

## International variations in blood pressure control and antihypertensive prescription patterns in chronic kidney disease

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## Abstract

Although blood pressure (BP) control is a major goal in chronic kidney disease (CKD), no worldwide overview of either its achievement or antihypertensive prescriptions is currently available. We compared crude prevalence of uncontrolled BP among 17 cohort studies, including 34 602 individuals with eGFR <60 ml/min/1.73m<sup>2</sup> and treated hypertension across 4 continents, and estimated observed to expected prevalence ratios (PR) ~~for each cohort~~, adjusted for potential confounders. Crude prevalence of BP ≥140/90 mm Hg varied from 28% to 61% and of BP ≥130/80 from 54% to 84%. Adjusted PR indicated poorer hypertension control than expected in cohorts from European countries, India, and Uruguay, and better control in those from North American and high-income Asian countries. More than 30% of participants ~~used~~ were prescribed four antihypertensive drug classes or more in North American and some European cohorts, but this practice was less common elsewhere. RAAS 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 BP control among individuals with CKD. The 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 ~~highly~~ prevalent in chronic kidney disease (CKD) and  
3 contributes ~~strongly~~ to its adverse outcomes.<sup>1</sup> The major benefits of lowering blood pressure  
4 (BP) for survival and cardiovascular outcomes are well established, as are those of inhibiting  
5 the renin angiotensin-aldosterone system (RAAS) to slow CKD progression ~~to end-stage~~  
6 ~~renal disease (ESRD)~~.<sup>2-8</sup> BP control and RAAS inhibitor use are therefore major goals in the  
7 management of patients with CKD,<sup>9</sup> although no consensus exists about the ideal BP level.  
8 Current guidelines agree on a systolic/diastolic BP target of less than 140/90 mm Hg in CKD  
9 patients without diabetes and albuminuria, but whether lower levels should be recommended  
10 for those with these conditions remains controversial.<sup>9-15</sup> Results from the SPRINT trial<sup>4</sup> and  
11 from recent ~~systematic reviews with~~ meta-analyses<sup>5,16</sup> suggest that patients with a broad  
12 spectrum of comorbidities, including CKD, may benefit from systolic BP as low as 120  
13 mm Hg. At the same time, there is concern about ~~intolerance and~~ adverse effects from  
14 aggressive BP lowering in frail or elderly individuals, and higher BP targets are therefore  
15 considered for this population.<sup>9,14</sup> Information about current practices in BP control and  
16 antihypertensive therapy in CKD worldwide remains sparse.

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

26 The international Network of Chronic Kidney Disease (iNET-CKD) cohort studies is an  
27 open network of independently funded CKD cohort studies. Endorsed by the International

1 Society of Nephrology, it was established to promote collaborative research, foster exchange  
2 of expertise, and create opportunities for research training.<sup>26</sup> We used data from these  
3 cohorts to conduct international comparisons of the prevalence of uncontrolled BP in adults  
4 with CKD before and after adjustment for well-known risk factors for poor hypertension  
5 control. We also described patterns of antihypertensive therapy prescription by study cohort  
6 and world region ~~in this population~~.

## 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, The percentage of individuals with a high educational level ( $\geq 12$  years of formal education) ranged from 0 to 70%, and diabetes prevalence from 20 to 100%, depending on the background population or study design. Median BMI was lowest (23 to 26 kg/m<sup>2</sup>) in cohort studies from Asia and highest (31 kg/m<sup>2</sup>) in those from the US. Overall, current smoking was uncommon, except in the Chinese C-STRIDE cohort where the observed high prevalence may be attributed to the pooling of current and former smokers. Prevalence of moderate and severe albuminuria (KDIGO A2 or A3) varied widely across cohort studies, from 20% in the incident Uruguayan NRHP to 91% in the Japanese CKD-JAC.~~

### ~~Table 1. Patient characteristics by study.~~

### 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. ~~Thus the lowest and highest prevalence rates differed by a factor of 1.4 for BP  $\geq 130/80$  mm Hg, by 2.2 for BP  $\geq 140/90$  mm Hg, and by 5.4 for BP  $\geq 150/90$  mm Hg in participants, all aged 60 years or older.~~ 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.

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

#### 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 Supp Tables 3 and 4). 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 that in CKD-REIN 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 the prevalence ratio of uncontrolled hypertension was highest in the ICKD cohort and then in most of the European studies (CKD-REIN, German GCKD, and PSI-BIND Netherlands). 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, the GCKD prevalence ratio in the German CKD study notably exceeded those from other studies (+54%, Supp Table 5). Consistently, prevalence ratios of uncontrolled hypertension (regardless of threshold or adjustment model) were significantly lower than 1 in cohorts from North America (US CRIC and CKDepps, CanPREDDICT), high-income Asia (KNOW-CKD, CKD-JAC), and Australia (CKD-QLD). Meta-regression analyses showed that adjusted prevalence ratios of BP  $\geq 140/90$  mm Hg were not associated with neither the year at study start ( $R^2$  5.6%,  $p=0.13$ , Figure 2) nor the type of BP measurement ( $R^2$  0.0%,  $p=0.67$ ). Adjusted odds ratios for uncontrolled hypertension associated with known risk factors were quite similar between BP  $\geq 130/80$  and  $\geq 140/90$  mm Hg (Supp Tables 6 and 7). Except for albuminuria and education, they tended to be non-significant for BP  $\geq 150/90$  mm Hg in individuals aged 60 or over (Supp Table 8).

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

### **Antihypertensive drugs prescribed**

The number of antihypertensive drug classes ~~prescribed~~ was highest in the cohorts from North America, where more than ~~60~~50% of individuals ~~were using~~had 3 drug classes or more (Figure 3, Supp Table 9). ~~Notably, 50% of CRIC participants were taking  $\geq 4$  drug classes.~~

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 lowest number of antihypertensive drug classes ~~prescribed~~: nearly 40% of participants ~~took~~had only one drug class. The most ~~used~~prescribed antihypertensive 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%). Asian cohorts also stood out for their high ~~use~~frequency of calcium-channel blockers (53 to 75%). Beta-blocker ~~use~~prescription ranged from 22% in CKD-JAC to 70% in CKDopps Germany, ~~with no evident pattern regarding world region. Wide variation was observed for and that of other~~ antihypertensive drug classes, from 2% in incident NRHP to 41% in CKDopps US. RAAS inhibitors were the drug class most frequently chosen for single-agent therapy, ~~except in the CRIC study in which no participant received RAAS inhibitors alone~~ (Table 3, Supp Tables 10.1 to 10.17). Overall, RAAS inhibitors were more often associated with diuretics, followed by calcium-channel blockers and beta-blockers at equal rates.

~~Figure 2. Number of antihypertensive drug classes prescribed by study.~~

~~Figure 3. Type of antihypertensive drug classes prescribed by study.~~

~~Table 3. Patterns of antihypertensive drug prescription.~~

## 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 individual 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 used-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 in which half the participants use four drug classes 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, with regional differences more pronounced in men than women. 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) and restricted to 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 ~~seven studies in four countries~~~~different countries even after adjusting for age, sex, eGFR and diabetes.~~<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. It also revealed that European participants had highest likelihood of white-coat hypertension, suggesting that clinic BP may be particularly overestimated in this population. Compared with CKD-JAC participants, CRIC study participants were less likely to have masked hypertension, but had similar prevalence of sustained hypertension, participants in the African American Study of Kidney Disease and Hypertension Cohort Study (AASK) were more likely to have masked and sustained hypertension, and those from the Italian and Spanish studies, less likely.

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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. But 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. ~~Because the composition of the cohorts might well influence BP control rates, we adjusted analyses for several major risk factors of high BP. Although this did not change the overall geographical pattern of BP control, adjustment for potential confounders brought several interesting points to light. For instance, after adjustment, the observed to expected prevalence of BP ≥140/90 mm Hg increased in cohorts from India (ICKD) and Uruguay (NRHP), while that from both Thailand (CORE-CKD) and the UK (RRID)~~

1 ~~became close to one. Adjustment also substantially reduced heterogeneity in prevalence~~  
2 ~~ratios across European cohorts, with albuminuria the most important confounder.~~  
3 ~~Nonetheless, variation in hypertension control among CKD patients remained largely~~  
4 ~~unexplained. The adoption of different BP targets in some populations might contribute in~~  
5 ~~part to these findings. An analysis by Wolf-Meyer et al. in the general population<sup>30</sup> showed~~  
6 ~~that the gap in hypertension control between North American and European countries was~~  
7 ~~more pronounced for the BP threshold of 140/90 mm Hg than for that of 160/95 mm Hg,~~  
8 ~~which was accompanied by a similar trend in hypertension treatment rates. Interestingly, in~~  
9 ~~our analyses, the higher the target BP, the higher the variation in hypertension control, a~~  
10 ~~finding that does not support this hypothesis.~~

11 Hypertension control may be more difficult to achieve in some specific groups that are  
12 overrepresented among CKD patients, such as the elderly, men, and individuals with  
13 established cardiovascular disease or diabetes.<sup>10</sup> It may be strongly related to individuals'  
14 lifestyle, including weight control and smoking cessation. Furthermore, in patients with CKD,  
15 blood pressure levels are influenced by eGFR and albuminuria level.<sup>18,24</sup> In our study,  
16 prevalence of the studied risk factors for uncontrolled hypertension differed greatly across  
17 cohorts. Nevertheless, these differences only partly explained the observed international  
18 variations in hypertension control in moderate to severe CKD. Likewise, the recruitment  
19 period and the type of BP measurement accounted for only a small portion of the  
20 heterogeneity across cohort studies. The adoption of different BP targets in some

21 populations might contribute in part to ~~these~~ this findings ~~heterogeneity~~. An analysis by Wolf-  
22 Meyer et al. in the general population<sup>30</sup> showed that the gap in hypertension control between  
23 North American and European countries was more pronounced for the BP threshold of  
24 140/90 mm Hg than for that of 160/95 mm Hg, which was accompanied by a similar trend in  
25 hypertension treatment rates. Interestingly, in our analyses, the higher the target BP, the  
26 higher the variation in hypertension control, a finding that does not support this hypothesis.

27 Although ~~unstudied geographical specificities characteristics~~ including genetics,<sup>35</sup>  
28 diet,<sup>36</sup> economic level,<sup>28</sup> and public health policies<sup>37</sup> certainly contribute to ~~these~~ international

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1 variations in hypertension control, patterns of antihypertensive drug prescription in CKD are  
2 likely to play an important role in our findings. Evidence from randomized clinical trials and  
3 observational studies indicates that most CKD patients will require at least 2 antihypertensive  
4 agents to achieve adequate hypertension control.<sup>9</sup> In our study, ~~a relatively better rate of~~  
5 ~~hypertension control — around 45% for BP < 130/80 mm Hg in the US CRIC study — was~~  
6 ~~accompanied by a much more aggressive antihypertensive strategy than in other study~~  
7 ~~cohorts: 50% of CRIC participants had ≥4 antihypertensive drugs classes prescribed. The~~  
8 ~~much lower rate of hypertension control at <130/80 mm Hg and the similarly lower number of~~  
9 ~~antihypertensive drug classes prescribed in CKDopps US suggest the importance of the~~  
10 ~~study setting (academic centers in the CRIC study versus nonacademic in CKDopps). Half~~  
11 ~~half~~ the participants in ~~study~~ cohorts with poor BP control (prevalence ratios <1) ~~were~~  
12 ~~using~~had at most 2 antihypertensive agents (except for participants in PROVALID and  
13 CKDopps DE). In Asian cohorts, the number of antihypertensive drug classes prescribed was  
14 also relatively low, but among them, target BP was more often achieved in those with ~~higher~~  
15 ~~more aggressive~~ antihypertensive ~~drug use~~treatment. This is, however, an ecological  
16 comparison and may be confounded by other factors.

17 RAAS inhibitors have been consistently recommended as the first-choice drug for  
18 hypertension management in CKD patients, particularly because of its renoprotective effect  
19 via proteinuria reduction.<sup>9,13,15</sup> Our results suggest quite good compliance with this  
20 recommendation across all the cohorts we analyzed. The frequency of RAAS inhibitor ~~use~~  
21 prescription was even surprisingly high in some cohorts given their mean eGFR: in CKD-  
22 JAC, for example (mean eGFR 26 ml/min/1.73m<sup>2</sup>), 89% of participants ~~used~~were prescribed  
23 RAAS inhibitors. For similar mean eGFR, the frequency of RAAS inhibitors across study  
24 cohorts fell to values as low as 54%, which is suggestive of underuse in some settings. GFR  
25 decrease and related risk of hyperkalemia or acute kidney injury may cause concern when  
26 prescribing RAAS inhibitors for patients with more severe CKD, since current evidence on  
27 their benefit-risk balance is contradictory.<sup>38–40</sup> Furthermore, it has been suggested that the

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1 type of physician may have an impact on the compliance with the RAAS inhibition  
2 recommendation in CKD.<sup>41–43</sup>

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3 Prescription patterns for other drug classes were heterogeneous. In particular, we  
4 showed that CCB was the second most frequently preferred-prescribed drug class in Asian  
5 cohorts, apparently mainly at the expense of diuretics~~-use~~. Some guidelines (either for CKD  
6 or hypertension management)<sup>13,15,44</sup> recommend a specific second drug in antihypertensive  
7 treatment more strongly than others do.<sup>9,45,46</sup> Hence, CCB use is recommended in Japan,  
8 Thailand, and UK, likely because of findings from the ACCOMPLISH trial, in which benazepril  
9 plus amlodipine was associated with better cardiovascular<sup>47</sup> and renal<sup>48</sup> outcomes than

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10 benazepril plus hydrochlorothiazide. Most guidelines emphasize individualization of  
11 treatment based on comorbidities, side effects, and other factors including drug availability.  
12 The highest prevalence of cardiovascular disease, including coronary artery disease and  
13 congestive heart failure, may at least partly explain the highest use of beta-blockers in some  
14 cohorts. But more subjective factors, such as prescriber preferences, may play a key role in  
15 treatment patterns. However, most guidelines emphasize individualization of treatment based  
16 on comorbidities, side effects, and other factors including drug availability and thus leave  
17 room for prescriber preferences. An analysis of national prescribing profiles in hypertension  
18 showed that prescription patterns varied among countries, notably with more frequent use of  
19 thiazide diuretics in the UK than in Norway, Germany, or France, and consumption of alpha-  
20 blockers twice as high in Norway than in any other country studied.<sup>49</sup> That study also asked

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21 clinical researchers and professionals in drug regulatory agencies about the possible  
22 reasons for these variations. Although factors such as clinical guidelines, the availability of  
23 generic drugs, and cost-awareness were recognized as potential explanatory variables,  
24 pharmaceutical marketing was considered to be the main driver for prescribing choices.

## 25 **Strengths and limitations**

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

This study also has limitations. ~~First, d~~ 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 a world region suggest that this was not a major source of bias. ~~Second, m~~ 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 neither efficacy nor precision in our models. ~~Third, w~~ 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 considerable heterogeneity in both type and number of antihypertensive drug classes

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

## 1   **Methods**

### 2   **Study design**

3           iNET-CKD membership prerequisites have been detailed elsewhere.<sup>26</sup> iNET-CKD  
4 includes observational studies with defined objectives, patient-level information, and  
5 prospective data collection, and focuses on individuals with predialysis CKD. The present  
6 analysis consists of baseline data from 17 studies including participants aged ≥18 years, with  
7 eGFR <60 ml/min/1.73m<sup>2</sup> (neither dialyzed nor transplanted) and treated hypertension (under  
8 antihypertensive drug use). Information about study country, recruitment years, target  
9 population, and prevalence of treated hypertension is summarized in Supp Table 1.

### 10   **Study variables**

11           A variable dictionary was sent to each participating cohort study in order to harmonize  
12 data regarding covariate definitions, labelling, and coding (Appendix 2). Glomerular filtration  
13 was estimated with ~~either the~~ CKD-EPI<sup>50</sup> equation, except in CanPREDDICT and CKD-JAC  
14 studies, in whicher the MDRD<sup>51</sup> equation and the 3-variable Japanese equation<sup>52</sup> were used,  
15 respectively. Albuminuria (or equivalent) was classified according to the Kidney Disease  
16 Improving Global Outcomes (KDIGO) 2012 guideline stages as A1 (normal to mildly  
17 increased), A2 (moderately increased), or A3 (severely increased).<sup>9</sup> Body mass index (BMI)  
18 was calculated as weight (Kg) divided by square height (m). Diabetes was defined as serum  
19 fasting glucose ≥7.0 mmol/L (≥126 mg/dl), non-fasting glucose ≥11.1 mmol/l (≥200 mg/dl),  
20 glycated hemoglobin A1c ≥6.5%, or use of glucose-lowering drugs. If such information was  
21 not available, diabetes was identified by self-report or medical records. History of  
22 cardiovascular disease was defined as history of coronary artery disease, prior  
23 revascularization, heart failure, stroke or peripheral vascular disease. Education levels  
24 corresponded to the number of years of formal education reported by the participant at the  
25 baseline visit. Smoking status was dichotomized into current and not current smoking, except  
26 for one study in which participants were classified as ever or never smokers.

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

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BP assessment method for each study is described in Supp Table 1. 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 ~~in-use~~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 ~~use~~prescribed. For each study, we also asked 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 have 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 ratios correspond to the ratio of the true prevalence of uncontrolled BP for a given study



1 cohort according to the model (predicted mean), divided by the prevalence that would be  
2 expected for a hypothetical cohort with the same case-mix and an intercept parameter equal  
3 to the population average (marginal mean)<sup>53</sup>. The respective 95% confidence intervals were  
4 estimated with bias-corrected bootstrap methods. All adjustment variables were not available  
5 for some of the participating studies, either because they were not collected or because they  
6 were missing for  $\geq 20\%$  of participants. Thus, we performed three adjustment models: ~~(the~~  
7 ~~first including 4age, gender, diabetes, and eGFR (4-covariate model), the second further~~  
8 ~~including albuminuria level, cardiovascular disease, and obesity status (7-covariate model),~~  
9 ~~and the third one further including smoking status and educational level or (9-covariate~~  
10 ~~models).~~ ~~which~~ These adjustment models included a different set of studies depending on  
11 variable availability (17, 14, or 10 studies, respectively). ~~We also ran crude models~~  
12 ~~corresponding to each of these sets of studies.~~ ~~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 surrogate of year at BP measurement, and on the type of~~  
16 ~~BP measurement.~~ Antihypertensive drugs were described in terms of number and type of  
17 drug classes ~~in use~~. Two-sided significance tests were used and  $P$ -values  $< 0.05$  were  
18 considered significant. ~~All s~~ Statistical analyses were performed with SAS 9.4 (SAS Institute  
19 Inc, Cary, NC) ~~and R, version 3.5.0.~~

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## 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 ~~Supplementary Table 4~~[Appendix 1 of](#)  
4 [the supplementary material](#).

## References

1. Bakris GL, Ritz E. The message for World Kidney Day 2009: hypertension and kidney disease: a marriage that should be prevented. *Kidney Int.* 2009;75(5):449-452. doi:10.1038/ki.2008.694
2. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence in hypertension: 10 - Should blood pressure management differ in hypertensive patients with and without diabetes mellitus? Overview and meta-analyses of randomized trials. *J Hypertens.* 2017;35(5):922-944. doi:10.1097/HJH.0000000000001276
3. Ku E, Gassman J, Appel LJ, et al. BP Control and Long-Term Risk of ESRD and Mortality. *J Am Soc Nephrol JASN.* 2017;28(2):671-677. doi:10.1681/ASN.2016030326
4. SPRINT Research Group, Wright JT, Williamson JD, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med.* 2015;373(22):2103-2116. doi:10.1056/NEJMoa1511939
5. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet.* 2016;387(10022):957-967. doi:10.1016/S0140-6736(15)01225-8
6. Ku E, Glidden DV, Johansen KL, et al. Association between strict blood pressure control during chronic kidney disease and lower mortality after onset of end-stage renal disease. *Kidney Int.* 2015;87(5):1055-1060. doi:10.1038/ki.2014.376
7. Blood Pressure Lowering Treatment Trialists' Collaboration, Ninomiya T, Perkovic V, et al. Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: meta-analysis of randomised controlled trials. *BMJ.* 2013;347:f5680.
8. Casas JP, Chua W, Loukogeorgakis S, et al. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. *Lancet Lond Engl.* 2005;366(9502):2026-2033. doi:10.1016/S0140-6736(05)67814-2
9. KDIGO (Kidney Disease: Improving Global Outcomes). Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl.* 2013;3:1-150.
10. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J.* August 2018. doi:10.1093/eurheartj/ehy339
11. Whelton PK, Carey RM. The 2017 Clinical Practice Guideline for High Blood Pressure. *JAMA.* 2017;318(21):2073-2074. doi:10.1001/jama.2017.18209
12. National Heart Foundation of Australia. Guideline for the diagnosis and management of hypertension in adults – 2016. [https://www.heartfoundation.org.au/images/uploads/publications/PRO-167\\_Hypertension-guideline-2016\\_WEB.pdf](https://www.heartfoundation.org.au/images/uploads/publications/PRO-167_Hypertension-guideline-2016_WEB.pdf). Accessed September 19, 2017.

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13. Shimamoto K, Ando K, Fujita T, et al. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014). *Hypertens Res Off J Jpn Soc Hypertens*. 2014;37(4):253-390. doi:10.1038/hr.2014.20
14. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311(5):507-520. doi:10.1001/jama.2013.284427
15. Chronic kidney disease in adults: assessment and management | Guidance and guidelines | NICE. <https://www.nice.org.uk/guidance/cg182/chapter/1-Recommendations#pharmacotherapy>. Accessed September 19, 2017.
16. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. *Lancet Lond Engl*. 2016;387(10017):435-443. doi:10.1016/S0140-6736(15)00805-3
17. Lee S, Oh HJ, Lee E-K, et al. Blood Pressure Control During Chronic Kidney Disease Progression. *Am J Hypertens*. 2017;30(6):610-616. doi:10.1093/ajh/hpx017
18. Muntner P, Anderson A, Charleston J, et al. Hypertension awareness, treatment, and control in adults with CKD: results from the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am J Kidney Dis Off J Natl Kidney Found*. 2010;55(3):441-451. doi:10.1053/j.ajkd.2009.09.014
19. Muntner P, Judd SE, Krousel-Wood M, McClellan WM, Safford MM. Low medication adherence and hypertension control among adults with CKD: data from the REGARDS (Reasons for Geographic and Racial Differences in Stroke) Study. *Am J Kidney Dis Off J Natl Kidney Found*. 2010;56(3):447-457. doi:10.1053/j.ajkd.2010.02.348
20. Altun B, Süleymanlar G, Utaş C, et al. Prevalence, awareness, treatment and control of hypertension in adults with chronic kidney disease in Turkey: results from the CREDIT study. *Kidney Blood Press Res*. 2012;36(1):36-46. doi:10.1159/000339025
21. Fraser SDS, Roderick PJ, McIntyre NJ, et al. Suboptimal blood pressure control in chronic kidney disease stage 3: baseline data from a cohort study in primary care. *BMC Fam Pract*. 2013;14:88. doi:10.1186/1471-2296-14-88
22. Titze S, Schmid M, Köttgen A, et al. Disease burden and risk profile in referred patients with moderate chronic kidney disease: composition of the German Chronic Kidney Disease (GCKD) cohort. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc*. 2015;30(3):441-451. doi:10.1093/ndt/gfu294
23. Konta T, Ikeda A, Ichikawa K, et al. Blood pressure control in a Japanese population with chronic kidney disease: a baseline survey of a nationwide cohort. *Am J Hypertens*. 2012;25(3):342-347. doi:10.1038/ajh.2011.217
24. Cai G, Zheng Y, Sun X, Chen X. Survey of Prevalence, Awareness, and Treatment Rates in Chronic Kidney Disease Patients with Hypertension in China Collaborative Group. Prevalence, awareness, treatment, and control of hypertension in elderly adults with chronic kidney disease: results from the survey of Prevalence, Awareness, and Treatment Rates in Chronic Kidney Disease Patients with Hypertension in China. *J Am Geriatr Soc*. 2013;61(12):2160-2167.

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25. Zhang W, Shi W, Liu Z, et al. A nationwide cross-sectional survey on prevalence, management and pharmacoepidemiology patterns on hypertension in Chinese patients with chronic kidney disease. *Sci Rep*. 2016;6:38768. doi:10.1038/srep38768
26. Dienemann T, Fujii N, Orlandi P, et al. International Network of Chronic Kidney Disease cohort studies (iNET-CKD): a global network of chronic kidney disease cohorts. *BMC Nephrol*. 2016;17:121. doi:10.1186/s12882-016-0335-2
27. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. *Lancet Lond Engl*. 2017;389(10064):37-55. doi:10.1016/S0140-6736(16)31919-5
28. Mills KT, Bundy JD, Kelly TN, et al. Global Disparities of Hypertension Prevalence and Control: A Systematic Analysis of Population-Based Studies From 90 Countries. *Circulation*. 2016;134(6):441-450. doi:10.1161/CIRCULATIONAHA.115.018912
29. Joffres M, Falaschetti E, Gillespie C, et al. Hypertension prevalence, awareness, treatment and control in national surveys from England, the USA and Canada, and correlation with stroke and ischaemic heart disease mortality: a cross-sectional study. *BMJ Open*. 2013;3(8):e003423. doi:10.1136/bmjopen-2013-003423
30. Wolf-Maier K, Cooper RS, Kramer H, et al. Hypertension treatment and control in five European countries, Canada, and the United States. *Hypertension*. 2004;43(1):10-17. doi:10.1161/01.HYP.0000103630.72812.10
31. Robinson BM, Tong L, Zhang J, et al. Blood pressure levels and mortality risk among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. *Kidney Int*. 2012;82(5):570-580. doi:10.1038/ki.2012.136
32. Duranton F, Kramer A, Szwarc I, et al. Geographical Variations in Blood Pressure Level and Seasonality in Hemodialysis Patients. *Hypertens Dallas Tex* 1979. 2018;71(2):289-296. doi:10.1161/HYPERTENSIONAHA.117.10274
33. Drawz PE, Brown R, De Nicola L, et al. Variations in 24-Hour BP Profiles in Cohorts of Patients with Kidney Disease around the World: The I-DARE Study. *Clin J Am Soc Nephrol CJASN*. 2018;13(9):1348-1357. doi:10.2215/CJN.13181117
34. Sarafidis PA, Li S, Chen S-C, et al. Hypertension awareness, treatment, and control in chronic kidney disease. *Am J Med*. 2008;121(4):332-340. doi:10.1016/j.amjmed.2007.11.025
35. Casiglia E, Tikhonoff V. Do genetics help epidemiologists? Arterial hypertension and cardiovascular events in the light of genetic demiology. *Hypertens Res Off J Jpn Soc Hypertens*. 2018;41(5):320-322. doi:10.1038/s41440-018-0022-8
36. Mente A, O'Donnell MJ, Rangarajan S, et al. Association of urinary sodium and potassium excretion with blood pressure. *N Engl J Med*. 2014;371(7):601-611. doi:10.1056/NEJMoa1311989
37. Karunaratne K, Stevens P, Irving J, et al. The impact of pay for performance on the control of blood pressure in people with chronic kidney disease stage 3-5. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc*. 2013;28(8):2107-2116. doi:10.1093/ndt/gft093

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38. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med.* 2000;160(5):685-693.
39. Hsu T-W, Liu J-S, Hung S-C, et al. Renoprotective effect of renin-angiotensin-aldosterone system blockade in patients with predialysis advanced chronic kidney disease, hypertension, and anemia. *JAMA Intern Med.* 2014;174(3):347-354. doi:10.1001/jamainternmed.2013.12700
40. Schmidt M, Mansfield KE, Bhaskaran K, et al. Serum creatinine elevation after renin-angiotensin system blockade and long term cardiorenal risks: cohort study. *BMJ.* 2017;356:j791.
41. Ricardo AC, Roy JA, Tao K, et al. Influence of Nephrologist Care on Management and Outcomes in Adults with Chronic Kidney Disease. *J Gen Intern Med.* 2016;31(1):22-29. doi:10.1007/s11606-015-3452-x
42. Samal L, Wright A, Waikar SS, Linder JA. Nephrology co-management versus primary care solo management for early chronic kidney disease: a retrospective cross-sectional analysis. *BMC Nephrol.* 2015;16:162. doi:10.1186/s12882-015-0154-x
43. Philipneri MD, Rocca Rey LA, Schnitzler MA, et al. Delivery patterns of recommended chronic kidney disease care in clinical practice: administrative claims-based analysis and systematic literature review. *Clin Exp Nephrol.* 2008;12(1):41-52. doi:10.1007/s10157-007-0016-3
44. Buranakitjaroen P, Wataganara T, Bunnag P, Puavilai W, Tejavaniya S. 2015 Thai Hypertension Guideline. <http://www.thaihypertension.org/files/2015%20Thai%20Hypertension%20Guideline.pdf>. Accessed May 24, 2018.
45. Task Force of the Latin American Society of Hypertension. Guidelines on the management of arterial hypertension and related comorbidities in Latin America. *J Hypertens.* 2017;35(8):1529-1545. doi:10.1097/HJH.0000000000001418
46. Shin J, Park JB, Kim K-I, et al. 2013 Korean Society of Hypertension guidelines for the management of hypertension: part III-hypertension in special situations. *Clin Hypertens.* 2015;21:3. doi:10.1186/s40885-014-0014-1
47. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med.* 2008;359(23):2417-2428. doi:10.1056/NEJMoa0806182
48. Bakris GL, Sarafidis PA, Weir MR, et al. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomised controlled trial. *Lancet Lond Engl.* 2010;375(9721):1173-1181. doi:10.1016/S0140-6736(09)62100-0
49. Fretheim A, Oxman AD. International variation in prescribing antihypertensive drugs: its extent and possible explanations. *BMC Health Serv Res.* 2005;5(1):21. doi:10.1186/1472-6963-5-21
50. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604-612.

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51. Levey AS, Greene T, Kusek JW, Beck GJ. A simplified equation to predict glomerular filtration rate from serum creatinine. *J Am Soc Nephrol*. 2000;11:155A.
52. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis Off J Natl Kidney Found*. 2009;53(6):982-992. doi:10.1053/j.ajkd.2008.12.034
53. Shahian DM, Normand S-LT. Comparison of "risk-adjusted" hospital outcomes. *Circulation*. 2008;117(15):1955-1963. doi:10.1161/CIRCULATIONAHA.107.747873

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

\*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= 87199006, 25.726.5%)	2 (n= 1108411360, 32.733.5%)	3 (n= 82698512, 24.425.1%)	≥4 (n= 58545048, 17.314.9%)	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%)
RAAS inhibitors	66.3%65.2%	71.1%70.3%	84.2%83.7%	93.4%94.3%	21.923.0%, alone	74.1%	68.7%	69.9%	64.9%
Diuretics	9.4%9.7%	53.7%52.7%	79.1%76.5%	91.7%90.6%	52.3%	4.6%, alone	56.1%	63.9%	69.1%
CCB	14.2%14.6%	35.1%34.9%	57.2%56.4%	89.3%83.4%	38.8%	44.9%	8.7%, alone	47.0%	63.0%
β-blockers	9.3%9.6%	32.6%32.1%	63.2%60.7%	85.0%82.0%	38.3%	49.6%	45.6%	5.9%, alone	54.5%
Other	0.9%0.9%	4.9%5.0%	10.3%10.4%	40.1%35.4%	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.

## Supplementary data

**Supplementary table 1.** Acknowledgement and funding for collaborating cohorts.

**Supplementary table 2.** Study description.

**Supplementary table 3.** Missing covariates, by study.

**Supplementary Table 4.** Crude and adjusted prevalence ratios of uncontrolled blood pressure  $\geq 130/80$  mm Hg, by study.

**Supplementary Table 5.** Crude and adjusted prevalence ratios of uncontrolled blood pressure  $\geq 140/90$  mm Hg, by study.

**Supplementary Table 6.** 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 7.** Adjusted odds ratios of uncontrolled blood pressure  $\geq 130/80$  mm Hg associated with patient characteristics.

**Supplementary Table 8.** Adjusted odds ratios of uncontrolled blood pressure  $\geq 140/90$  mm Hg associated with patient characteristics.

**Supplementary Table 9.** 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 10.** Number and type of antihypertensive drug classes prescribed by study.

**Supplementary tables 11.1 to 11.17.** Patterns of antihypertensive drug prescription. On the left, frequency of each antihypertensive drug class according to the number of classes prescribed.