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

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1 **Abstract**

2 Although blood pressure control is a major goal in chronic kidney disease, no worldwide
3 overview of either its achievement or antihypertensive prescriptions is currently available. To
4 evaluate this we compared crude prevalence of uncontrolled blood pressure among 17 cohort
5 studies, including 34 602 individuals with estimated glomerular filtration rate under 60
6 ml/min/1.73m² and treated hypertension across four continents, and estimated observed to
7 expected prevalence ratios, adjusted for potential confounders. Crude prevalence of blood
8 pressure of 140/90 mm Hg or more varied from 28% to 61% and of blood pressure of 130/80
9 or more from 54% to 84%. Adjusted prevalence ratios indicated poorer hypertension control
10 than expected in cohorts from European countries, India, and Uruguay, and better control in
11 patients from North American and high-income Asian countries. Four antihypertensive drug
12 classes or more were prescribed to more than 30% of participants in North American and
13 some European cohorts, but this practice was less common elsewhere. Renin angiotensin
14 aldosterone system inhibitors were the most common antihypertensive drugs, prescribed for
15 54% to 91% of cohort participants. Differences for other drug classes were much stronger,
16 ranging from 11% to 79% for diuretics, 22% to 70% for beta-blockers, and 27% to 75% for
17 calcium-channel blockers. The confounders studied explain only a part of the international
18 variation in blood pressure control among individuals with chronic kidney disease. Thus,
19 considerable heterogeneity in prescription patterns worldwide calls for further investigation
20 into the impact of different approaches on patient outcomes.

21

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

1 **Introduction**

2 Arterial hypertension is prevalent in chronic kidney disease (CKD) and contributes to
3 its adverse outcomes.¹ 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.²⁻⁸ BP control and RAAS
6 inhibitor use are therefore major goals in the management of patients with CKD,⁹ 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.⁹⁻¹⁵ Results from the SPRINT trial⁴ and from recent meta-analyses^{5,16} 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.^{9,14} 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 Korea¹⁷ and the US^{18,19} to more than
19 70% in Turkey²⁰; that of BP above 130/80 mm Hg varies from 55% to 65% in the US,^{18,19}
20 65% in the UK,²¹ 75% in Germany,²² 80% in Japan,²³ and close to 90% in China.^{24,25} 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.²⁶ 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.

1 **Results**

2 **Participant characteristics by study**

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

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

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

20 **Prevalence ratios of uncontrolled hypertension**

21 Ratios of observed to expected prevalence rates of uncontrolled hypertension were not
22 substantially affected by adjustment for age, gender, diabetes, and eGFR, regardless of BP
23 threshold (Figure 1A and Tables S1 and S2). In contrast, further adjustment for history of
24 cardiovascular disease, BMI, and most importantly for albuminuria (Figure 1B) increased the
25 prevalence ratios of BP \geq 140/90 mm Hg in the ICKD and NRHP incident cohorts (from +11%
26 to +26% and +10% to +23%, respectively), while in CKD-REIN it decreased from +39% to
27 +29%. In the UK RRID study and the Thai CORE-CKD, prevalence ratios of BP \geq 140/90

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

15 **Antihypertensive drugs prescribed**

16 The number of antihypertensive drug classes was highest in the cohorts from North America,
17 where more than 50% of individuals had 3 drug classes or more (Figure 3). This number was
18 also high in German cohorts (CKDopps and GCKD), PROVALID, and CKDopps Brazil.
19 CSTRIDE and NRHP (both incident and prevalent) cohorts had the fewest antihypertensive
20 drug classes: nearly 40% of participants had only one drug class. The most prescribed drug
21 class was that of RAAS inhibitors (Figure 4). Its frequency ranged from 54% in CKDopps US
22 to 91% in KNOW-CKD. Diuretics were more frequently prescribed to participants from
23 CKDopps Brazil (about 80%), and from European (52 to 78%) and North American cohorts
24 (66 to 74%). Conversely, their frequency was particularly low in Asian cohorts, especially
25 CSTRIDE (11%). Specifically, the use of mineralocorticoid receptor antagonists in cohorts
26 with available information ranged from $<1\%$ in ICKD to 9% in CKDopps-BR (Table S7). Asian
27 cohorts stood out for their high frequency of calcium-channel blockers (53 to 75%). Beta-
28 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.

1 **Discussion**

2 This study confirms the overall inadequate achievement of BP control in patients with
3 moderate and advanced CKD worldwide, but highlights large international variations that are
4 only partly explained by patient characteristics. The main novelty of the study is to show how
5 heterogeneous prescription patterns were across world regions, both in terms of the number
6 and types of antihypertensive drug classes, with the exception of RAAS inhibitors, which are
7 commonly prescribed as first-line treatment in all countries. Our finding that cohorts with the
8 highest number of prescribed antihypertensive drug classes also had the lowest prevalence
9 rates of uncontrolled BP $\geq 140/90$ points out room for improvement in many countries.
10 Nonetheless, the remaining prevalence of uncontrolled BP $\geq 130/80$ mm Hg above 50% in all
11 cohorts suggests that so low a BP target is unlikely to be achieved.

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

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

10 Our findings about international variations in office BP control among individuals with
11 earlier CKD stages (eGFR<60 ml/min/1.72m² not requiring renal replacement therapy) are
12 more consistent with those reported among the general population²⁷⁻³⁰ than among
13 hemodialysis patients.^{31,32} Hypertension control was poorer in cohorts in Europe, South
14 America, and India than in those in high-income Asia and North America. Overall, a
15 substantial portion of study participants had high BP: 28 to 61% ≥140/90 mm Hg and 64 to
16 84% ≥130/80 mm Hg. Hypertension control may be more difficult to achieve in some specific
17 groups that are overrepresented among CKD patients, such as the elderly, men, and
18 individuals with established cardiovascular disease or diabetes.¹⁰ It may be strongly related to
19 individuals' lifestyle, including weight control and smoking status. Furthermore, in patients
20 with CKD, blood pressure levels are influenced by eGFR and albuminuria level.^{18,24} In our
21 study, prevalence of the studied risk factors for uncontrolled hypertension differed greatly
22 across cohorts. Nevertheless, these differences only partly explained the observed
23 international variations in hypertension control in moderate to severe CKD. Likewise, the
24 recruitment period and the type of BP measurement accounted for only a small portion of the
25 heterogeneity across cohort studies. The adoption of different BP targets in some
26 populations might contribute in part to this heterogeneity. An analysis by Wolf-Meyer et al. in
27 the general population³⁰ showed that the gap in hypertension control between North
28 American and European countries was more pronounced for the BP threshold of 140/90

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

4 Although unstudied characteristics including genetics,³⁴ diet,³⁵ economic level,²⁸ and
5 public health policies³⁶ certainly contribute to these variations in hypertension control,
6 patterns of antihypertensive drug prescription in CKD are likely to play an important role in
7 our findings. Evidence from randomized clinical trials and observational studies indicates that
8 most CKD patients will require at least 2 antihypertensive agents to achieve adequate
9 hypertension control.⁹ In our study, half the participants in cohorts with poor BP control
10 (prevalence ratios >1) had at most 2 antihypertensive agents (except for participants in
11 PROVALID and CKDopps DE). In Asian cohorts, the number of antihypertensive drug
12 classes prescribed was also relatively low, but among them, target BP was more often
13 achieved in those with more aggressive antihypertensive treatment. This is, however, an
14 ecological comparison and may be confounded by other factors.

15 RAAS inhibitors have been consistently recommended as the first-choice drug for
16 hypertension management in CKD patients, particularly because of its renoprotective effect
17 via proteinuria reduction.^{9,13,15} Our results suggest quite good compliance with this
18 recommendation across all the cohorts we analyzed. The frequency of RAAS inhibitor
19 prescription was even surprisingly high in some cohorts given their mean eGFR: in CKD-
20 JAC, for example (mean eGFR 26 ml/min/1.73m²), 89% of participants were prescribed
21 RAAS inhibitors. For similar mean eGFR, the frequency of RAAS inhibitors across study
22 cohorts fell to values as low as 54%, which is suggestive of underuse in some settings. GFR
23 decrease and related risk of hyperkalemia or acute kidney injury may cause concern when
24 prescribing RAAS inhibitors for patients with more severe CKD, since current evidence on
25 their benefit-risk balance is contradictory.³⁷⁻³⁹ Furthermore, it has been suggested that the
26 type of physician (primary care physician versus nephrologist) may have an impact on
27 adherence to the RAAS inhibition recommendation for CKD patients.⁴⁰⁻⁴²

1 Prescription patterns for other drug classes were heterogeneous. In particular, we
2 showed that CCB was the second most frequently prescribed drug class in Asian cohorts,
3 apparently mainly at the expense of diuretics. Some guidelines (either for CKD or
4 hypertension management) ^{13,15,43} recommend a specific second drug in antihypertensive
5 treatment more strongly than others do. ^{9,44,45} Hence, CCB use is recommended in Japan,
6 Thailand, and UK, likely because of findings from the ACCOMPLISH trial, in which benazepril
7 plus amlodipine was associated with better cardiovascular⁴⁶ and renal⁴⁷ outcomes than
8 benazepril plus hydrochlorothiazide. Mineralocorticoid receptor antagonists are of particular
9 interest in the treatment of resistant hypertension.⁴⁸ They also have been shown to reduce
10 BP and proteinuria in adults with CKD in association with RAAS inhibitors, although with
11 increased risk of hyperkalemia.⁴⁹ In our study, the prescription of mineralocorticoid receptor
12 antagonists varied internationally, but was rather uncommon.

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

26 **Strengths and limitations**

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

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

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

26 **Conclusions**

27 Worldwide variation in hypertension control in patients with moderate to severe CKD
28 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.

1 **Methods**

2 **Study design**

3 iNET-CKD membership prerequisites have been detailed elsewhere.²⁶ 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/1.73m² (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 Table S9.

10 **Study variables**

11 A variable dictionary was sent to each participating cohort study in order to harmonize
12 data regarding covariate definitions, labeling, and coding (Appendix S1). Glomerular filtration
13 was estimated with the CKD-EPI⁵¹ equation, except in CanPREDDICT and CKD-JAC
14 studies, in which the MDRD⁵² equation and the 3-variable Japanese equation⁵³ 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).⁹ 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 $\geq 6.5\%$, 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**

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

9 **Statistical analyses**

10 To address the study aims, we asked each study cohort to provide descriptive
11 statistics regarding participants' characteristics and antihypertensive drug prescriptions. For
12 each study, we also asked for three datasets containing grouped information including the
13 number of participants having a particular profile, and respective number of participants with
14 uncontrolled BP (one dataset for each BP threshold). This was equivalent to having
15 individual data for each categorized covariate. Characteristics considered for participant
16 profiling were age (< 65 or ≥ 65 years), gender, diabetes, eGFR (≥ 30 or < 30 ml/min/1.73m²),
17 history of cardiovascular disease, BMI (< 30 or ≥ 30 kg/m²), albuminuria (A1, A2 or A3),
18 education attainment (< 12 or ≥ 12 years of formal education), and smoking status (current or
19 not). If 20% or more data was missing for a given variable, this variable was excluded from
20 the dataset. Any participant with missing information for the remaining variables was
21 excluded.

22 Using these data, we described participants' characteristics and BP control by study,
23 world region (Asia, Australia, Europe, North America, and South America), and recruitment
24 setting (nephrology or general practices). Categorical variables were presented as
25 percentages and continuous variables as means \pm standard deviations or medians
26 (interquartile range). Using mixed logistic regression models with study-specific random
27 intercepts and participant characteristics as fixed effects, we estimated prevalence ratios of
28 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) ⁵⁴. 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](http://www.kidney-international.org).

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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/m ² , median IQR)	Current smoking (%)	eGFR (ml/min/1.73m ² , 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**
Nephrology cohorts						
Asia						
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
Australia						
CKD-QLD	133.6 (20.2)	71.4 (11.6)	64.0	38.5	24.1	Office BP
Europe						
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
North America						
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
South America						
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
GP cohorts						
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%)
RAAS inhibitors	66.3%	71.1%	84.2%	93.4%	23.0%, alone	74.1%	68.7%	69.9%	64.9%
Diuretics	9.4%	53.7%	79.1%	91.7%	52.3%	4.6%, alone	56.1%	63.9%	69.1%
CCB	14.2%	35.1%	57.2%	89.3%	38.8%	44.9%	8.7%, alone	47.0%	63.0%
β-blockers	9.3%	32.6%	63.2%	85.0%	38.3%	49.6%	45.6%	5.9%, alone	54.5%
Other	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.

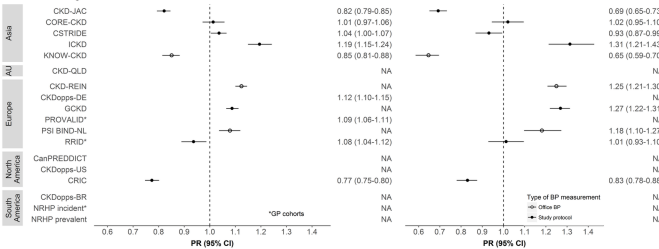
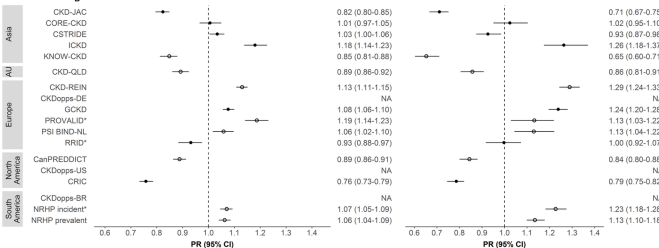
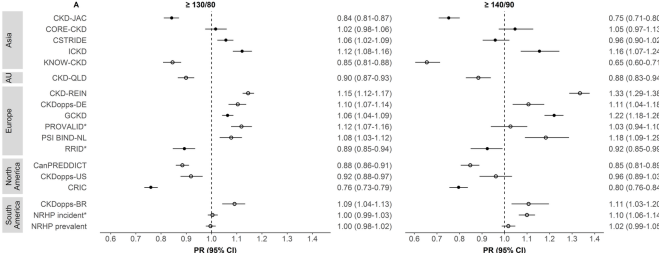
Prevalence ratio values above 1 indicate lower frequency of blood pressure control than expected, given study patient characteristics. R^2 , β , and p values were estimated with meta-regression analysis of prevalence ratios of uncontrolled blood pressure $\geq 140/90$ mm Hg adjusted for age, gender, 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.

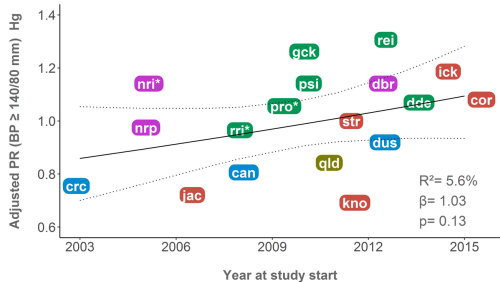
Figure 3. Number of antihypertensive drug classes prescribed by study.

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.

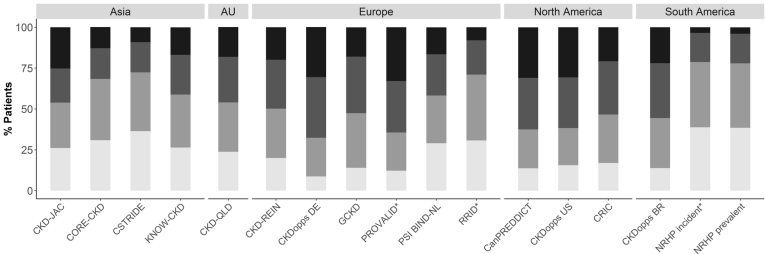




- a Asia
- a Australia
- a Europe
- a North America
- a South America

- 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
- rri = RRID
- *GP cohorts

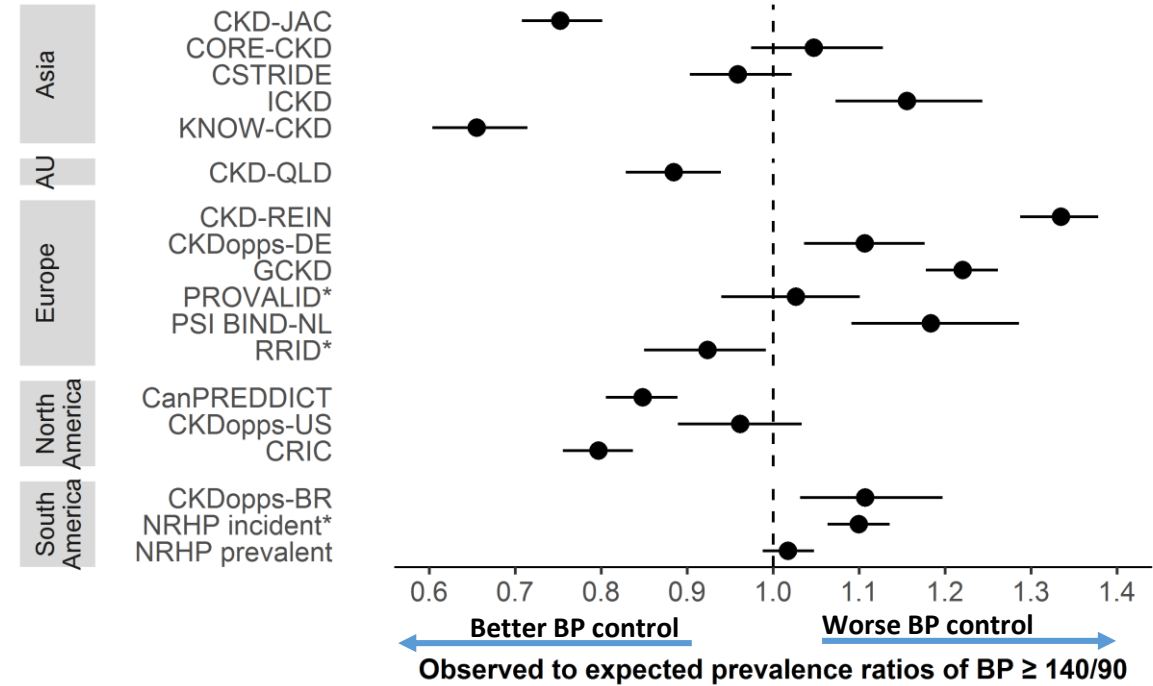
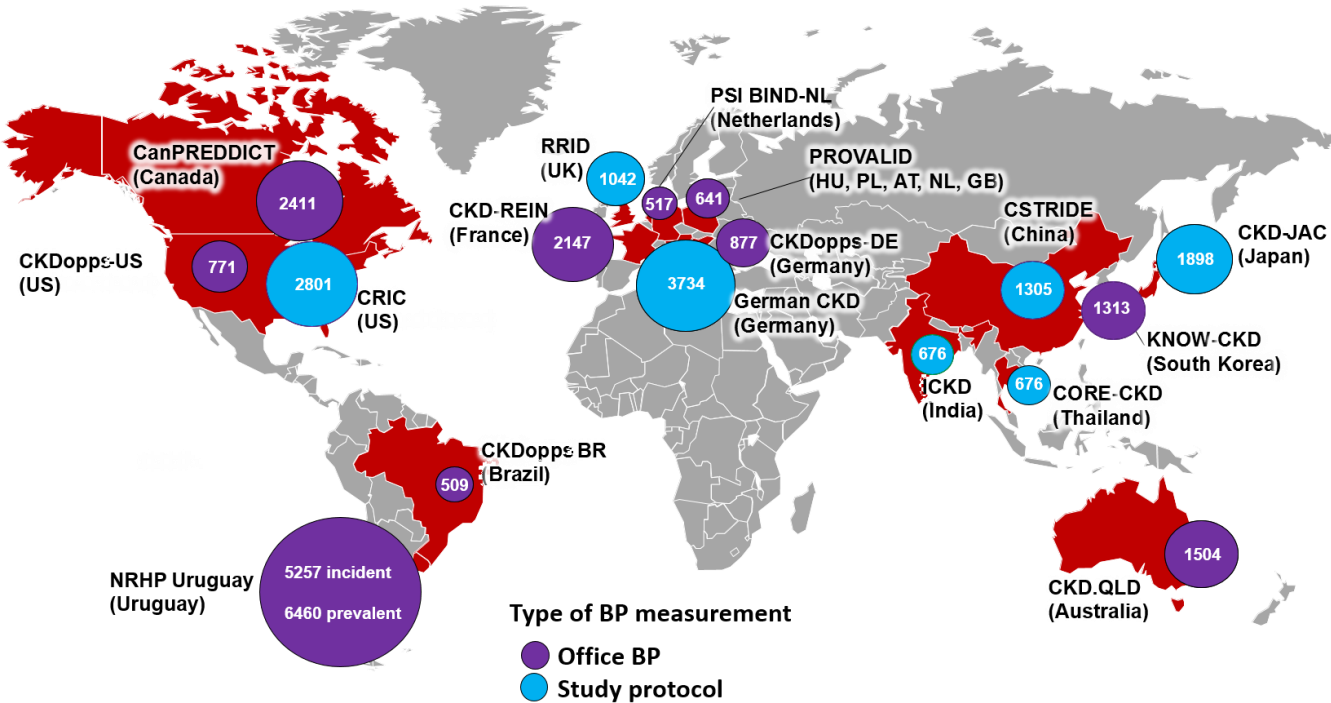
Number of drug classes



*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/1.73m² 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.