Hypertension Pharmacogenomics in CKD: The Clinical Relevance and Public Health Implications

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CKD is a rising public health issue affecting approximately 10% of adults worldwide, and progressive CKD is associated with higher risks of cardiovascular disease and premature death (1). Hypertension is a well-established modifiable risk factor of CKD (1). Although antihypertensive medications are some of the most commonly used drugs (2), BP control is only achieved in half of patients under treatment (3). Several barriers to hypertension care have been identified at multiple levels, including physician (inertia to initiate or intensify treatment), health systems (time constraints in busy clinical practices and cost), and patient-level challenges (poor adherence and lack of social support) (4). In addition, interpatient variability in response to different antihypertensive drugs and dosages contributes to uncontrolled hypertension. For example, patients with hypertension who are of African ancestry are considered to be more salt sensitive and respond better to calcium-channel blockers and diuretics than to angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers than White adults (5,6). Furthermore, plasma renin activity, another biomarker for predicting the response to antihypertensive agents, may also partially explain the heterogeneity in BP response, although its clinical utility remains limited especially in self-reported Black patients (7).

With the growing appreciation of the Human Genome Project, approximately 30 genes and >1477 common single nucleotide polymorphisms have been identified to be associated with BP traits (8,9). The genetic loci from the Genome-Wide Association Study provide great opportunities for research on drug-gene interactions (DGIs) for hypertension treatment. Using the genetic signals to predict an individual’s response to particular drugs is pharmacogenomics technology, which has the potential to guide the clinicians to select the right drugs and doses for the right patients (10). The approach of pharmacogenomics-based precision medicine has already been adopted by oncologists, infectious disease experts, and psychiatrists in routine practice for several conditions, and is evolving in other specialties (11–13). The Food and Drug Administration recently updated an extensive list of pharmacogenomic biomarkers in drug labels (14). A review of the genomics of hypertension summarized the BP-lowering properties of several medications with genetic loci for pharmacogenetic interaction (15).

Pharmacogenomics has tremendous potential to benefit the clinical treatment of hypertension in multiple aspects. These include predicting responses to different drugs, avoiding adverse side effects, improving optimal BP control rates efficiently, and contributing to the prevention of CKD and cardiovascular disease through treatment guided by genetic architecture, instead of physicians’ empirical judgment (16,17). In addition, evidence has shown that using genomic data significantly improves the efficacy and safety rates across the drug development pipeline, accelerating the development of new drugs (18). However, several challenges need to be navigated before the deployment of pharmacogenomics-driven algorithms could be promoted in clinical settings, for example, the validation of findings in well-conducted trials, the feasibility of translation into routine clinical practice, variability in the number needed to screen in different populations, and the clinical utility of pharmacogenomic testing, acceptability and cost effectiveness of testing, incomplete understanding and interpretation of the DGIs by the providers, implications on future insurance premiums of individuals, and the potentially increased inequality in health care accessibility (17).

In this issue of Kidney360, Eadon et al. (19) evaluated the association of DGIs with uncontrolled hypertension among 382 adults with hypertension and/or CKD. A clinical genotyping assay was developed for 40 variants and 11 drug-gene pairs relevant to hypertension control, selected on the basis of the strength of evidence, minor allele frequency, Food and Drug Administration label annotations, and guidelines including the Dutch Pharmacogenomic Working Group and Clinical Pharmacogenomics Implementation Consortium (20). Participants were tested via blood or saliva samples and genetic data were deposited into electronic health records. Almost half of patients had uncontrolled hypertension, and 78% had CKD stage 3 or worse. Of these, the majority (58%) had the primary outcome of an actionable DGI, that
is, ≥1 genetic variants predicted a reduced response to their prescribed antihypertensive drugs. Black participants (61%) had a significantly higher prevalence of DGI compared with White participants (43%) (P<0.001). Compared with those without, patients with DGIs were associated with a higher prevalence of uncontrolled hypertension (odds ratio, 1.8; 95% confidence interval [95% CI], 1.2 to 2.8) after adjusting for race, eGFR, and health system. Significant DGIs were observed among participants who were prescribed losartan (angiotensin-receptor blockers), or metoprolol (beta blocker), and carvedilol (alpha and beta blocker). Specifically, variants in CYP2C9 exhibited reduced efficacy of losartan, indicating slow metabolism of prodrug to its active metabolite, which was associated with uncontrolled hypertension. Further, CYP2D6 intermediate or poor metabolizers had higher circulating levels of metoprolol or carvedilol and were less likely to have uncontrolled hypertension.

Furthermore, among the 335 patients (92% of the cohort) followed over 1 year, the decline in systolic BP (−4.0 mm Hg; 95% CI, −6.5 to −1.6) and diastolic BP (−3.3 mm Hg, 95% CI, −4.6 to −2.0) relative to baseline were improved. This change was similar between individuals with and without a DGI. The surveys indicated that among 36% of all patients, the physicians changed their clinical management using the genetic testing results. In addition, >96% of the patients reported they would be more engaged in hypertension management if they knew the genetic susceptibility.

The findings from Eadon and colleagues’ study emphasize the importance of investigating hypertension pharmacogenomics and extending the same to patients with CKD. Their findings suggest a potential association between the presence of reduced efficacy DGI and uncontrolled hypertension, and vice versa. Moreover, they also show it is possible to implement a pharmacogenetic-driven algorithm for antihypertensive medications to diverse populations (Black patients, 40%, and women, 50%) across various settings, including safety-net health systems providing care to disadvantaged people with CKD. Moreover, the physicians reported that genetic testing altered their diagnosis or management in more than one third of patients, thereby demonstrating substantial engagement and utilization.

The metabolism of losartan by CYP2CP is shown in Figure 1. CYP2C9 can oxidize losartan and the aldehyde E-3179 to carboxylic acid E-3174, which is the predominant active species. The oxidation of losartan was significantly reduced in the CYP2C9.2 or CYP2C9.3 compared with CYP2C9.1 (21). A recent meta-analysis reported that CYP2C9*2 or *3 carriers showed lower AUC0–∞ of losartan E-3174, compared with those with *1/*1 in healthy volunteers (22). In addition, the preliminary results in patients with kidney disease suggested greater improvement in urinary protein excretion with losartan in the presence of the *1/*1 genotype versus genotypes comprising the *2 and/or *3 alleles (23). Future studies could provide in-depth analysis of the carrier state of CYP2CP in relation to the DGIs with losartan across patients with different stages of CKD.

Eadon et al.'s study is a step toward the application of pharmacogenomics in CKD, although the findings need to be interpreted with some limitations. First, the study was conducted predominantly among patients with different stages of CKD, and the prevalence of hypertension increased with the severity of CKD. Of note, it is well established that hypertension becomes more volume related as CKD progresses, especially in CKD stages 4 and 5, requiring a diuretic as the first-line agent and the antihypertensive agent of choice (24). However, the role of kidney function was not sufficiently evaluated in this analysis. For instance, it remains unclear whether the association of DGIs with BP is consistent across different stages of CKD. Likewise, the presence of albuminuria, which marks the severity of CKD and adverse prognosis, was not accounted for. These results could have substantial clinical relevance on management of hypertension in patients with different stages of CKD. Second, although Black participants were more likely to have DGI, it is unclear whether it was independently associated with uncontrolled hypertension and BP change over time in this racial subgroup. There is intense debate on the appropriateness of self-reported categorization of race on the basis of ill-defined social construct, which includes a high degree of ancestral admixture. A stratified analysis by ethnicity would help shed light on the risk attributable by biologic versus social construct of ethnicity and race. Third, and perhaps most important, it is well established that the presence of a genetic variant associated with a particular condition does not necessarily translate into its phenotypic expression, which the environmental and behavioral factors could influence during the lifespan. Unfortunately, the observational study design is not ideal for discerning causality between...

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**Figure 1.** The metabolism of losartan by CYP2CP. AT1, angiotensin II type 1 receptor.
DGI and uncontrolled hypertension. Several factors, including adherence to antihypertensive medications, behaviors, such as dietary sodium intake, overall diet, physical activity, smoking, obesity, and social determinants of CKD, including education and socioeconomic status, could influence the phenotypic expression, and therefore, confound the observed associations. Moreover, unmeasured bias, prevalent drug user bias, and confounding by indication are additional major concerns in observational pharmacoepidemiology (25). Thus, the findings by Eadon and colleagues should be interpreted with caution and could be viewed as hypothesis generating. Randomized controlled trials, the gold standard for causality evaluation, are warranted to validate the findings in the future.

Finally, it is essential to underscore that most people with hypertension and CKD live in low- and middle-income countries (26). However, there is limited scientific capacity and a lack of infrastructure and resources for pharmacogenomics and its application (27). Thus, it is vital to foster international collaborations to strengthen pharmacogenomics research, coupled with clinical electronic health systems, and encourage the uptake of pharmacogenomics knowledge by stakeholders in low- and middle-income countries. Only then will pharmacogenomics have the potential for meaningful benefits on CKD care globally.

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Author Contributions
T. Jafar conceptualized the study; T.-T. Geng and T. Jafar wrote the original draft.

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See related article, “Pharmacogenomics of Hypertension in CKD: The CKD-PGX study,” on pages 307–316.