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Original Investigation

Hypertension and Prehypertension and Prediction of Development of Decreased Estimated GFR in the General Population: A Meta-analysis of Cohort Studies

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Background: Whether blood pressure (BP) plays an independent predictive role in the onset of decreased glomerular filtration rate (GFR) remains ill-defined because existing meta-analyses have incorporated data from studies that included individuals with low GFRs at baseline. This question is critical to optimize chronic kidney disease prevention in the general population.

Study Design: Systematic review and meta-analysis of longitudinal cohort studies.

Setting & Population: Adults from general population.

Selection Criteria for Studies: We identified in PubMed, EMBASE, and the Cochrane Library database all cohort studies evaluating the role of BP in the incidence of decreased estimated GFR (eGFR; defined as eGFR < 60 mL/min/1.73 m^2) in individuals without decreased kidney function at baseline.

Predictors: Hypertension (BP $>$ 140/90 mm Hg), prehypertension (systolic BP of 120-139 and/or diastolic BP of 80-89 mm Hg), and BP as a continuous variable.

Outcomes: Risk for decreased eGFR reported as relative risk (RR) and 95% CI. Heterogeneity (I^2) was also evaluated.

Results: Data from 16 cohorts (315,321 participants) were analyzed. All studies had a Newcastle-Ottawa score in the range of 6 to 8, denoting high quality. During a mean follow-up of 6.5 years, decreased eGFR occurred in 6.6% of participants. The presence of prehypertension and hypertension increased renal risk (RRs of 1.19 [95% CI, 1.07-1.33; $I^2 = 23.8\%$] and 1.76 [95% CI, 1.58-1.97; $I^2 = 37.7\%$], respectively). Similarly, we found that every 10–mm Hg increase in systolic and diastolic BPs associated with higher risk for decreased eGFR (RRs of 1.08 [95% CI, 1.04-1.11; $I^2 = 60.0\%$] and 1.12 [95% CI, 1.04-1.20; $I^2 = 51.4\%$], respectively). Metaregression analysis showed greater risk with older age ($P = 0.03$), whereas other covariates were not significant.

Limitations: No individual patient-level data.

Conclusions: Prehypertension and hypertension, as BP levels, are independent predictors of decreased GFR in the general population, with the effect being more pronounced in the elderly. These findings are important for improving risk stratification in the general population.

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INDEX WORDS: Hypertension; pre-hypertension; blood pressure (BP); chronic kidney disease (CKD); estimated glomerular filtration rate (eGFR); renal function; risk factor; risk stratification; meta-analysis.

Hypertension and chronic kidney disease (CKD) represent global public health challenges due to their growing prevalence worldwide[1-3] and the associated higher risk for fatal and nonfatal cardiovascular events.[4,5] These 2 conditions are strictly inter-related because hypertension not only is a main complication of CKD, but can also act as its determinant. Glomerular filtration rate (GFR) decline is associated with a higher prevalence of hypertension and worse control rates.[6,7] However, hypertension is generally thought to be a leading cause of CKD. It is important to note that this notion is mainly derived from end-stage renal disease (ESRD) registries that identify "hypertension" as the main cause of treated chronic kidney failure; however, this information gained from registries may not be adequate because of common misclassification.[8] Studies from the general population, which is the ideal setting to study hypertension as a cause of CKD, have provided heterogeneous results on the role of hypertension and prehypertension in the onset of CKD.[9-12] Therefore, this association remains controversial.

In this regard, it is interesting to note that to our knowledge, no systematic review or meta-analysis to

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date has addressed the predictive role of hypertension and prehypertension in the development of decreased estimated GFR (eGFR) in individuals with eGFR $\geq$ 60 mL/min/1.73 m^2 at baseline. This aspect is essential to dissect the role of high or high-normal blood pressure (BP) as a promoter of a de novo decrease in kidney function. Recently, a meta-analysis has shown a significant association between prehypertension and ESRD[13]; however, this study included patients with low kidney function at baseline. Therefore, whether hypertension and prehypertension act per se as predictors of new-onset decreased eGFR in the general population is undefined. This question is critical to improve risk stratification and consequently to optimize preventive strategies aimed at reducing the CKD burden.

To fill this important gap of knowledge, we performed a systematic review and meta-analysis of longitudinal studies including cohorts of adults derived from the general population in order to determine the independent role of BP as a continuous and categorical variable (hypertension and prehypertension) in the risk for new-onset decreased eGFR.

METHODS

Search Strategies

This review was carried out in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines.[14,15] A systematic search of articles published in all languages was performed using PubMed, EMBASE, and the Cochrane Library database to identify relevant studies published until July 15, 2015. The following Medical Subject Headings (MeSH) and text words were used: "pre-hypertension," "pre-hypertensive," "prehypertension," "prehypertensive," "blood pressure," "borderline hypertension," "hypertension," "hypertensive" and "chronic kidney disease," "chronic kidney failure," "chronic kidney insufficiency," "chronic kidney dysfunction," "chronic renal failure," "chronic renal insufficiency" and "risk factors," "predictors," and "predictor." The detailed search syntax for the database PubMed is reported in Item S1 (provided as online supplementary material). Bibliographies of relevant articles and reviews were manually screened for additional potentially relevant studies.

Study Selection

Criteria for inclusion were as follows: (1) observational longitudinal studies of cohorts involving adults from the general population; (2) presence at baseline of normal kidney function, defined as eGFR $\geq$ 60 mL/min/1.73 m^2; (3) studies reporting risk for new decreased eGFR (defined as eGFR $<$ 60 mL/min/1.73 m^2), alone or associated with proteinuria, and expressed as either hazard ratio (HR) or odds ratio (OR) with 95% confidence intervals (CIs) related to hypertension (systolic BP [SBP] $\geq$ 140 mm Hg and/or diastolic BP [DBP] $\geq$ 90 mm Hg) or prehypertension (SBP of 120-139 mm Hg and/or DBP of 80-89 mm Hg) or as continuous SBP and DBP. We collected data from the most adjusted model.

In the case of overlapping studies in the same cohort, we only considered those with longer follow-up. We excluded studies that were not published as full reports, such as conference abstracts, letters to editors, commentaries, and reviews.

Predictors and Outcomes

Outcome was decreased eGFR de novo defined as eGFR $<$ 60 mL/min/1.73 m^2 and predictors were hypertension, prehypertension, and BP level as continuous variable (10−mm Hg increments).

Data Extraction

Two investigators (CG and MP) independently obtained the full reports of potentially relevant studies and reviewed each article using predefined eligibility criteria. Any discrepancy between the 2 reviewers on study eligibility was resolved by consensus agreement.

Quality Assessment

The Newcastle-Ottawa Scale was used for quality assessment[16] (Table S1). Risk for bias was assessed among the cohort studies for 3 aspects: (1) selection of participants (containing 4 domains), (2) comparability (1 domain), and (3) outcome measure (containing 3 domains). Each domain was rated as "Yes," "No," or "Unclear." Each quality domain was categorized as low risk for bias (Yes) when the study reported adequate data and met criteria and high risk (No) when the study reported adequate data but did not meet criteria for that quality domain. Studies that did not report data to assess quality were categorized as Unclear and thus potentially at high risk for bias. Yes was scored 1, and No or Unclear was scored 0. A quality bar was plotted for each domain to examine limitations of the studies. Studies of high quality were defined as score $>$ 5 points. Disagreements in scores were resolved by discussion and consensus between 2 reviewers (CG and MP).

Quantitative Data Synthesis

We quantified the inter-rater agreement for study selection and quality assessment. Extracted results on risk estimate (HR or OR) for decreased eGFR de novo were pooled in the meta-analysis. When we found increments of SBP or DBP different from 10 mm Hg, we standardized data to the same pre-established increment. As for a conservative approach, results were pooled by using a random-effects model that allows for variation of true effects across studies. The summary estimate was given as a relative risk (RR), which can be interpreted approximately as an OR or HR. Heterogeneity was analyzed using χ^2 test on N − 1 *df* and with the I^2 test.[17] I^2 values of 25%, 50%, and 75% correspond to cutoff points for low, moderate, and high degrees of heterogeneity. The 95% CIs were estimated. However, the fixed-effects model was also used to ensure the robustness of the model and reduce the susceptibility to outliers. Results were illustrated as a forest plot.

To exclude the possibility that a study was exerting excessive influence on heterogeneity, we conducted a sensitivity analysis by omitting one study at a time and then reanalyzing the data to assess the change in effect size.[18] Moreover, to explore possible sources of heterogeneity, we performed subgroup analysis, univariate random-effects metaregression, and moderator analysis. Metaregression was used to test difference between subgroups. Metaregression is a regression model that relates the treatment effect to study-level covariates while assuming the additivity of within- and between-study components of variance. Restricted maximum likelihood estimators were used to estimate model parameters.[19] Permutation test (using 1,000 reallocations) was used for assessing the true statistical significance of an observed metaregression finding.[20] Furthermore, publication bias was assessed by Begg test.[21] Statistical significance was defined as a 95% CI with no overlap with the null effect value. All statistical tests are 2 sided and $P < 0.05$ is regarded as significant.