Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 61, No. 24, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.12.061

Prevalence and Prognostic Role of Resistant Hypertension in Chronic Kidney Disease Patients

Luca De Nicola, MD, PhD,* Francis B. Gabbai, MD,† Rajiv Agarwal, MD,‡ Paolo Chiodini, MSc,§ Silvio Borrelli, MD,* Vincenzo Bellizzi, MD, PhD,‖ Felice Nappi, MD,¶ Giuseppe Conte, MD,* Roberto Minutolo, MD, PhD*

Naples, Salerno, and Nola, Italy; San Diego, California; and Indianapolis, Indiana

Objectives This study sought to evaluate in chronic kidney disease (CKD) prevalence and prognosis of true resistant hypertension (RH) (i.e., confirmed by ambulatory blood pressure [ABP] monitoring).

Background In CKD, uncontrolled hypertension is a major risk factor, but no study has properly investigated the role of RH.

Methods We prospectively studied 436 hypertensive CKD patients under nephrology care. Four groups were constituted by combining 24-h ABP with diagnosis of RH (office blood pressure ≥130/80 mm Hg, despite adherence to ≥3 full-dose antihypertensive drugs including a diuretic agent or ≥4 drugs): control (ABP <125/75 mm Hg without RH); pseudoresistance (ABP <125/75 mm Hg with RH); sustained hypertension (ABP ≥125/75 mm Hg without RH); and true resistance (ABP ≥125/75 mm Hg with RH). Endpoints of survival analysis were renal (end-stage renal disease or death) and cardiovascular events (fatal and nonfatal cardiovascular event).

Results Age was 65 ± 14 years, men 58%, diabetes 36%, cardiovascular disease 30%, median proteinuria 0.24 (interquartile range 0.09 to 0.83) g/day, estimated glomerular filtration rate 43 ± 20 ml/min/1.73 m^2, office blood pressure 146 ± 19/82 ± 12 mm Hg, and 24-h ABP 129 ± 17/72 ± 10 mm Hg. True resistant patients were 22.9%, and pseudoresistant patients were 7.1%, whereas patients with sustained hypertension were 42.9%, and control subjects were 27.1%. Over 57 months of follow-up, 109 cardiovascular events and 165 renal events occurred. Cardiovascular risk (hazard ratio [95% confidence interval]) was 1.24 (0.55 to 2.78) in pseudoresistance, 1.11 (0.67 to 1.84) in sustained hypertension, and 1.98 (1.14 to 3.43) in true resistance, compared with control subjects. Corresponding hazards for renal events were 1.18 (0.45 to 3.13), 2.14 (1.35 to 3.40), and 2.66 (1.62 to 4.37).

Conclusions In CKD, pseudoresistance is not associated with an increased cardio-renal risk, and sustained hypertension predicts only renal outcome. True resistance is prevalent and identifies patients carrying the highest cardiovascular risk. (J Am Coll Cardiol 2013;61:2461–7) © 2013 by the American College of Cardiology Foundation

Poorly controlled hypertension is a major risk factor in non-dialysis chronic kidney disease (CKD). Current guidelines for CKD patients recommend an office blood pressure (BP) target <130/80 mm Hg (1–3). These recommendations, largely extrapolated from post hoc analysis of renal trials, are being debated (4–6). Recent trials and cohort studies have in fact disclosed a lack of association between more aggressive treatment or achieved BP and prognosis (7–10). The absence of a predictive role of office BP in treated CKD might relate, at least in part, to the high prevalence of white coat hypertension (i.e., high office BP and normal ambulatory blood pressure [ABP]) (3,11,12), which might also explain why ABP better predicts mortality and end-stage renal disease (ESRD) than office BP (13,14).

See page 2468

More importantly, the common observation that many patients with essential hypertension remain hypertensive despite polytherapy has led to an increased interest in the independent role of resistant hypertension (RH). Resistant hypertension is estimated to affect 15% to 30% of patients

From the *Department of Nephrology, Second University of Naples, Naples, Italy; †Department of Medicine, Veterans Administration San Diego Healthcare System and University of California at San Diego Medical School, San Diego, California; ‡Division of Nephrology, Department of Medicine, Indiana University School of Medicine and Richard L. Roudebush Veterans Administration Medical Center, Indianapolis, Indiana; §Medicine and Public Health, Second University of Naples, Naples, Italy; ‖Department of Nephrology, Salerno Hospital, Salerno, Italy; and the ¶Department of Nephrology, Nola Hospital, Nola, Italy. Dr. Agarwal has served as consultant to Roche, Merck, Takeda, Daiichi Sankyo, Sigma Tau; serves on the Speakers' bureau of Merck and Abbott and steering committees of Abbott and Reata; and has received research support from the National Institutes of Health, Veterans Administration, and Daiichi Sankyo. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received October 11, 2012; revised manuscript received November 26, 2012, accepted December 12, 2012.

Abbreviations and Acronyms

ABP = ambulatory blood pressure
BMI = body mass index
BP = blood pressure
CI = confidence interval
CKD = chronic kidney disease
ESRD = end-stage renal disease
GFR = glomerular filtration rate
HR = hazard ratio
IQR = interquartile range
LVH = left ventricular hypertrophy
OR = odds ratio
RH = resistant hypertension

with essential hypertension and be associated with higher cardiovascular morbidity and mortality (15–17); therefore, it has been defined as a priority area of research by the American Heart Association (15). Resistant hypertension is diagnosed when office BP is not at goal in patients who are adhering to full doses of at least 3 different antihypertensive drugs—including a diuretic agent—or normal or elevated BP in the setting of 4 or more antihypertensive agents (15). Diagnosis of RH requires the exclusion of white coat hypertension, which identifies pseudoresistance (15–18). In the general RH population, pseudoresistance is frequent and heralds a lower cardiovascular risk as compared with true RH (19).

To date, RH has not been properly evaluated in CKD patients. Indeed, CKD is currently recognized as a frequent cause of RH in the general hypertensive population, but no study has adequately addressed the burden of RH in the specific setting of hypertensive CKD patients. Preliminary observations suggest that diagnosis of RH increases after the first 6 months of nephrology care, due to intensification of therapy by the nephrologist (20). However, that exploratory analysis is limited by the retrospective design and inconsistent ABP assessment.

On the basis of the information available in essential hypertension (15–17), we can hypothesize that CKD patients would be at higher risk of RH and that RH would be associated with poor prognosis. Therefore, we evaluated prevalence, correlates, and long-term prognosis (up to 9 years) of true RH (i.e., confirmed by ambulatory BP monitoring as recommended by the American Heart Association) (15) in a large cohort of hypertensive patients with nondialysis CKD under regular nephrology care.

Methods

This is a multicenter prospective cohort study of consecutive patients attending 4 outpatient nephrology clinics in Italy between 2003 and 2005. The participating institutions share standardized protocols for the management of CKD, including ABP monitoring in patients with hypertension, defined as office systolic BP ≥130 mm Hg and/or diastolic BP ≥80 mm Hg or antihypertensive treatment. Patients were always seen by the same nephrologist in the clinic. Participating nephrologists are all well-versed and committed to the recommended goal of office BP <130/80 mm Hg (2). Patients were instructed to restrict dietary salt (<6 g/day). Antihypertensive agents were titrated to maximal tolerated dose, used in combination when the BP goal was not reached, and distributed from 8:00 AM to 10:00 PM. At each visit, compliance with pharmacological therapy was also evaluated; physicians asked the number of times the patient had not taken the prescribed medications in the last 2 weeks. The patient was identified as poorly compliant and excluded if the missing rate was ≥20%.

As previously described (14), hypertensive patients were included if they had CKD Stages II to V (not receiving dialysis/transplant), ≥6 months of follow-up, and ≥2 visits in the renal clinic before the initiation of study. Exclusion criteria included office BP <130/80 mm Hg without antihypertensive therapy, changes in glomerular filtration rate (GFR) >30% in the previous 3 months, changes in antihypertensive therapy 2 weeks before baseline visit, atrial fibrillation, or inadequate ABP reading. Institutional review boards of the participating centers approved the protocol, and informed consent was obtained from all patients before study enrollment.

Medical, laboratory, and medication information were collected at baseline, including history of previous cardiovascular events and left ventricular hypertrophy (LVH) diagnosed by echocardiography (yes/no). During the physician visit (8:00 AM to 11:00 AM), office BP was measured by a nephrologist according to standard methods (21). Office BP values were the mean of the 6 values recorded in the 2 consecutive days in which ABP device was placed and removed.

Participating centers shared similar ABP protocols: Spacelabs 90207 monitors (Spacelabs, Snoqualmie, Washington) were used, cuff-size was chosen on the basis of patient arm circumference and fixed to the nondominant arm, and 3 BP readings were taken concomitantly with sphygmomanometric measurements to ensure a difference <5 mm Hg between the 2 sets of values. The monitor recorded BP every 15 min between 7:00 AM and 10:00 PM and every 30 min between 11:00 PM and 7:00 AM. Daytime and nighttime periods were derived from the diaries recorded by the patients. The ABP was always obtained on a workday and under regular antihypertensive treatment. Patients had no access to the ABP values. Accuracy of 24-h urine collection was assessed as previously described (10).

Classification of patients. For the purpose of this study, patients were classified according to 24-h ABP normal (<125/75 mm Hg) or high (≥125 mm Hg and/or ≥75 mm Hg) and absence or presence of RH (office BP ≥130/80 mm Hg on ≥3 full-dose drugs including a diuretic agent or any office BP if the patient was taking ≥4 drugs). We chose 24-h ABP, because it includes both activity and resting BPs. Indeed, nocturnal BP is a main prognostic indicator of the cardiovascular outcome in CKD patients (13,14). The cutoff of 125/75 mm Hg was selected, because it is the lower threshold of normality indicated in large population-based studies (22). Therefore, patients were included into 4 groups: control (normal ABP without RH); pseudoresistance (normal ABP with RH); sustained