

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/1.73m²) 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 ≤3 antihypertensive drugs, 62.3% uncontrolled hypertension ≥140/90 mm Hg on ≤2 drugs, and 6.5% apparent treatment-resistant hypertension (aTRH) ≥140/90 mm Hg with ≥3 drugs or use of ≥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 aTRH, 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.

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KEYWORDS: cardiovascular; chronic kidney disease; hypertension

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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, ≥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 Hg 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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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 $\geq 140/90$ 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 $\geq 140/90$ 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, myocardial infarction, 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

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