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## **Considerable international variation exists in blood pressure control and antihypertensive prescription patterns in chronic kidney disease.**

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## Abstract

Although blood pressure control is a major goal in chronic kidney disease, no worldwide overview of either its achievement or antihypertensive prescriptions is currently available. To evaluate this we compared crude prevalence of uncontrolled blood pressure among 17 cohort studies, including 34 602 individuals with estimated glomerular filtration rate under 60 ml/min/1.73m<sup>2</sup> and treated hypertension across four continents, and estimated observed to expected prevalence ratios, adjusted for potential confounders. Crude prevalence of blood pressure of 140/90 mm Hg or more varied from 28% to 61% and of blood pressure of 130/80 or more from 54% to 84%. Adjusted prevalence ratios indicated poorer hypertension control than expected in cohorts from European countries, India, and Uruguay, and better control in patients from North American and high-income Asian countries. Four antihypertensive drug classes or more were prescribed to more than 30% of participants in North American and some European cohorts, but this practice was less common elsewhere. Renin angiotensin aldosterone system inhibitors were the most common antihypertensive drugs, prescribed for 54% to 91% of cohort participants. Differences for other drug classes were much stronger, ranging from 11% to 79% for diuretics, 22% to 70% for beta-blockers, and 27% to 75% for calcium-channel blockers. The confounders studied explain only a part of the international variation in blood pressure control among individuals with chronic kidney disease. Thus, considerable heterogeneity in prescription patterns worldwide calls for further investigation into the impact of different approaches on patient outcomes.

**Keywords:** chronic kidney disease, hypertension control, antihypertensive treatment, international health

## 1 Introduction

2 Arterial hypertension is prevalent in chronic kidney disease (CKD) and contributes to  
3 its adverse outcomes.<sup>1</sup> The major benefits of lowering blood pressure (BP) for survival and  
4 cardiovascular outcomes are well established, as are those of inhibiting the renin  
5 angiotensin-aldosterone system (RAAS) to slow CKD progression.<sup>2–8</sup> BP control and RAAS  
6 inhibitor use are therefore major goals in the management of patients with CKD,<sup>9</sup> although no  
7 consensus exists about the ideal BP level. Current guidelines agree on a systolic/diastolic BP  
8 target of less than 140/90 mm Hg in CKD patients without diabetes and albuminuria, but  
9 whether lower levels should be recommended for those with these conditions remains  
10 controversial.<sup>9–15</sup> Results from the SPRINT trial<sup>4</sup> and from recent meta-analyses<sup>5,16</sup> suggest  
11 that patients with a broad spectrum of comorbidities, including CKD, may benefit from  
12 systolic BP as low as 120 mm Hg. At the same time, there is concern about adverse effects  
13 from aggressive BP lowering in frail or elderly individuals, and higher BP targets are  
14 therefore considered for this population.<sup>9,14</sup> Information about current practices in BP control  
15 and antihypertensive therapy in CKD worldwide remains sparse.

16 Several studies have reported poor BP control in CKD with an apparent two-fold  
17 variability across countries. Prevalence of uncontrolled hypertension above 140/90 mm Hg in  
18 individuals with CKD ranges from near 35% in South Korea<sup>17</sup> and the US<sup>18,19</sup> to more than  
19 70% in Turkey<sup>20</sup>; that of BP above 130/80 mm Hg varies from 55% to 65% in the US,<sup>18,19</sup>  
20 65% in the UK,<sup>21</sup> 75% in Germany,<sup>22</sup> 80% in Japan,<sup>23</sup> and close to 90% in China.<sup>24,25</sup> Some  
21 sources of these variations among different populations may include CKD severity,  
22 prevalence of risk factors, and patterns of antihypertensive treatment. Better understanding  
23 of these would help define priorities for prevention and identify best practices in BP  
24 management.

25 The international Network of Chronic Kidney Disease (iNET-CKD) cohort studies is an  
26 open network of independently funded CKD cohort studies. Endorsed by the International  
27 Society of Nephrology, it was established to promote collaborative research, foster exchange

1 of expertise, and create opportunities for research training.<sup>26</sup> We used data from these  
2 cohorts to conduct international comparisons of the prevalence of uncontrolled BP in adults  
3 with CKD before and after adjustment for well-known risk factors for poor hypertension  
4 control. We also describe patterns of antihypertensive therapy prescription by study cohort  
5 and world region.

## **Results**

### **Participant characteristics by study**

Analysis included 34 602 participants from 17 studies. Table 1 presents the participants' characteristics by study. They were mainly elderly, with median age mostly exceeding 60 years. Participants were more often men, except in the Australian CKD-QLD and the CKDopps Brazil, in which the sex ratios approached 1:1 and in the European PROVALID and RRID, both of which included general practice (GP) patients, predominantly women. Other study variables were more heterogeneous. For instance, prevalence of moderate and severe albuminuria (KDIGO A2 or A3) varied widely across cohorts, from 20% in the incident Uruguayan NRHP to 91% in the Japanese CKD-JAC.

### **Mean blood pressure and prevalence of uncontrolled hypertension by study**

Mean systolic BP differed by 15 mm Hg between the lowest (Korean KNOW-CKD) and highest (French CKD-REIN) values in the cohorts we analyzed (Table 2). Likewise, a 12-mm Hg-variation in mean diastolic BP was observed between the lowest (Canadian CanPREDDICT) and highest (Indian CKD) values. In contrast, standard deviations for both measures were homogeneous across studies. The higher the BP threshold, the larger the variation in prevalence of uncontrolled hypertension. Overall, the prevalence of uncontrolled BP was lower in cohorts from high-income Asian and North American countries, and higher in nephrology cohorts from Europe.

### **Prevalence ratios of uncontrolled hypertension**

Ratios of observed to expected prevalence rates of uncontrolled hypertension were not substantially affected by adjustment for age, gender, diabetes, and eGFR, regardless of BP threshold (Figure 1A and Tables S1 and S2). In contrast, further adjustment for history of cardiovascular disease, BMI, and most importantly for albuminuria (Figure 1B) increased the prevalence ratios of BP  $\geq$ 140/90 mm Hg in the ICKD and NRHP incident cohorts (from +11% to +26% and +10% to +23%, respectively), while in CKD-REIN it decreased from +39% to +29%. In the UK RRID study and the Thai CORE-CKD, prevalence ratios of BP  $\geq$ 140/90

mm Hg became close to one and were no longer significant after adjustment. In the final and most complex adjustment model (further including education level and current smoking, Figure 1C), this prevalence ratio was highest in the ICKD cohort and in most of the European studies. Results were similar for BP  $\geq 130/80$  mm Hg, but for BP  $\geq 150/90$  mm Hg in individuals aged 60 years or over, prevalence ratio in the German CKD study notably exceeded those from other studies (+54%, Table S3). Consistently, prevalence ratios of uncontrolled hypertension (regardless of threshold or adjustment model) were significantly lower than 1 in cohorts from North America, high-income Asia (KNOW-CKD, CKD-JAC), and Australia. Meta-regression analyses showed that adjusted prevalence ratios of BP  $\geq 140/90$  mm Hg were not associated with either the year at study start ( $R^2$  5.6%,  $p=0.13$ , Figure 2) or the type of BP measurement ( $R^2$  0.0%,  $p=0.67$ ). Adjusted odds ratios for uncontrolled hypertension associated with known risk factors were similar between BP  $\geq 130/80$  and  $\geq 140/90$  mm Hg (Tables S4 and S5). Except for albuminuria and education, they tended to be non-significant for BP  $\geq 150/90$  mm Hg in individuals aged 60 or over (Table S6).

### **Antihypertensive drugs prescribed**

The number of antihypertensive drug classes was highest in the cohorts from North America, where more than 50% of individuals had 3 drug classes or more (Figure 3). This number was also high in German cohorts (CKDopps and GCKD), PROVALID, and CKDopps Brazil. CSTRIDE and NRHP (both incident and prevalent) cohorts had the fewest antihypertensive drug classes: nearly 40% of participants had only one drug class. The most prescribed drug class was that of RAAS inhibitors (Figure 4). Its frequency ranged from 54% in CKDopps US to 91% in KNOW-CKD. Diuretics were more frequently prescribed to participants from CKDopps Brazil (about 80%), and from European (52 to 78%) and North American cohorts (66 to 74%). Conversely, their frequency was particularly low in Asian cohorts, especially CSTRIDE (11%). Specifically, the use of mineralocorticoid receptor antagonists in cohorts with available information ranged from  $<1\%$  in ICKD to 9% in CKDopps-BR (Table S7). Asian cohorts stood out for their high frequency of calcium-channel blockers (53 to 75%). Beta-blocker prescription ranged from 22% in CKD-JAC to 70% in CKDopps Germany, and that of



- 1 other antihypertensive drug classes, from 2% in incident NRHP to 41% in CKDopps US.
- 2 RAAS inhibitors were the drug class most frequently chosen for single-agent therapy (Table
- 3 3, Tables S8.1 to S8.17). Overall, RAAS inhibitors were more often associated with diuretics,
- 4 followed by calcium-channel blockers and beta-blockers at equal rates.

## Discussion

This study confirms the overall inadequate achievement of BP control in patients with moderate and advanced CKD worldwide, but highlights large international variations that are only partly explained by patient characteristics. The main novelty of the study is to show how heterogeneous prescription patterns were across world regions, both in terms of the number and types of antihypertensive drug classes, with the exception of RAAS inhibitors, which are commonly prescribed as first-line treatment in all countries. Our finding that cohorts with the highest number of prescribed antihypertensive drug classes also had the lowest prevalence rates of uncontrolled BP  $\geq 140/90$  points out room for improvement in many countries.

Nonetheless, the remaining prevalence of uncontrolled BP  $\geq 130/80$  mm Hg above 50% in all cohorts suggests that so low a BP target is unlikely to be achieved.

Disparities in BP levels,<sup>27</sup> as well as in hypertension prevalence and control,<sup>28–30</sup> have been extensively described in the general population. The most recent large report about international variation in BP is that from the Non-Communicable Diseases Risk Factor Collaboration.<sup>27</sup> Age-standardized prevalence of high BP ( $\geq 140/90$  mm Hg) in that study tended to be higher in Africa, South and Southeast Asia, Europe, and South America than in Australia-New Zealand, high-income Asia, or North America. Likewise, hypertension control was shown to vary considerably across world regions in a systematic analysis including population-based data: only 26% of people receiving antihypertensive medication in low-and middle-income countries had BP  $<140/90$  mm Hg, versus 50% of those in high-income countries.<sup>28</sup> To the best of our knowledge, three studies have analyzed international BP data in CKD; two of them were part of the Dialysis Outcomes and Practice Patterns Study (DOPPS) in individuals undergoing hemodialysis.<sup>31,32</sup> Crude comparisons showed predialysis BP was lower in participants from Australia, New Zealand, and Europe (44% had BP  $<140/90$  mm Hg) than in those from North America (32%) and Japan (26%).<sup>31</sup> An analysis including patients from 7 European countries found geographical variations in BP that appeared to be partly explained by latitude.<sup>32</sup> In that study, participants from northern countries had higher

BP levels than those in southern ones, with an increase of 5.1 and 4.4 mm Hg in systolic and diastolic BP, respectively, for each 10° increase in latitude, independent of patient characteristics and baseline dialysis prescription. More recently, a study from the International Database of Ambulatory BP in Renal Patients (I-DARE) collaborative group showed wide variations in 24-hour BP profiles in patients with nondialysis CKD from 7 studies in 4 countries.<sup>33</sup> Like ours, that study showed poor BP control in European cohorts, either according to clinic BP or to combined clinic and ambulatory BP. Its finding that European participants had the highest likelihood of white-coat hypertension suggests that clinic BP may be particularly overestimated in this population.

Our findings about international variations in office BP control among individuals with earlier CKD stages (eGFR<60 ml/min/1.72m<sup>2</sup> not requiring renal replacement therapy) are more consistent with those reported among the general population<sup>27–30</sup> than among hemodialysis patients.<sup>31,32</sup> Hypertension control was poorer in cohorts in Europe, South America, and India than in those in high-income Asia and North America. Overall, a substantial portion of study participants had high BP: 28 to 61% ≥140/90 mm Hg and 64 to 84% ≥130/80 mm Hg. Hypertension control may be more difficult to achieve in some specific groups that are overrepresented among CKD patients, such as the elderly, men, and individuals with established cardiovascular disease or diabetes.<sup>10</sup> It may be strongly related to individuals' lifestyle, including weight control and smoking status. Furthermore, in patients with CKD, blood pressure levels are influenced by eGFR and albuminuria level.<sup>18,24</sup> In our study, prevalence of the studied risk factors for uncontrolled hypertension differed greatly across cohorts. Nevertheless, these differences only partly explained the observed international variations in hypertension control in moderate to severe CKD. Likewise, the recruitment period and the type of BP measurement accounted for only a small portion of the heterogeneity across cohort studies. The adoption of different BP targets in some populations might contribute in part to this heterogeneity. An analysis by Wolf-Meyer et al. in the general population<sup>30</sup> showed that the gap in hypertension control between North American and European countries was more pronounced for the BP threshold of 140/90

mm Hg than for that of 160/95 mm Hg, which was accompanied by a similar trend in hypertension treatment rates. Interestingly, in our analyses, the higher the target BP, the higher the variation in hypertension control, a finding that does not support this hypothesis.

Although unstudied characteristics including genetics,<sup>34</sup> diet,<sup>35</sup> economic level,<sup>28</sup> and public health policies<sup>36</sup> certainly contribute to these variations in hypertension control, patterns of antihypertensive drug prescription in CKD are likely to play an important role in our findings. Evidence from randomized clinical trials and observational studies indicates that most CKD patients will require at least 2 antihypertensive agents to achieve adequate hypertension control.<sup>9</sup> In our study, half the participants in cohorts with poor BP control (prevalence ratios >1) had at most 2 antihypertensive agents (except for participants in PROVALID and CKDopps DE). In Asian cohorts, the number of antihypertensive drug classes prescribed was also relatively low, but among them, target BP was more often achieved in those with more aggressive antihypertensive treatment. This is, however, an ecological comparison and may be confounded by other factors.

RAAS inhibitors have been consistently recommended as the first-choice drug for hypertension management in CKD patients, particularly because of its renoprotective effect via proteinuria reduction.<sup>9,13,15</sup> Our results suggest quite good compliance with this recommendation across all the cohorts we analyzed. The frequency of RAAS inhibitor prescription was even surprisingly high in some cohorts given their mean eGFR: in CKD-JAC, for example (mean eGFR 26 ml/min/1.73m<sup>2</sup>), 89% of participants were prescribed RAAS inhibitors. For similar mean eGFR, the frequency of RAAS inhibitors across study cohorts fell to values as low as 54%, which is suggestive of underuse in some settings. GFR decrease and related risk of hyperkalemia or acute kidney injury may cause concern when prescribing RAAS inhibitors for patients with more severe CKD, since current evidence on their benefit-risk balance is contradictory.<sup>37–39</sup> Furthermore, it has been suggested that the type of physician (primary care physician versus nephrologist) may have an impact on adherence to the RAAS inhibition recommendation for CKD patients.<sup>40–42</sup>

Prescription patterns for other drug classes were heterogeneous. In particular, we showed that CCB was the second most frequently prescribed drug class in Asian cohorts, apparently mainly at the expense of diuretics. Some guidelines (either for CKD or hypertension management)<sup>13,15,43</sup> recommend a specific second drug in antihypertensive treatment more strongly than others do.<sup>9,44,45</sup> Hence, CCB use is recommended in Japan, Thailand, and UK, likely because of findings from the ACCOMPLISH trial, in which benazepril plus amlodipine was associated with better cardiovascular<sup>46</sup> and renal<sup>47</sup> outcomes than benazepril plus hydrochlorothiazide. Mineralocorticoid receptor antagonists are of particular interest in the treatment of resistant hypertension.<sup>48</sup> They also have been shown to reduce BP and proteinuria in adults with CKD in association with RAAS inhibitors, although with increased risk of hyperkalemia.<sup>49</sup> In our study, the prescription of mineralocorticoid receptor antagonists varied internationally, but was rather uncommon.

Most guidelines emphasize individualization of treatment based on comorbidities, side effects, and other factors including drug availability. The highest prevalence of cardiovascular disease, including coronary artery disease and congestive heart failure, may at least partly explain the higher use of beta-blockers in some cohorts. But more subjective factors, such as prescriber preferences, may play a key role in treatment patterns. An analysis of national prescribing profiles in hypertension showed that prescription patterns varied among countries, notably with more frequent use of thiazide diuretics in the UK than in Norway, Germany, or France, and consumption of alpha-blockers twice as high in Norway than in any other country studied.<sup>50</sup> That study also asked clinical researchers and professionals in drug regulatory agencies about the possible reasons for these variations. Although factors such as clinical guidelines, the availability of generic drugs, and cost-awareness were recognized as potential explanatory variables, pharmaceutical marketing was considered to be the main driver for prescribing choices.

## **Strengths and limitations**

To our knowledge, this is the first international comparison of hypertension control and treatment patterns in non-dialysis CKD. We included a large number of CKD patients

from 17 study cohorts across the world, which was possible because of the use of grouped information (number of participants with a given profile) for analysis. International comparisons are often adjusted at most for age and sex. By using logistic regression models, we were able to adjust analyses for several major risk factors for high BP, including kidney function and albuminuria, which are critical for determining BP levels in CKD. Moreover, we had information about the main drug classes in hypertension management in CKD.

This study also has limitations. Differences in study design between cohorts such as recruitment years and setting, and BP measurement procedures are likely to affect comparisons of hypertension control. The definition of uncontrolled hypertension based on a single-visit BP, mostly obtained through routine measurements, may have led to misclassification or even overestimation of its prevalence in some settings. Nevertheless, the consistent results among cohorts within world regions suggest that this was not a major source of bias. Most cohorts included individuals under nephrology care and may not be representative of the overall population with moderate or advanced CKD in their country; generalization to this population is thus precluded. We performed complete-case analysis, assuming that covariates were missing completely at random. Although this is a strong assumption, we believed that multiple imputation with available data would not substantially improve either efficiency or precision in our models. We did not have complete covariate information for some of the study cohorts, thus all analyses were not fully adjusted. Furthermore, adjustment for confounders may not be optimal because of the use of grouped data. However, this approach facilitated data transfer procedures and increased study participation. Finally, our comparisons did not consider some relevant factors, particularly medication adherence. An analysis of the REGARDS study, for example, showed that poor adherence to antihypertensive treatment among CKD participants was common (about 30%) and associated with a higher likelihood of uncontrolled hypertension.<sup>19</sup>

## **Conclusions**

Worldwide variation in hypertension control in patients with moderate to severe CKD appears to be only partly explained by individual characteristics. In this study, we highlight a

1 considerable heterogeneity in both type and number of antihypertensive drug classes  
2 prescribed. Whether a specific drug combination or a more aggressive treatment is  
3 associated with better kidney and cardiovascular outcomes in real life remains to be  
4 evaluated. The widespread prescription of RAAS inhibitors, which are consistently  
5 recommended in CKD, underscores the role of guidelines in the adoption of best practices.  
6 Further investigation of hypertension management in CKD is needed to bridge the gaps in  
7 current recommendations and improve patient outcomes.

## **Methods**

### **Study design**

iNET-CKD membership prerequisites have been detailed elsewhere.<sup>26</sup> iNET-CKD includes observational studies with defined objectives, patient-level information, and prospective data collection, and focuses on individuals with predialysis CKD. The present analysis consists of baseline data from 17 studies including participants aged  $\geq 18$  years, with eGFR  $< 60$  ml/min/1.73m<sup>2</sup> (neither dialyzed nor transplanted) and treated hypertension (under antihypertensive drug use). Information about study country, recruitment years, target population, and prevalence of treated hypertension is summarized in Table S9.

### **Study variables**

A variable dictionary was sent to each participating cohort study in order to harmonize data regarding covariate definitions, labeling, and coding (Appendix S1). Glomerular filtration was estimated with the CKD-EPI<sup>51</sup> equation, except in CanPREDDICT and CKD-JAC studies, in which the MDRD<sup>52</sup> equation and the 3-variable Japanese equation<sup>53</sup> were used, respectively. Albuminuria (or equivalent) was classified according to the Kidney Disease Improving Global Outcomes (KDIGO) 2012 guideline stages as A1 (normal to mildly increased), A2 (moderately increased), or A3 (severely increased).<sup>9</sup> Body mass index (BMI) was calculated as weight (Kg) divided by square height (m). Diabetes was defined as serum fasting glucose  $\geq 7.0$  mmol/L ( $\geq 126$  mg/dl), non-fasting glucose  $\geq 11.1$  mmol/l ( $\geq 200$  mg/dl), glycated hemoglobin A1c  $\geq 6.5\%$ , or use of glucose-lowering drugs. If such information was not available, diabetes was identified by self-report or medical records. History of cardiovascular disease was defined as history of coronary artery disease, prior revascularization, heart failure, stroke or peripheral vascular disease. Education levels corresponded to the number of years of formal education reported by the participant at the baseline visit. Smoking status was dichotomized into current and not current smoking, except for one study in which participants were classified as ever or never smokers.

### **Blood pressure control and antihypertensive treatment**



BP assessment method for each study is described in Table S9. Most studies (10 of 17) provided an office BP value, while the other provided the mean of 3 BP readings obtained in compliance with a study protocol. We classified participants' BP control status according to three thresholds for systolic and diastolic BP: 130/80 mm Hg, 140/90 mm Hg, and 150/90 mm Hg, the latter only in participants aged  $\geq 60$  years only. Antihypertensive drugs prescribed were identified by self-report or medical reports and classified into the following classes: renin-angiotensin-aldosterone system (RAAS) inhibitors, diuretics, calcium-channel blockers, beta-blockers, and other.

### **Statistical analyses**

To address the study aims, we asked each study cohort to provide descriptive statistics regarding participants' characteristics and antihypertensive drug prescriptions. For each study, we also asked for three datasets containing grouped information including the number of participants having a particular profile, and respective number of participants with uncontrolled BP (one dataset for each BP threshold). This was equivalent to having individual data for each categorized covariate. Characteristics considered for participant profiling were age ( $<65$  or  $\geq 65$  years), gender, diabetes, eGFR ( $\geq 30$  or  $<30$  ml/min/1.73m<sup>2</sup>), history of cardiovascular disease, BMI ( $<30$  or  $\geq 30$  kg/m<sup>2</sup>), albuminuria (A1, A2 or A3), education attainment ( $<12$  or  $\geq 12$  years of formal education), and smoking status (current or not). If 20% or more data was missing for a given variable, this variable was excluded from the dataset. Any participant with missing information for the remaining variables was excluded.

Using these data, we described participants' characteristics and BP control by study, world region (Asia, Australia, Europe, North America, and South America), and recruitment setting (nephrology or general practices). Categorical variables were presented as percentages and continuous variables as means  $\pm$  standard deviations or medians (interquartile range). Using mixed logistic regression models with study-specific random intercepts and participant characteristics as fixed effects, we estimated prevalence ratios of uncontrolled BP ( $\geq 130/80$ ,  $140/90$ , or  $150/90$  mm Hg) for each cohort study. Prevalence

1 ratios correspond to the ratio of the true prevalence of uncontrolled BP for a given study  
2 cohort according to the model (predicted mean), divided by the prevalence that would be  
3 expected for a hypothetical cohort with the same case-mix and an intercept parameter equal  
4 to the population average (marginal mean) <sup>54</sup>. The respective 95% confidence intervals were  
5 estimated with bias-corrected bootstrap methods. All adjustment variables were not available  
6 for some of the participating studies, either because they were not collected or because they  
7 were missing for  $\geq 20\%$  of participants (Table S10). Thus, we performed three adjustment  
8 models: the first included age, gender, diabetes, and eGFR (4-covariate model); the second  
9 further included albuminuria level, cardiovascular disease, and obesity status (7-covariate  
10 model), and the third one added smoking status and educational level (9-covariate model).  
11 These adjustment models included a different set of studies depending on variable  
12 availability (17, 14, or 10 studies, respectively). To test the era effect and the impact of the  
13 type of BP measurement in prevalence ratio estimates, we performed meta-regressions of  
14 the prevalence ratio of uncontrolled BP  $\geq 140/90$  mm Hg obtained with the 4-covariate model  
15 on the first year of recruitment, as a surrogate for year at BP measurement, and on the type  
16 of BP measurement. Antihypertensive drugs were described in terms of number and type of  
17 drug classes. Two-sided significance tests were used and *P*-values  $<0.05$  were considered  
18 significant. Statistical analyses were performed with SAS 9.4 (SAS Institute Inc, Cary, NC)  
19 and R version 3.5.0.

1    **Disclosure**

2    All authors declare that they have no relevant financial interests. Fundings of studies  
3    contributing in this iNET-CKD analysis are presented in Appendix S2 of the supplementary  
4    material.

## **Supplementary material**

**Supplementary Table S1.** Crude and adjusted prevalence ratios of uncontrolled blood pressure  $\geq 130/80$  mm Hg, by study.

**Supplementary Table S2.** Crude and adjusted prevalence ratios of uncontrolled blood pressure  $\geq 140/90$  mm Hg, by study.

**Supplementary Table S3.** Crude and adjusted prevalence ratios of uncontrolled blood pressure  $\geq 150/90$  mm Hg in patients aged 60 years or older, by study.

**Supplementary Table S4.** Adjusted odds ratios of uncontrolled blood pressure  $\geq 130/80$  mm Hg associated with patient characteristics.

**Supplementary Table S5.** Adjusted odds ratios of uncontrolled blood pressure  $\geq 140/90$  mm Hg associated with patient characteristics.

**Supplementary Table S6.** Adjusted odds ratios of uncontrolled blood pressure  $\geq 150/90$  mm Hg in patients aged 60 years or older associated with patient characteristics.

**Supplementary Table S7.** Number and type of antihypertensive drug classes prescribed by study.

**Supplementary Tables S8.1 to S8.17.** Patterns of antihypertensive drug prescription.

**Supplementary Table S9.** Study description and references.

**Supplementary Appendix S1.** Variable dictionary.

**Supplementary Table S10.** Missing covariates, by study.

**Supplementary Appendix S2.** Acknowledgement and funding for collaborating cohorts.

Supplementary information is available at Kidney International's website.

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## **The International Network of Chronic Kidney Disease cohort studies (iNET-CKD)**

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**Table 1.** Patient characteristics by study.

Study	N	Age (years, median IQR)	Gender (female, %)	Education (≥12 years, %)	Diabetes (%)	CVD (%)	BMI (kg/m², median IQR)	Current smoking (%)	eGFR (ml/min/1.73m², median IQR)	Albuminuria category (%)		
										A1	A2	A3
Nephrology cohorts												
Asia												
CKD-JAC	1898	63 (55-70)	34.9	41.8	44.9	29.6	23.2 (21.1-25.8)	16.9	27.2 (18.3-37.4)	9.3	28.2	62.5
CORE-CKD	739	65 (58-70)	34.0	54.3	52.8	21.7	25.7 (23.2-29.1)	6.6	36.6 (28.1-47.4)	30.7	25.4	43.8
CSTRIDE	1305	52 (42-62)	39.2	27.1	29.7	14.1	24.5 (22.0-26.8)	39.9*	32.3 (22.4-43.2)	22.1	23.3	54.6
ICKD	676	50 (41-58)	31.2	45.4	30.9	12.9	24.1 (21.6-27.3)	16.0	39.5 (33.5-47.6)	56.8	17.3	25.9
KNOW-CKD	1313	58 (50-65)	36.3	36.9	34.7	17.4	24.1 (21.6-26.3)	15.3	33.1 (22.6-45.0)	30.4	23.2	46.5
Australia												
CKD-QLD	1504	72 (63-79)	47.9	NA	54.3	56.3	30.2 (26.0-35.4)	8.4	34.0 (24.0-42.0)	27.6	31.4	41.0
Europe												
CKD-REIN	2147	69 (61-77)	33.5	35.1	44.2	43.1	28.0 (24.9-32.0)	11.9	31.2 (22.9-40.2)	26.8	31.2	42
CKDopps DE	877	75 (67-80)	42.6	NA	43.3	30.7	29.0 (25.5-32.7)	NA	26.0 (21.7-32.8)	NA	NA	NA
GCKD	3734	65 (57-70)	36.9	46.8	39.2	34.6	29.3 (26.0-33.5)	14.4	42.0 (34.0-49.0)	43.1	30.8	26.1
PSI BIND-NL	517	63 (52-71)	33.1	78.9	20.1	38.1	27.0 (24.3-30.9)	16.8	30.9 (21.5-43.3)	27.5	21.1	51.5
North America												
CanPREDDICT	2411	71 (62-77)	37.4	NA	49.5	57.3	28.7 (25.1-33.2)	NA	27.0 (20.1-34.7)	25.5	35.6	38.9
CKDopps US	771	71 (61-78)	45.7	NA	60.7	45.7	31.3 (26.7-37.5)	9.7	25.0 (18.0-33.0)	NA	NA	NA
CRIC	2801	61 (54-67)	44.9	76.5	53.5	38.0	31.3 (27.3-36.5)	13.0	39.8 (31.0-47.9)	35.2	27.5	37.3
South America												
CKDopps BR	509	68 (59-77)	49.7	8.8	47.3	44.8	NA	7.3	24.0 (17.0-31.0)	42.8	17.5	24.2
NRHP prevalent	6460	73 (65-79)	41.9	NA	38.9	36.5	28.5 (25.3-32.1)	5.6	35.8 (26.9-44.8)	75.8	10.1	14.0
GP cohorts												
NRHP incident	5257	72 (65-79)	43.6	NA	38.4	37.3	28.8 (25.6-32.5)	7.1	38.3 (29.8-46.5)	79.9	9.4	10.7
PROVALID	641	69 (64-79)	57.3	NA	100**	45.6	30.8 (25.2-34.5)	7.8	48.0 (39.4-51.1)	62.7	27.5	9.8
RRID	1042	76 (70-81)	53.4	23.1	22.2	27.0	28.7 (25.9-32.0)	4.1	48.1 (41.6-54.1)	77.4	19.2	3.4

Abbreviations: IQR, interquartile range; CVD, cardiovascular disease; BMI, body mass index; eGFR, estimated glomerular filtration rate; GP: general practice; NA, not available or missing at ≥20%.

\*Current or former smoking. \*\*PROVALID included only patients with diabetes.

**Table 2.** Mean systolic and diastolic blood pressure (mm Hg), and prevalence of uncontrolled hypertension according to blood pressure target, by study.

Study	SBP (mean, SD)	DBP (mean, SD)	BP ≥130/80 (%)	BP ≥140/90 (%)	BP ≥150/90* (%)	Type of BP measurement**
<b>Nephrology cohorts</b>						
<b>Asia</b>						
CKD-JAC	132.2 (18.0)	76.6 (11.7)	60.6	32.6	19.9	Study protocol
CORE-CKD	138.9 (18.6)	77.7 (12.0)	73.1	45.5	27.4	Study protocol
CSTRIDE	133.8 (17.6)	82.8 (11.1)	75.8	40.1	24.9	Study protocol
ICKD	135.2 (19.8)	83.2 (10.8)	80.2	47.3	32.7	Study protocol
KNOW-CKD	129.2 (16.8)	76.6 (11.1)	60.5	27.3	17.8	Office BP
<b>Australia</b>						
CKD-QLD	133.6 (20.2)	71.4 (11.6)	64.0	38.5	24.1	Office BP
<b>Europe</b>						
CKD-REIN	143.9 (20.2)	78.5 (12.2)	83.8	60.9	42.6	Office BP
CKDopps DE	138.5 (16.7)	76.2 (9.9)	79.7	49.5	23.6	Office BP
GCKD	140.6 (20.6)	78.7 (12.0)	75.2	51.0	38.0	Study protocol
PSI BIND-NL	138.9 (19.8)	82.5 (11.7)	77.2	50.1	41.5	Office BP
<b>North America</b>						
CanPREDDICT	134.3 (20.0)	70.8 (11.9)	63.6	37.5	23.6	Office BP
CKDopps US	136.6 (20.8)	72.7 (11.8)	66.4	43.5	23.7	Office BP
CRIC	131.0 (22.3)	71.2 (12.9)	54.3	33.9	20.9	Study protocol
<b>South America</b>						
CKDopps BR	134.1 (21.0)	79.3 (12.0)	79.2	49.5	32.3	Office BP
NRHP prevalent	133.1 (20.6)	75.7 (12.3)	70.6	43.6	27.9	Office BP
<b>GP cohorts</b>						
NRHP incident	134.7 (22.4)	76.0 (12.9)	70.9	46.7	30.2	Office BP
PROVALID	136.4 (20.4)	77.8 (11.8)	81.0	46.6	7.9	Office BP
RRID	134.7 (19.1)	70.9 (11.1)	61.7	37.6	20.2	Study protocol

\*Among patients aged 60 years or over.

\*\*See more details about BP measurement methods in Supp Table 1.

Abbreviations: GP, general practice; SBP, systolic blood pressure; DBP, diastolic blood pressure.

**Table 3.** Patterns of antihypertensive drug prescription. In the left table, frequency of each antihypertensive drug class is reported according to the number of prescribed classes. The right table reports the frequency of two-by-two associations between antihypertensive drug classes.

Drug classes	Number of antihypertensive drug classes				Type of antihypertensive drug classes				
	1 (n= 9006, 26.5%)	2 (n= 11360, 33.5%)	3 (n= 8512, 25.1%)	≥4 (n= 5048, 14.9%)	RAAS inhibitors (n= 25930, 76.4%)	Diuretics (n= 18313, 54.0%)	CCB (n= 14642, 43.2%)	Beta-blockers (n= 14209, 41.9%)	Other (n= 3542, 10.4%)
<b>RAAS inhibitors</b>	66.3%	71.1%	84.2%	93.4%	23.0%, alone	74.1%	68.7%	69.9%	64.9%
<b>Diuretics</b>	9.4%	53.7%	79.1%	91.7%	52.3%	4.6%, alone	56.1%	63.9%	69.1%
<b>CCB</b>	14.2%	35.1%	57.2%	89.3%	38.8%	44.9%	8.7%, alone	47.0%	63.0%
<b>β-blockers</b>	9.3%	32.6%	63.2%	85.0%	38.3%	49.6%	45.6%	5.9%, alone	54.5%
<b>Other</b>	0.9%	4.9%	10.3%	40.1%	8.9%	13.4%	15.2%	13.6%	2.2%, alone

Abbreviations: RAAS inhibitors, renin-angiotensin-aldosterone system inhibitors; CCB, calcium channel blockers.

## Figures

**Figure 1A-C.** Adjusted prevalence ratios of blood pressure  $\geq 130/80$  or  $\geq 140/90$  mm Hg by study.

Values above 1 indicate lower frequency of blood pressure control than expected, given study patient characteristics. A: Adjusted for age, gender, diabetes status, and eGFR category; B: Further adjusted for history of cardiovascular disease, obesity, and albuminuria category; C: Further adjusted for education and smoking status. Abbreviations: AU, Australia; PR, prevalence ratio; CI, confidence interval; GP, general practice; NA, not available.

**Figure 2.** Adjusted prevalence ratios of uncontrolled blood pressure  $\geq 140/90$  mm Hg according to the year at study start, by study.

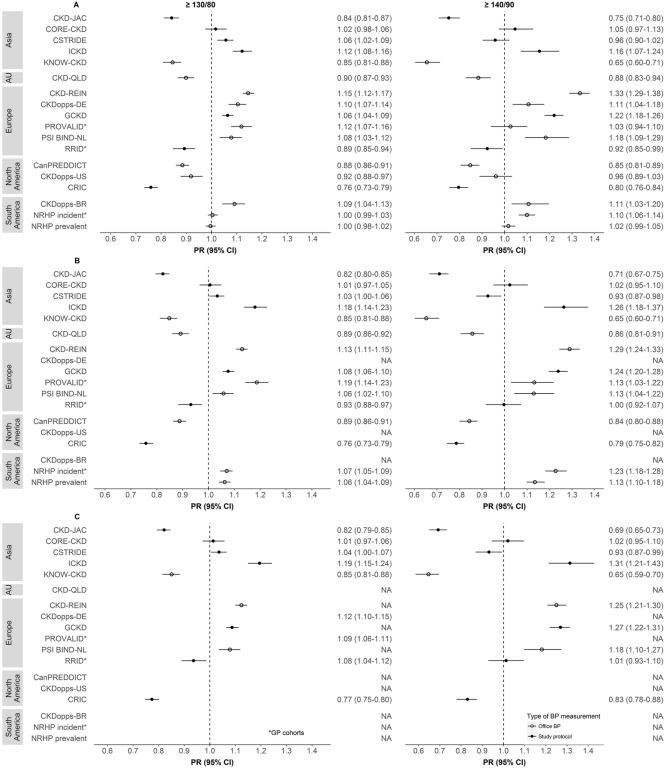
Prevalence ratio values above 1 indicate lower frequency of blood pressure control than expected, given study patient characteristics.  $R^2$ ,  $\beta$ , and p values were estimated with meta-regression analysis of prevalence ratios of uncontrolled blood pressure  $\geq 140/90$  mm Hg adjusted for age, gender, diabetes status, and eGFR category on the year at study start, as surrogate of year at BP measurement. Abbreviations: PR, prevalence ratio; BP, blood pressure; GP, general practice.

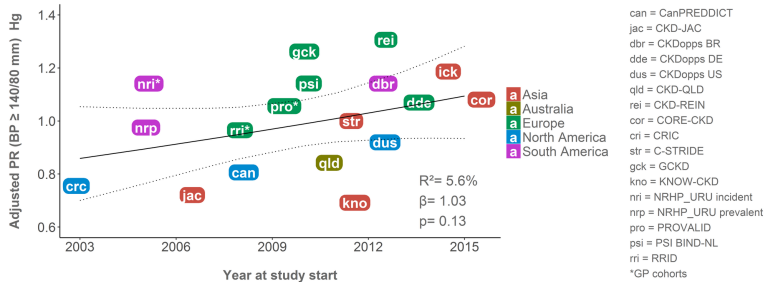
**Figure 3.** Number of antihypertensive drug classes prescribed by study.

Abbreviations: AU, Australia; GP, general practice.

**Figure 4.** Type of antihypertensive drug classes prescribed by study.

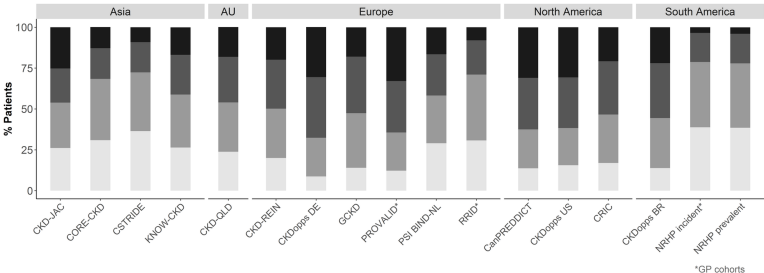
Abbreviations: RAAS, Renin-angiotensin-aldosterone system; GP, general practice.







Number of drug classes



\*GP cohorts

% Patients

100  
75  
50  
25  
0

RAAS inhibitors

Diuretics

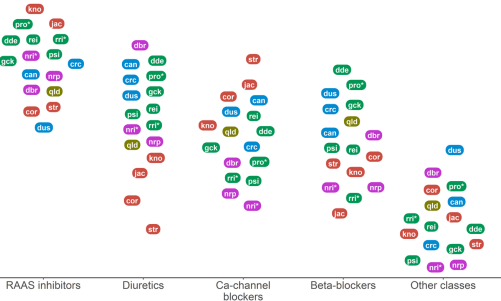
Ca-channel  
blockers

Beta-blockers

Other classes

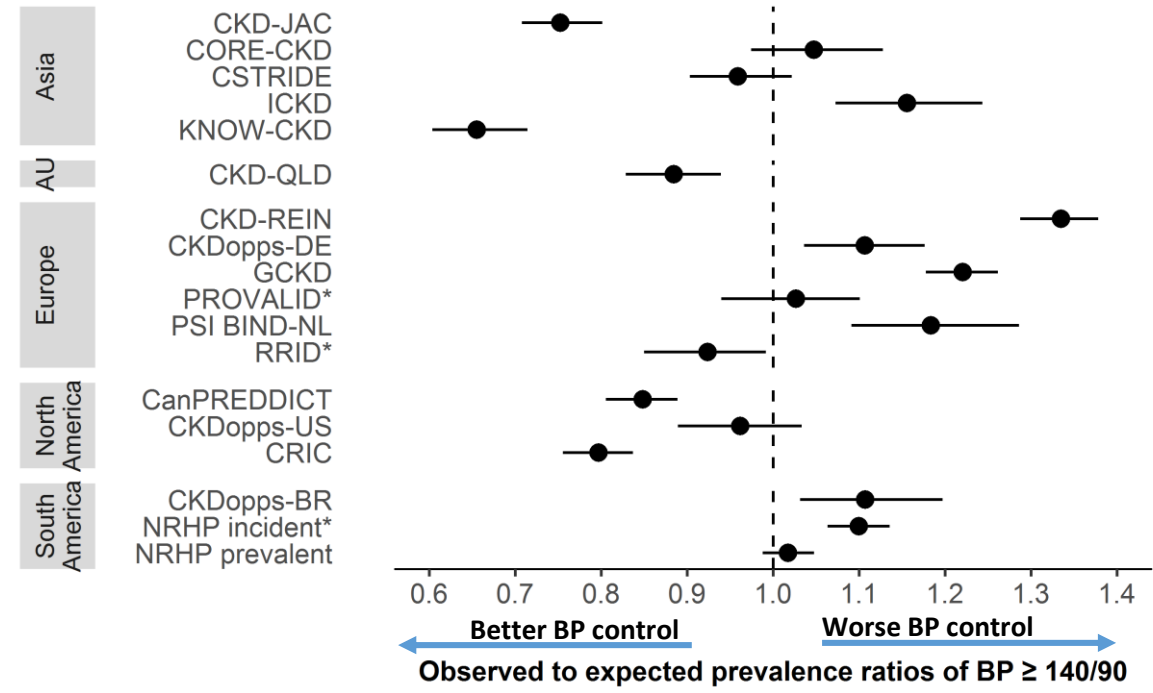
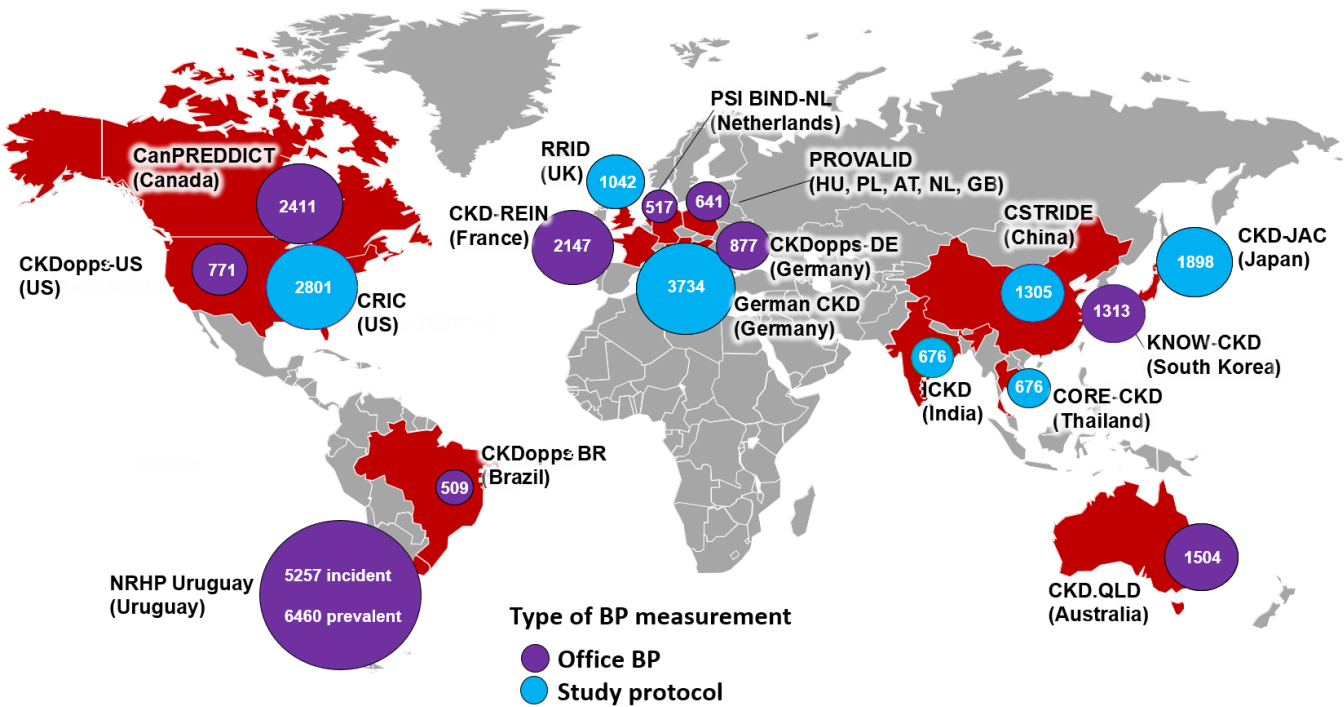
Asia  
Australia  
Europe  
North America  
South America

can = CanPREDDICT  
jac = CKD-JAC  
dbr = CKDopps BR  
dde = CKDopps DE  
dus = CKDopps US  
qld = CKD-QLD  
rei = CKD-REIN  
cor = CORE-CKD  
cri = CRIC  
str = C-STRIDE  
gck = GCKD  
kno = KNOW-CKD  
nri = NRHP\_URU incident  
nrp = NRHP\_URU prevalent  
pro = PROVALID  
psi = PSI BIND-NL  
ri = RRID  
\*GP cohorts



# Considerable international variation exists in blood pressure control and antihypertensive prescription patterns in chronic kidney disease.

34 602 individuals with eGFR <60 ml/min/1.73m<sup>2</sup> and treated hypertension across 17 cohort studies in 4 continents



**Prescription pattern of antihypertensive drug classes across cohorts**  
RAAS inhibitors: 54 to 91%; diuretics: 11% to 79%; beta-blockers: 22% to 70%; calcium-channel blockers: 27% to 75%.

**CONCLUSION:**  
Substantial worldwide variation in hypertension control exists. Heterogeneity in prescription patterns calls for further investigation into the impact on patient outcomes.