Comparative risk of renal, cardiovascular, and mortality outcomes in controlled, uncontrolled resistant, and nonresistant hypertension

John J. Sim[1], Simran K. Bhandari[1], Jiaxiao Shi[2], Kristi Reynolds[2], David A. Calhoun[3], Kamyar Kalantar-Zadeh[4] and Steven J. Jacobsen[2]

[1]Division of Nephrology and Hypertension, Kaiser Permanente Los Angeles Medical Center, Los Angeles, California, USA; [2]Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, California, USA; [3]Department of Cardiovascular Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA and [4]Division of Nephrology and Hypertension, University of California Irvine School of Medicine, University of California Irvine Medical Center, Irvine, California, USA

We sought to compare the risk of end-stage renal disease (ESRD), ischemic heart event (IHE), congestive heart failure (CHF), cerebrovascular accident (CVA), and all-cause mortality among 470,386 individuals with resistant and nonresistant hypertension (non-RH). Resistant hypertension (60,327 individuals) was subcategorized into two groups: 23,104 patients with cRH (controlled on four or more medicines) and 37,223 patients with uRH (uncontrolled on three or more medicines) in a 5-year retrospective cohort study. Cox proportional hazard modeling was used to estimate hazard ratios adjusting for age, gender, race, body mass index, chronic kidney disease (CKD), and comorbidities. Resistant hypertension (cRH and uRH), compared with non-RH, had multivariable adjusted hazard ratios (95% confidence intervals) of 1.32 (1.27–1.37), 1.24 (1.20–1.28), 1.46 (1.40–1.52), 1.14 (1.10–1.19), and 1.06 (1.03–1.08) for ESRD, IHE, CHF, CVA, and mortality, respectively. Comparison of uRH with cRH had hazard ratios of 1.25 (1.18–1.33), 1.04 (0.99–1.10), 0.94 (0.89–1.01), 1.23 (1.14–1.31), and 1.01 (0.97–1.05) for ESRD, IHE, CHF, CVA, and mortality, respectively. Men and Hispanics had a greater risk for ESRD within all three cohorts. Individuals with resistant hypertension had a greater risk for ESRD, IHE, CHF, CVA, and mortality. The risk of ESRD and CVA were 25% and 23% greater, respectively, in uRH compared with cRH, supporting the linkage between blood pressure and both outcomes.

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Correspondence: *John J. Sim, Division of Nephrology and Hypertension, Kaiser Permanente Los Angeles Medical Center, 4700 Sunset Blvd, Los Angeles, California 90027, USA. E-mail: John.j.sim@kp.org*

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Patients with difficult-to-control or resistant hypertension are encountered by many clinicians, and yet there remain many unknown aspects about this population. The prognosis and comparative outcomes in resistant hypertension deserve better understanding, as it would provide valuable insights into the management of this population. Less is known about individuals with refractory hypertension who never achieve blood pressure control despite multiple antihypertensive medicines. These knowledge gaps may be partly owing to the fact that resistant hypertension itself is difficult to identify owing to patient, physician, and confounders inherent to the healthcare environment such as heterogeneity of care.[1–3] In addition, those with resistant hypertension represent a relatively small subpopulation accounting for 10–15% of those with hypertension.[4–9] Longitudinal observations in resistant hypertension are relatively few, and the comparisons of outcomes with nonresistant hypertension have been limited in various ways.[10–14]

The descriptive studies on resistant hypertension have reported high rates of vascular disease and end-organ damage.[9,15,16] Other studies have shown high rates of cardiovascular morbidity and mortality[10,12,14] particularly among persons with pre-existing ischemic heart disease and chronic kidney disease (CKD).[17–19] Past studies have compared the resistant hypertension population among specialized populations such as those with pre-existing ischemic heart disease, incident resistant hypertension, or small cohorts. Overall, these studies have shown a greater risk for cardiovascular and mortality outcomes in persons with resistant hypertension compared with those with nonresistant hypertension.[10,11,17,18,20] The assumption is that the resistant hypertension population has an adverse physiology and is therefore at greater risk for morbidity and mortality. These risks may be in addition to those conferred by higher blood pressures or their associated adverse effects.

We previously described a resistant hypertension cohort within a large ethnically diverse hypertension population using an electronic health record–based approach.[9] This was

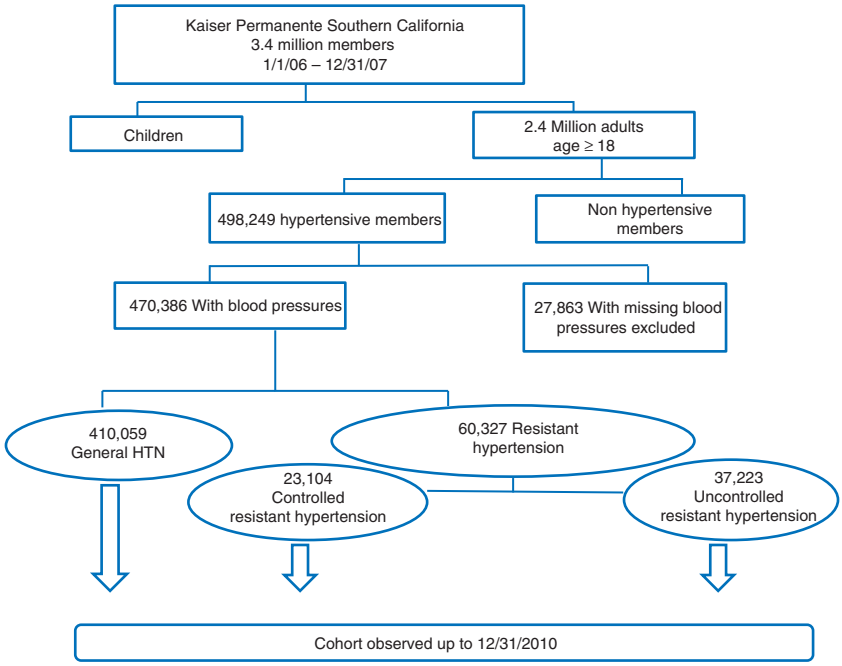

Figure 1 | Study population. Among ~2.4 million adult Kaiser Permanente Southern California (KPSC) members, 470,386 individuals were identified with hypertension (HTN). Resistant hypertension was identified in 60,327 (12.8%) individuals, with 4.9% having controlled resistant hypertension (cRH) and 7.9% having uncontrolled resistant hypertension (uRH).

one of the largest and most diverse populations with resistant hypertension assembled to date, and it used a single healthcare system with reliable clinical encounter information and medication use. With this cohort and passive follow-up through a comprehensive electronic health record, we sought to evaluate and compare the risk of renal, cardiovascular, and mortality outcomes among individuals identified with controlled resistant hypertension (cRH), uncontrolled resistant hypertension (uRH), and nonresistant hypertension (non-RH).

RESULTS

Cohort characteristics

A total of 470,386 individuals were identified for the study cohort (Figure 1), as previously described.[9] The mean age (s.d.) was 65 years,[11] with 45% men (Table 1). The race/ethnic composition was 43% white, 21% Hispanic, 13% black, and 8% Asian. The mean blood pressure of the entire study cohort was 133/75 mm Hg. Resistant hypertension was identified in 60,327 (12.8%) individuals, of whom 23,104 met our criteria for cRH and 37,223 met our criteria for uRH. Thus, uRH accounted for 61.7% of the resistant hypertension population and 7.9% of all hypertensive individuals.

Compared with the non-RH population, the RH population had a greater prevalence of comorbid conditions including diabetes mellitus (DM; 48% vs. 30%), CKD (45% vs. 24%), ischemic heart disease (41% vs. 22%), and cerebrovascular disease (16% vs. 9%; $P<0.001$ for all). cRH and uRH were similar in age, body mass index (BMI), race/ethnicity composition, and comorbidities. Blood pressures were highest in uRH (154/79 mm Hg) compared with both cRH (123/67 mm Hg) and non-RH (132/75 mm Hg).

Antihypertensive drug usage

Diuretics were the most frequently prescribed class of medications in all three groups (Figure 2). Individuals with cRH were more likely to be prescribed an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (93%) compared with the non-RH (47%) and uRH populations (88%).

Outcomes

Overall, 114,364 events occurred among the cohort, and 18.5% experienced at least one event (Table 2). Mortality occurred in 43,580 (9.3%) individuals. In addition, there were 26,894 IHE, 12,306 CHF, 16,799 CVA, and 14,785 incident ESRD events (Table 2). The resistant hypertension population had greater proportions of those who reached any of the outcomes (31.0% vs. 16.7%) compared with the non-RH population ($P<0.001$). The total number of all outcomes combined for each group was 87,217 in non-RH, 12,039 in cRH, and 15,218 in uRH. The rate of any outcome was highest in cRH (34.8%), followed by uRH (28.7%) and non-RH (16.7%).

After adjustment for age, gender, race, BMI, CKD, Charlson comorbidity index, and the comorbidities of DM, ischemic heart disease, CHF, CKD, and cerebrovascular disease, the resistant hypertension (cRH and uRH) population, compared