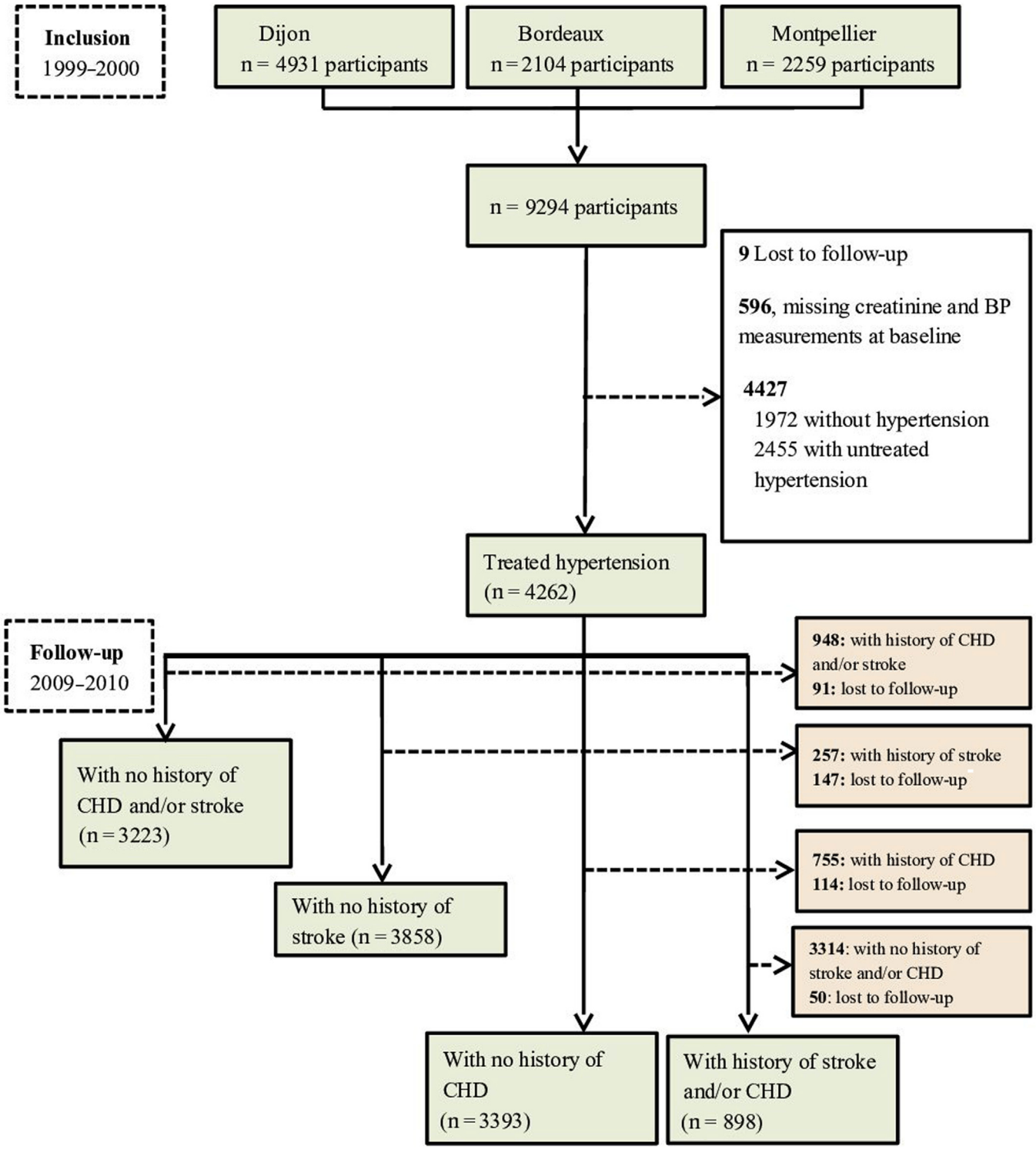

Figure 1. Flowchart of the study participants. BP, blood pressure; CHD, coronary heart disease.

event that persisted for more than 24 hours. If a participant had multiple cardiovascular events during follow-up, the date of the first event was used in the statistical analyses.[25]

Assessment of Chronic Kidney Disease

Serum creatinine was measured in a single laboratory with the Jaffé assay and further standardized to the isotope dilution mass spectrometry (IDMS) traceable enzymatic creatinine assay, as described elsewhere.[30] We calculated the estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) equation without correcting for race, which was unavailable.[30] CKD was defined as an eGFR of <60 ml/min per 1.73 m^2.[31]

Other Data Collection

Trained staff administered standardized questionnaires and performed clinical examinations at baseline. Sociodemographic data, smoking status, and history of cardiovascular diseases (CVD) (coronary heart disease, myocardial infarction, heart failure, stroke, peripheral artery disease, artery surgery, or angioplasty) were recorded. Body mass index (BMI) was calculated and categorized (<25, $25-30$, ≥ 30 kg/m^2). We used the World Health Organization's Anatomical Therapeutic chemical classification system to code drugs. All three centers collected blood at baseline. Hypercholesterolemia was defined as use of statins or fasting serum cholesterol of ≥ 6.2 mmol/l. Diabetes was defined as the current use of antidiabetic drugs and/or fasting serum glucose of ≥ 7.2 mmol/l, or nonfasting serum glucose of ≥ 11 mmol/l.

Statistical Analyses

We classified participants into 6 groups combining 2 categories of CKD status based on eGFR $<$ or 60 ml/min per 1.73 m^2 and the following 3 categories of hypertension control status: controlled hypertension, uncontrolled hypertension, and aTRH. Participants with controlled hypertension and no CKD formed the reference group for the other 5 groups.

We first compared participants' baseline characteristics among the 6 groups as defined above, with a nonparametric Wilcoxon test, analysis of variance, or a χ^2 test, as appropriate. Second, we estimated crude rates of all-cause and cardiovascular mortality, as well as of fatal or nonfatal stroke and coronary heart disease, and other cardiovascular deaths for each group (Figure 1). Follow-up of participants for all outcomes started from the date of interview with BP measurements, which took place between 1999 and 2001, and then participants were examined 5 times over a 10-year period. Participants who did not develop the events of interest at the time point in 2009 to 2010 were censored at this date. For all-cause mortality, participants lost to follow-up ($n = 9$) were censored at their last follow-up date. As we used a cause-specific Cox regression model, participants who did not develop the outcomes of interest (e.g., stroke or coronary heart disease, or cardiovascular death other than stroke and coronary heart disease) at the time point in 2009 to 2010 were also censored at this time for the study of these outcomes. Those who had no follow-up date for stroke or coronary heart disease were considered lost to follow-up for this event. The administrative censoring date was the date of first event or the date of last visit for that event, or 2009 to 2010 time point. We estimated the hazard ratios (HRs) and 95% confidence intervals (95% CIs) of mortality and cardiovascular outcomes associated with exposure (combined hypertension control status and CKD). In all models, we adjusted for established cardiovascular risk factors including sex, diabetes, body mass index, history of cardiovascular disease, smoking status, hypercholesterolemia, and education level. Third, we estimated incidence rates and adjusted HRs (95% CIs) for fatal or nonfatal stroke or coronary heart diseases associated with hypertension control status and CKD in 3223 participants without a history of either of these diseases at baseline (Figure 1). Similarly, we estimated crude incidence rates (using a person-years method) and adjusted HRs (95% CIs) for first occurrence of nonfatal or fatal stroke and coronary heart diseases separately in 3858 and 3393 participants without a previous stroke or coronary heart disease, respectively. Finally, we estimated incidence rates and adjusted HRs (95% CIs) for recurrent stroke or coronary heart disease, together and separately, in 898 participants with a history of either stroke or coronary heart disease (Figure 1). All HRs were adjusted for sex, diabetes, body mass index, smoking status, hypercholesterolemia, and education level.

In all Cox proportional hazards regression models, we used age at baseline as a time-scale to better control for the confounding effect of age on studied outcomes in this longitudinal study comprising elderly participants.[32,33] We formally tested the interaction between CKD and hypertension control status in their relations with all studied outcomes by using Cox models including hypertension control status and CKD separately, as well as an interaction term. Similarly, we also tested interactions between the variable of interest (combined CKD and hypertension control status) and diabetes, sex, history of CVD, and body mass index (BMI) in relation to the outcomes studied. The proportional hazards assumption was tested for all models using the Schoenfeld residuals method. All analyses were conducted with SAS software 9.4 (SAS Institute, Cary, NC); all probabilities were 2-tailed, and a P value of ≤ 0.05 was considered as statistically significant.

RESULTS

Participant Characteristics

At baseline, the mean age of the 4262 study participants treated for hypertension was 75.1 $\pm$ 5.6 years; 40% were men and 60% were women. Overall, 31.2% had controlled hypertension, 62.3% uncontrolled hypertension, and 6.5% aTRH; 19.1% had CKD. In those with CKD, 57.0% had uncontrolled hypertension and 11.8% aTRH, compared to 63.6% and 5.2%, respectively, of those without CKD. Participants with CKD or uncontrolled hypertension or aTRH were on average older, more often men, current or former smokers, or obese, and more often had diabetes,

hypercholesterolemia, and a history of CVD than their counterparts with controlled hypertension and no CKD (Table 1). The maximum follow-up was 10 years irrespective of the outcome of interest. Median systolic and diastolic BPs were of the same order of magnitude in participants with and without CKD for those with controlled or uncontrolled hypertension, but systolic BP was higher in participants with aTRH and CKD. The percentage of participants on more than 4 antihypertensive drug classes was twice as high in those with compared to those without CKD.

All-Cause and Cardiovascular Mortality According to CKD and Hypertension Control Status

Over a median (interquartile range) follow-up of 8.8 (7.6−9.4) years, 9 participants were lost to follow-up for mortality, and 1115 deaths were reported, 305 of them from cardiovascular causes: 38 from stroke, 79 from coronary heart disease, and 188 from other cardiovascular causes. Compared with the reference group with controlled hypertension and no CKD, participants with uncontrolled hypertension or aTRH and no CKD did not have a higher risk of all-cause or cardiovascular mortality after multivariable adjustment (Table 2). In participants with CKD, controlled hypertension was associated with a significantly higher risk of all-cause and cardiovascular mortality than in the reference group, mainly from causes other than stroke and coronary heart disease (73% from heart failure), whereas aTRH was associated with a significantly higher risk of mortality from coronary heart disease (Table 2). Uncontrolled hypertension in participants with CKD was not associated with higher mortality than in the reference group. Because of the small number of stroke deaths (7 among the 812 participants with CKD, and only 1 among the 96 with aTRH), we were unable to estimate HRs for this outcome. Interactions between CKD and hypertension control status in relation to all-cause or stroke and coronary heart disease mortality were not statistically significant, but the interaction with the relation to cardiovascular mortality from other causes did approach statistical significance (P for interaction = 0.07). No significant interaction was found with sex, BMI, diabetes, or history of CVD in the relations that we studied. The inclusion of diuretic use as a criterion in the definition of aTRH yielded similar results (Supplementary Table S1).

Incident Stroke and Coronary Events According to CKD and Hypertension Control Status

For combined nonfatal and fatal strokes or coronary heart disease, the median follow-up (interquartile

Table 1. Participant baseline characteristics according to CKD and hypertension control status

	Without CKD (n = 3450)			With CKD (n = 812)			
Baseline characteristic	cHT n = 1077	ucHT n = 2194	aTRH n = 179	cHT n = 253	ucHT n = 463	aTRH n = 96	*P* value[a]
Age, yr[c]	74.4 ± 5.3	74.6 ± 5.4	75.1 ± 5.6	76.9 ± 5.8	77.7 ± 5.8	77.9 ± 6.1	<0.001
Men	31.8	43.6	46.9	32.8	37.4	44.8	<0.001
Low education level	20.7	20.8	24.6	17.8	24.6	16.7	0.170
Current or former smoker	34.3	40.2	43.6	37.9	37.8	43.8	0.016
BMI ≥30 kg/m^2	17.2	17.5	29.1	17.4	17.1	27.1	<0.001
Hypercholesterolemia	57.4	57.2	56.4	67.6	58.3	62.5	0.047
Diabetes[b]	11.0	14.3	31.3	9.5	10.8	29.2	<0.001
History of CVD	13.2	10.5	24.6	18.2	12.1	32.3	<0.001
eGFR, ml/min/1.73m^2[c]	79.4 ± 13.2	79.0 ± 12.7	79.8 ± 14.6	50.3 ± 8.2	50.8 ± 7.9	48.1 ± 8.7	<0.001
Blood pressure, mm Hg							
SBP, median (IQR)	129 (121–135)	157 (148–170)	159 (149–175)	130 (122–135)	157 (148–172)	167 (151–179)	
DBP, median (IQR)	75 (69–80)	87 (80–94)	86 (80–93)	73 (67–80)	86 (79–93)	85 (79–91)	
No. of drugs, median (IQR)[d]	5 (4–7)	5 (3–7)	7 (6–9)	6 (4–8)	5 (4–7)	7 (6–9)	
Antihypertensive drugs							
1 class	66.5	68.5		50.2	57.0		
2 classes	28.1	31.5		37.9	42.9		
3 classes	5.4		89.9	11.8		79.2	
≥4 classes			9.1			20.8	

All values are percentages if not indicated otherwise.
aTRH, apparent treatment-resistant hypertension (defined as systolic and diastolic blood pressure ≥140/90 while taking ≥3 antihypertensive drugs or number of antihypertensive drugs ≥4); BMI, body mass index; CKD, chronic kidney disease (defined as estimated glomerular filtration rate <60 ml/min/1.73 m^2); cHT, controlled hypertension (defined as systolic and diastolic blood pressure <140/90 mm Hg while taking 1−3 antihypertensive drugs); CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate calculated with the Modification of Diet for Renal Diseases equation; IQR, interquartile range; SPB, systolic blood pressure; ucHT, uncontrolled hypertension (defined as systolic and diastolic blood pressure ≥140/90 while taking 1 or 2 antihypertensive drugs).
[a]*P* value for global comparison of baseline characteristics of participants according to hypertension control and CKD status.
[b]Diabetes defined as use of antidiabetic medication or fasting glycemia ≥7.2 mmol/l or nonfasting glycemia ≥11 mmol/l.
[c]Values are mean ± SD.
[d]No. of drugs refers to total number of drug classes.

Table 2. Crude mortality rates and adjusted hazard ratios for all-cause and cardiovascular deaths according to CKD and hypertension control status

Mortality	n	Person-years	Events	Crude IR [95% CI] per 1000 person-years	Adjusted HR [95% CI][a]	*P* for interaction[b]
All-cause						0.95
All participants	4262	33,904	1115	32.9 [31.0–34.9]		
Without CKD						
cHT (Ref)	1077	8778	260	29.6 [26.2–33.4]	1	
ucHT	2194	17,758	480	27.0 [24.7–29.5]	0.86 [0.74–1.01]	
aTRH	179	1368	59	43.1 [33.1–55.2]	1.09 [0.82–1.46]	
With CKD						
cHT	253	1867	100	53.5 [43.8–64.8]	1.33 [1.06–1.68]	
ucHT	463	3476	170	48.9 [42.0–56.7]	1.14 [0.93–1.39]	
aTRH	96	656	46	70.1 [51.9–92.6]	1.34 [0.98–1.85]	
All cardiovascular[c]						0.68
All participants	4262	33,904	305	9.0 [8.0–10.0]		
Without CKD						
cHT (Ref)	1077	8778	68	7.7 [6.1–9.8]	1	
ucHT	2194	17,758	119	6.7 [5.6–8.0]	0.82 [0.60–1.11]	
aTRH	179	1368	21	15.4 [9.8–23]	1.34 [0.81–2.23]	
With CKD						
cHT	253	1867	33	17.7 [12.4–24.5]	1.63 [1.07–2.48]	
ucHT	463	3476	49	14.1 [10.6–18.5]	1.28 [0.87–1.87]	
aTRH	96	656	15	22.8 [13.3–36.7]	1.56 [0.88–2.77]	
Coronary heart disease						0.21
All participants	4262	33,904	79	2.3 [1.9–2.9]		
Without CKD						
cHT (Ref)	1077	8778	15	1.7 [1.0–2.7]	1	
ucHT	2194	17,758	36	2.0 [1.4–2.8]	1.01 [0.54–1.88]	
aTRH	179	1368	3	2.2 [0.6–5.9]	0.71 [0.2–2.53]	
With CKD						
cHT	253	1867	5	2.7 [1.0–5.9]	1.10 [0.40–3.07]	
ucHT	463	3476	12	3.5 [1.9–5.8]	1.36 [0.62–2.99]	
aTRH	96	656	8	12.2 [5.7–23.0]	3.27 [1.34–7.99]	
Cardiovascular death other than stroke or coronary heart disease[d]						0.07
All participants	4262	33,904	188	5.5 [4.8–6.4]		
Without CKD						
cHT (Ref)	1077	8778	44	5.0 [3.7–6.7]	1	
ucHT	2194	17,758	63	3.5 [2.8–4.5]	0.70 [0.47–1.04]	
aTRH	179	1368	16	11.7 [7.0–18.5]	1.69 [0.93–3.08]	
With CKD						
cHT	253	1867	26	13.9 [9.3–20.1]	1.94 [1.18–3.18]	
ucHT	463	3476	33	9.5 [6.7–13.2]	1.37 [0.86–2.19]	
aTRH	96	656	6	9.1 [3.8–18.8]	1.02 [0.43–2.42]	

aTRH, apparent treatment-resistant hypertension (systolic and/or diastolic blood pressure ≥140 and/or ≥90 while taking ≥3 antihypertensive drugs or number of antihypertensive drugs ≥4); CHD, coronary heart diseases; cHT, controlled hypertension; CKD, chronic kidney disease (defined as estimated glomerular filtration rate <60 ml/min/1.73m^2; cHT: systolic and diastolic blood pressure <140/90 mm Hg while taking 1–3 antihypertensive drugs); HR, hazard ratio; IR, incidence rate; ucHT, uncontrolled hypertension (defined as systolic and/or diastolic blood pressure ≥140 and/or ≥90 while taking 1 or 2 antihypertensive drugs).

[a]All models were adjusted for center, sex, diabetes (defined as use of antidiabetic medication or fasting glycemia ≥7.2 mmol/L or nonfasting glycemia ≥11 mmol/l), history of cardiovascular events, body mass index, hypercholesterolemia, smoking status, and education level.

[b]All interaction between hypertension control status and chronic kidney disease.

[c]All cardiovascular mortality included deaths from stroke, coronary heart disease, strict sudden death, heart failure, and other cardiovascular deaths.

[d]Cardiovascular deaths other than stroke or coronary heart disease included heart failure, strict sudden death, myocardiopathy, unlocalized aneurysm, and other cardiovascular deaths.

range) was 8.4 (5.4—9.2) years, 8.5 (5.6–9.2) for nonfatal and fatal strokes, and 8.4 (5.5–9.2) for nonfatal and fatal coronary heart diseases. A total of 169 participants had no follow-up date for nonfatal and fatal stroke, 155 for nonfatal and fatal coronary heart disease, and 141 for both. Because of the exclusion of prevalent cases at baseline, the number of participants lost to follow-up for these events varies. During follow-up, 178 incident fatal or nonfatal strokes and 225 coronary events were reported; 349 participants had 1 or both events. Cause-specific Cox regression models showed that, compared with the reference group, participants with uncontrolled hypertension and no CKD had a 50% higher risk of stroke, and those with aTRH had a risk more than 2 times higher, whether or not they had CKD (Table 3). There was no significant interaction with

Table 3. Crude incidence rates and adjusted hazard ratios for first fatal and nonfatal stroke or coronary heart disease according to CKD and hypertension control status

Baseline characteristic	n	Person-years	Events	Crude IR [95% CI] per 1000 person-years	Adjusted HR [95% CI][a]	*P* for interaction[b]
Stroke or coronary heart disease[c]						0.74
All participants	3223	23,245	349	15 [13.5–16.7]		
Without CKD						
cHT	786	5872	75	12.8 [10.1–15.9]	1	
ucHT	1745	12,650	194	15.3 [13.3–17.6]	1.01 [0.77–1.32]	
aTRH	113	762	20	26.2 [16.5–39.7]	1.50 [0.90–2.47]	
With CKD						
cHT	168	1184	15	12.7 [7.4–20.4]	0.91 [0.52–1.59]	
ucHT	356	2405	38	15.8 [11.4–21.4]	0.95 [0.64–1.42]	
aTRH	55	370	7	18.9 [8.4–37.1]	0.98 [0.45–2.15]	
Stroke						0.87
All participants	3858	28,284	178	6.3 [5.4–7.3]		
Without CKD						
cHT	970	7354	31	4.2 [2.9–5.9]	1	
ucHT	2034	15,071	103	6.8 [5.6–8.3]	1.51 [1.00–2.28]	
aTRH	157	1088	12	11.0 [6–18.7]	2.33 [1.18–4.61]	
With CKD						
cHT	219	1535	8	5.2 [2.5–9.8]	1.08 [0.49–2.35]	
ucHT	404	2750	18	6.5 [4.0–10.1]	1.27 [0.70–2.29]	
aTRH	74	485	6	12.4 [5.1–25.5]	2.12 [0.87–5.17]	
Coronary heart disease						0.68
All participants	3393	24,588	225	9.2 [8.0–10.4]		
Without CKD						
cHT	829	6305	50	8.1 [6.0–10.5]	1	
ucHT	1821	13,449	121	9.1 [7.6–10.8]	0.92 [0.65–1.28]	
aTRH	124	861	12	14.0 [7.7–23.8]	1.14 [0.59–2.17]	
With CKD						
cHT	175	1263	10	8.0 [4.1–14.2]	0.94 [0.47–1.86]	
ucHT	380	2625	24	9.3 [6.1–13.6]	0.89 [0.54–1.47]	
aTRH	64	403	8	19.9 [9.4–37.5]	1.69 [0.79–3.62]	

aTRH, apparent treatment-resistant hypertension (defined as systolic and/or diastolic blood pressure ≥140 and/or ≥90 while taking ≥3 antihypertensive drugs or number of antihypertensive drugs ≥4); cHT, controlled hypertension (defined as systolic and diastolic blood pressure <140/90 mm Hg while taking 1–3 antihypertensive drugs); CKD, chronic kidney disease (defined as estimated glomerular filtration rate < 60 mL/min/1.73m^2); HR, hazard ratio; IR, incidence rate; ucHT, uncontrolled hypertension (defined as systolic and/or diastolic blood pressure ≥140 and/or ≥90 while taking 1 or 2 antihypertensive drugs).

[a]All models were adjusted for center, sex, diabetes, history of cardiovascular events, body mass index, hypercholesterolemia, smoking status and education level.

[b]All interaction between hypertension control status and chronic kidney disease.

[c]Combined incident fatal and nonfatal stroke or coronary heart disease: defined as the first occurrence of stroke or coronary heart disease, whichever occurred first. (Participants with history of stroke and/or coronary heart disease, stroke, or coronary heart disease were excluded when estimating the risk for combined fatal and nonfatal incident stroke or coronary heart disease, incident stroke, and incident coronary heart disease respectively).

CKD in the association between hypertension control status and risk of stroke. Neither aTRH nor uncontrolled hypertension was significantly associated with a higher risk of coronary events, with or without CKD. In the sensitivity analysis, the use of the diuretic drug criterion in the definition of aTRH tended to weaken the HR estimates for stroke (Supplementary Table S2).

Recurrent Stroke and Coronary Events According to CKD and Hypertension Control Status

For combined recurrent strokes or coronary heart diseases, the median follow-up (interquartile range) was 6.4 (3.5–8.8) years, 6.1 (3.5–8.6) for recurrent strokes, and 6.8 (3.6–8.9) for recurrent coronary heart diseases. Participants with CKD and uncontrolled hypertension or aTRH had a risk of combined recurrent stroke or coronary event (i.e., any second stroke or coronary event) that was approximately twice as high as that in the reference group, mostly due to coronary heart disease, whereas their counterparts without CKD had no such excess risk (Table 4). The interaction between CKD and hypertension control status, however, was not statistically significant. As above, the sensitivity analysis tended to weaken the HR estimates (Supplementary Table S3).

DISCUSSION

In this community-dwelling elderly population, participants with CKD had an overall higher risk of all-cause and cardiovascular mortality, regardless of their hypertension control status. As expected, both aTRH and uncontrolled hypertension were associated with higher risks of incident stroke, apparently unmodified by CKD; participants with both CKD and aTRH also had significantly higher risks of coronary death and of combined recurrent stroke or coronary events. The

Table 4. Crude incidence rates and adjusted hazard ratios for recurrent fatal or nonfatal stroke or coronary heart disease according to CKD and hypertension control status

Baseline characteristics	Number	Person-years	Events	Crude IR [95% CI] (per 1000 person-years)	Adjusted HR [95% CI][a]	*P* for interaction[b]
Stroke or coronary heart disease[c]						0.10
All participants	898	5373	204	38.0 [33.0–43.5]		
Without CKD						
cHT	245	1554	50	32.2 [24.2–42.1]	1	
ucHT	404	2492	94	37.7 [30.7–45.9]	1.08 [0.76–1.53]	
aTRH	59	381	8	21.0 [9.9–39.6]	0.60 [0.28–1.29]	
With CKD						
cHT	66	352	13	36.9 [20.7–61.3]	1.10 [0.59–2.06]	
ucHT	89	434	25	57.6 [38.2–83.6]	1.70 [1.04–2.80]	
aTRH	35	159	14	87.8 [50.3–143.3]	2.15 [1.16–3.98]	
Stroke						
All participants	235	1381	32	23.2 [16.1–32.3]		
Without CKD						
cHT	59	377	6	15.9 [6.6–32.8]	1	
ucHT	106	636	16	25.2 [15.0–39.9]	Not estimated	
aTRH	14	90	1	11.1 [1.0–51.8]	Not estimated	
With CKD						
cHT	10	49	0	Not estimated	Not estimated	
ucHT	34	165	7	42.3 [18.9–83.1]	Not estimated	
aTRH	12	64	2	31.0 [6.2–99.4]	Not estimated	
Coronary heart disease						0.13
All participants	714	4379	143	32.7 [27.6–38.3]		
Without CKD						
cHT	198	1270	38	29.9 [21.5–40.6]	1	
ucHT	322	2063	64	31 [24.1–39.3]	1.00 [0.66–1.52]	
aTRH	48	310	4	12.9 [4.3–30.7]	0.40 [0.14–1.15]	
With CKD						
cHT	59	322	12	37.3 [20.4–63.1]	1.25 [0.64–2.43]	
ucHT	61	299	16	53.4 [31.8–84.7]	1.98 [1.08–3.64]	
aTRH	26	114	9	78.5 [38.8–143.2]	2.04 [0.95–4.37]	

aTRH, apparent treatment-resistant hypertension (defined as systolic and/or diastolic blood pressure ≥140 and/or ≥90 while taking ≥3 antihypertensive drugs or number of antihypertensive drugs ≥4); cHT, controlled hypertension (defined as systolic and diastolic blood pressure <140/90 mm Hg while taking 1–3 antihypertensive drugs); CKD, chronic kidney disease (defined as estimated glomerular filtration rate <60 mL/min/1.73m^2); HR, hazard ratio; IR, incidence rate; ucHT, uncontrolled hypertension (systolic and/or diastolic blood pressure ≥140 and /or ≥90 while taking 1 or 2 antihypertensive drugs).
[a]All models were adjusted for center, sex, diabetes, body mass index, hypercholesterolemia, smoking status, and education level.
[b]All interactions between hypertension control status and chronic kidney disease.
[c]Combined fatal and nonfatal stroke and CHD: defined as the recurrence of either a stroke or CHD.

most intriguing finding was the excess cardiovascular mortality risk from other causes, mainly heart failure, observed in participants with CKD and well-controlled hypertension.

The findings of our study are difficult to compare with those of others, which have usually included younger participants, have not systematically assessed CKD as a potential effect modifier in the relation of aTRH with outcomes, and have sometimes used BP values of ≥130/80 mm Hg rather than ≥140/90 to define poor BP control in individuals with CKD. It was nevertheless somewhat surprising to find that aTRH in these elderly participants was not significantly associated with a higher risk of all-cause mortality. This finding differs from some,[10,11,34] although not all,[12,35] non-CKD cohort studies that have compared all-cause mortality between individuals with and without aTRH after adjusting for CKD. In the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT), aTRH did not significantly increase all-cause mortality in participants older than 65 years.[34] The somewhat higher HR for all-cause mortality associated with aTRH in our study in participants with CKD compared with the reference group (with controlled hypertension and no CKD) is probably due to the well-established higher risk conferred by CKD,[36] which we have previously reported for this population,[30] rather than to aTRH. Among participants with CKD, those with aTRH were not at higher risk than those with controlled hypertension, in contrast to findings from 2 other CKD cohorts.[9,13]

Our findings regarding cardiovascular risk are consistent with previous studies for several points but differ for others. First, we observed a risk of mortality from coronary heart disease associated with aTRH in participants with CKD, but not in those without CKD, and no significantly higher rate of coronary heart disease events. Several studies have shown higher rates of coronary heart disease events associated with

aTRH, both before and after adjustment for CKD.[11,12,37] Discrepancies in findings about coronary heart disease events between these studies and ours may be due to a lack of power in our study. It may also result, however, from the impact of CKD *per se* on mortality rather than on the incidence of coronary heart disease in relation to aTRH. Support for this hypothesis comes from repeated findings that the concomitant presence of CKD increases mortality risk in a variety of chronic diseases.[38,39]

Second, participants with aTRH had a risk of incident stroke that was more than twice as high as that in the reference group, with HRs of similar magnitude with or without CKD. This was true for either aTRH definition that we used, although study power was stronger without diuretic use as a criterion. Participants with uncontrolled hypertension were also at higher risk for stroke, although the association was statistically significant only in those without CKD. These findings confirm the well-established role of hypertension in the occurrence of stroke.[12,34,35] In addition, we showed that CKD appears to influence the recurrence of stroke and coronary heart disease.

One of the most striking observations of our study is that participants with CKD and controlled hypertension were at significantly higher risk for cardiovascular mortality from other causes than those with controlled hypertension without CKD. In ALLHAT, patients with aTRH were at higher risk for fatal, hospitalized, or treated nonhospitalized heart failure.[34] Although unexpected, this finding is in line with some studies showing an adverse effect of excessive BP reduction,[24] demonstrated by the J-shaped association between BP and mortality risk in patients with CKD, whether or not they were on dialysis.[20,40,41] In apparent contrast, SPRINT, which compared the effect of tight systolic BP control to a level of <120 mm Hg versus standard BP control (<140 mm Hg) in hypertensive patients over a median follow-up of 3.3-years, showed significant risk reductions for cardiovascular outcomes and all-cause mortality, even in the subgroup of patients older than 75 years.[18] It also showed a significant reduction in the risk of heart failure. Nonetheless, this trial did not include patients with difficult-to-control hypertension, and there were important adverse events in the intervention arm, especially severe hypotension, syncope, and acute kidney injury, which do not preclude a worse long-term prognosis for these patients.[42] Moreover, SPRINT failed to demonstrate that intensive treatment that lowered BP to its target ranges had any effect on outcomes in patients with CKD. In our study, heart failure was classified as the primary cause of death for three-fourths of the participants who died of other cardiovascular diseases. It is possible that a lower BP level at baseline reflects the heart's compromised capacity to maintain an adequate ejection fraction and thus makes it easier to achieve BP control. The frequency of heart failure due to nonischemic heart disease increases as CKD progresses. Coronary atherosclerosis is the most common cause of death in the general population, but not among patients with CKD. In this population, decreased cardiac perfusion of various causes and diffuse interstitial myocardial fibrosis with increased oxygen diffusion distance are the major causes of congestive heart failure, arrhythmia, and sudden cardiac death.[43,44] Moreover, other factors such as concomitant diabetes, electrolyte shifts, divalent ion abnormalities, sympathetic overactivity, impaired baroreflex effectiveness, inflammation, infection, and inappropriate drug use also contribute to the higher risk of mortality in patients with CKD.[43–46] Thus, we cannot exclude the possibility that participants with CKD and controlled hypertension at baseline had low BP due to incipient heart failure.

Major strengths of this study include its large sample size and the low number of participants lost to follow-up for mortality. In addition, standardized BP was measured by trained nurses during in-home examination in the majority of participants, which lessens the risk of white-coat hypertension. Home BP monitoring has been shown to be superior to office BP in predicting target organ damage and all-cause mortality[47] and functional decline in elderly individuals.[48] Moreover, creatinine measurements were taken in a single laboratory with further calibration to the IDMS reference method, and long-term follow-up and adjudication of cardiovascular events. Of note, we used the MDRD equation with which eGFR was normally distributed, in contrast to the CKD-EPI equation in this elderly population. Previous analyses showed that both equations provided similar prevalence estimates of CKD[8] and similar hazard ratios of all-cause and cardiovascular mortality associated with CKD.[30]

Our study also has limitations. First, we included only elderly participants, precluding extrapolation to other age groups. Second, as treatment adherence and ambulatory BP data were not available, true treatment-resistant hypertension may have been misclassified with pseudo-resistance in a number of cases. Third, albuminuria was not available at baseline and therefore could not be adjusted for in the multivariable analyses or used in the definition of CKD. Fourth, we may have lacked statistical power in some of the associations studied, particularly for stroke events. There was also a significant loss to follow-up for stroke and coronary events, with the ensuing potential selection bias. Finally, the observational design of the study makes causal interpretation impossible.

In conclusion, we found that community-dwelling elderly individuals with both CKD and aTRH were at higher risk for coronary heart disease mortality and incident stroke. In this study, the presence of CKD did not appear to amplify the risks for the occurrence of these 2 disease entities associated with aTRH (P value for interaction not statistically significant), but we cannot rule out that it may enhance the lethality of coronary heart disease (P for interaction = 0.07). Using either definition of aTRH, with or without the diuretic use criteria, did not alter the main conclusion of this study. Adequate monitoring of kidney function and appropriate titration of antihypertensive medication with decreasing GFR may help to decrease aTRH and thereby impede its harmful prognosis. The reasons that older people with CKD and controlled hypertension might be at higher risk for CV mortality from heart failure require further study. Randomized controlled studies are needed to assess whether or not strict BP control, compared to less strict control, is beneficial in elderly people, and whether or not mild-to-moderate CKD is an additional aggravating condition.

DISCLOSURE

CH received lecture fees from a commercial sponsor in November 2014. TBD received consulting and lectures fees during 2014-2015 from Amgen, FMC, and Kirin. BS received consulting fees from MSD and grants from Amgen, Baxter, FMC, Lilly, MSD, and Otsuka for a research project. All the other authors declared no competing interests.

ACKNOWLEDGMENTS

The Three-City Study is conducted under a partnership agreement between the Institut National de la Santé and la Recherche Médicale (INSERM), the Victor Segalen Bordeaux II University, and Sanofi-Aventis. The Fondation pour la Recherche Médicale funded the preparation and initiation of the study. The Fondation Plan Alzheimer partly funded the follow-up of the study. The 3C Study is also supported by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, MGEN, Institut de la Longévité, Conseils Régionaux of Aquitaine and Bourgogne, Fondation de France, and Ministry of Research–INSERM Programme "Cohortes et collections de données biologiques". The study also received a grant from the Agence Nationale de la Recherche (ANR). The CKD ancillary study at the 4-year follow-up was funded by the French-speaking Society of Nephrology. No donors played a role in the design and the conduct of the study.

Jean Kaboré is supported by a research grant from the French Ministry of Research.

We thank Jo-Ann Cahn for editing the English version.

SUPPLEMENTARY MATERIAL

Table S1. Crude mortality rates and adjusted hazard ratios for all-cause and cardiovascular deaths according to chronic kidney disease and hypertension control status

Table S2. Crude incidence rates and adjusted hazard ratios for stroke and coronary heart disease according to chronic kidney disease and hypertension control status

Table S3. Crude incidence rates and adjusted hazard ratios for recurrent stroke and coronary heart disease according to chronic kidney disease and hypertension control status

Supplementary material is linked to the online version of the paper at http://www.kireports.org.

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