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Impact of pharmacist intervention for blood pressure control in patients with chronic kidney disease: A meta-analysis of randomized clinical trials

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Abstract

What is known and Objective: Hypertension (HTN) and chronic kidney disease (CKD) are recognized as silent killers because they are asymptomatic conditions that contribute to the burden of multiple comorbidities. The achievement of a blood pressure (BP) goal can dramatically reduce the risks of CKD. In this study, we aimed to assess the effectiveness of pharmacist intervention on BP control in patients with CKD and evaluate the usefulness of home-based BP telemonitoring.

Methods: The terms "chronic kidney disease," "pharmacist," "BP" and "randomized controlled trial (RCT)" were used five databases to search for information regarding pharmacist intervention on BP control in patients with CKD. The inclusion criteria were as follows: (a) studies for adult patients with uncontrolled HTN and (b) studies with adequate data for meta-analysis. The primary outcome was an evaluation of achievement of BP goal in patients with CKD. The secondary outcome was usefulness of home-based BP telemonitoring by pharmacists in patients with CKD.

Results and discussion: Six RCTs were identified and included in the meta-analysis with a total of 2573 patients (mean age 66.0 years and 63.9% male). Pharmacist interventions resulted in significantly better BP control vs usual care (OR = 1.53, 95% CI = 1.15-2.04, $P < .01$). Pharmacist interventions using home-based BP telemonitoring were significantly superior to control/usual care (OR = 2.03, 95% CI = 1.49-2.77, $P < .01$), whereas pharmacist interventions without home-based BP telemonitoring did not significantly improve BP control compared to that with control/usual care (OR = 1.30, 95% CI = 0.97-1.75, $P = .08$). Home-based BP telemonitoring supported team-based care for HTN in these studies. In addition, patient self-monitoring with telemedicine devices might enhance patients' abilities to manage their condition by pharmacist instruction.

What is new and conclusion: The findings of this meta-analysis showed that pharmacist interventions with home-based BP telemonitoring improve BP control among adult patients with CKD.

KEYWORDS
blood pressure, chronic kidney disease, hypertension, pharmacist intervention, telemonitoring

1 | WHAT IS KNOWN AND OBJECTIVE

Hypertension (HTN) is recognized as a silent killer because it is asymptomatic and contributes to the burden of cardiovascular disease (CVD),[1,2] stroke, kidney failure, and premature mortality and disability.[3] The achievement of target blood pressure (BP) goals can dramatically reduce the risks of these complications.[4,5] Previous studies have investigated the usefulness of team-based care methods, including pharmacists and nurses, to improve HTN treatment and achieve better BP control.[6-9] These studies aimed to (a) achieve close collaboration among medical staff, (b) adequately review therapeutic interventions and (c) improve patient adherence to HTN treatment. In particular, pharmacists played a principal role in assessing the HTN medication regimen.[10-14]

Because the achievement of BP goals reduces CVD events,[15-18] long-term BP monitoring is essential in HTN management and may include home BP (HBP) monitoring. Home-based BP telemonitoring is useful for BP monitoring of ambulatory patients, and several recent studies showed that pharmacist interventions through telemonitoring are effective for improving HTN therapy.[12,14,19] In these studies, home-based BP telemonitoring was used for the assessment of medication regimen and adherence, as well as consultation for lifestyle improvement by pharmacists.

Chronic kidney disease (CKD) is associated with multiple comorbidities, including increasing the risk of CVD.[20,21] Because HTN is a risk factor for CKD progression,[22,23] the target BP goal of patients with CKD is lower than that of patients without CKD.[24-26] However, the rate of BP goal achievement is only around 50% in patients with CKD.[27,28] A previous meta-analysis comprising 39 RCTs reported that pharmacist interventions improve BP control,[8] but this study did not specifically evaluate the impact of pharmacist interventions in patients with CKD. Currently, there is no published meta-analysis on the effectiveness of pharmacist intervention on BP control in patients with CKD. Therefore, in the present study, we conducted a meta-analysis using RCTs that studied pharmacist intervention on BP control in adult patients with CKD. In addition, we evaluated the usefulness of home-based BP telemonitoring by pharmacists for BP control in patients with CKD.

2 | METHODS

2.1 | Study identification

The present meta-analysis was conducted according to the PRISMA guidelines.[29] A database search of the PubMed/MEDLINE, Scopus, Embase and Cochrane Library was conducted in May 2020. In addition, we used Google Scholar as another source. We searched for available articles published between January 1972 and March 2019. To search the database for RCTs on pharmacist interventions in patients with HTN and CKD, the terms "chronic kidney disease," "pharmacist," "BP" and "randomized controlled trial (RCT)" were used. Articles published in English were extracted, and duplicate records were removed from the search results. The search strategy is summarized in Figure 1.

2.2 | Study selection

The relevant studies were screened and selected by two pharmacists with expertise in CKD pharmacotherapy according to the following criteria: (a) studies in adult patients with uncontrolled HTN and (b) studies with adequate data for meta-analysis (including pharmacist intervention, the number of patients with CKD and the number of patients who achieved their BP goal).

Research protocols, meta-analysis studies and studies with inadequate data for meta-analysis were excluded. The BP goal was defined by the guidelines used in each included study.

2.3 | Data extraction

Two reviewers independently reviewed the studies and met to consolidate the extracted data. Any differences in data collection were resolved by consensus. Extracted data included patient characteristics, study setting, study outcome and methods of interventions. Patient characteristics included sample size, age, gender and comorbidities. Outcomes of the studies included the number of patients who achieved BP goals as per the study definition.

2.4 | Risk of bias assessment

Three reviewers independently assessed risk of bias for each study. Any differences in assessment of risk of bias were resolved by consensus. The risk of bias was assessed using the Cochrane risk of bias tool (RoB 2.0).[30] This tool assesses six domains as follows: (a) randomization process; (b) intended interventions; (c) missing outcome data; (d) measurement of the outcome; (e) selection of the reported result; and (f) overall risk. The responses to these domains were reported as "low" or "high" risk of bias, or "some concerns." The overall risk of bias corresponded to the worst risk of bias in any of the domains. If a study was judged to have "some concerns" with risk of

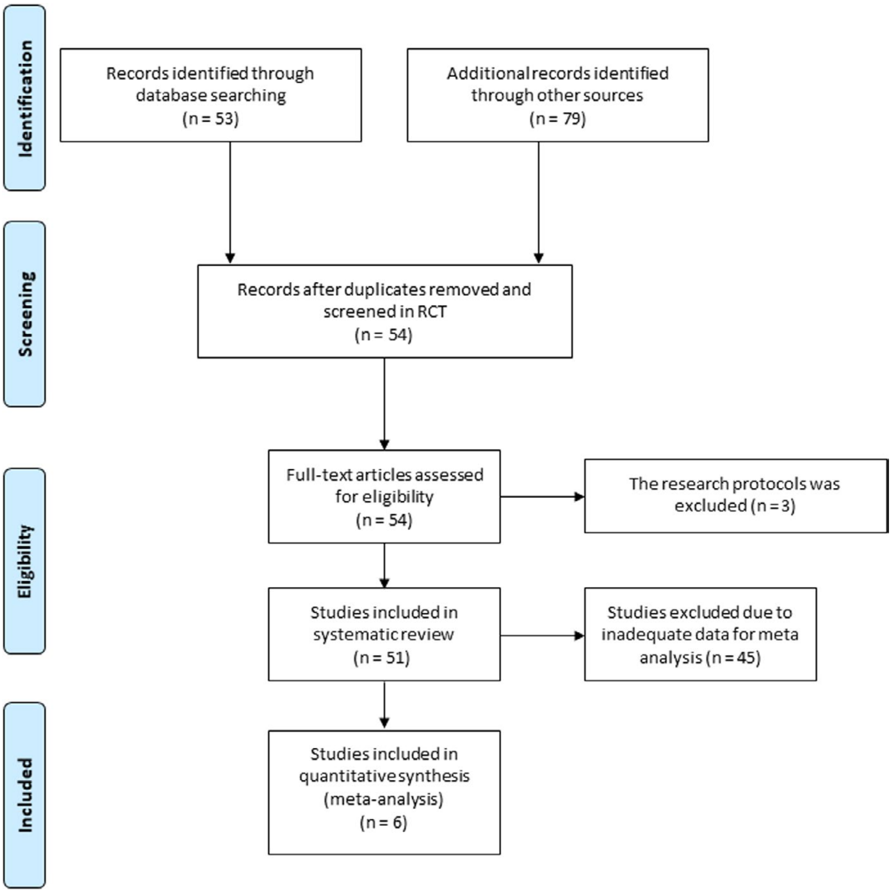

FIGURE 1 Flow diagram of screening

bias in multiple domains, it was determined to have a high overall risk of bias.

2.5 | Outcomes and data analysis

The primary outcome of this meta-analysis was the evaluation of BP goal achievement in patients with CKD. As a secondary outcome, we evaluated the impact on BP control of pharmacist interventions with home-based BP telemonitoring in patients with CKD. The number of patients who achieved their BP goal was treated as a dichotomous measure, and analyses were performed using the meta-analysis software Review Manager (RevMan) Version 5.3 (Cochrane Collaboration, Oxford, UK). The results were presented by constructing a Forest plot using a random effects model for primary and secondary outcomes. Both risk and rate ratios are presented with the 95% confidence interval (CI). Since the present study was a literature review and analysis, there were no related ethical or human subject protection issues.

3 | RESULTS

The literature search yielded 132 articles. After removing duplicates, the articles were screened to identify RCTs. The remaining 54 articles underwent full-text screening, and three research protocols were excluded. In addition, 45 records were excluded because they either did not report interventions by pharmacists on patients with HTN and CKD or had no data on the number of patients who achieved BP goals and/or the number of patients with CKD. Six studies met our inclusion criteria and were included in data collection to perform this meta-analysis (see Figure 1).

3.1 | Study characteristics

Six RCTs were identified and included in this analysis (Table 1). Four studies were conducted in a primary care clinic.[11,12,14,31] Two studies were conducted in a medical office.[10,13] All studies were performed in the United States. The baseline mean age was <65 years for four of the included studies[10,12-14] and ≥65 years for two studies.[11,31] Two studies had all subjects with CKD defined by each study and reported that pharmacists received study intervention-specific training.[11,31] The remaining four studies included non-CKD patients. In two studies, pharmacist intervention was conducted with home-based BP telemonitoring.[12,14] The follow-up periods were 6 (n = 1),[12] 9 (n = 2),[10,13] 12 (n = 2)[11,31] and 18 (n = 1)[14] months. In all studies, pharmacists conducted assessments of patient HTN medication regimens and provided consultation for improvements in lifestyle. Because one study included two types of intervention groups (brief and sustained, defined by intervention periods),[10] the baseline mean age, percentage of male

TABLE 1 Characteristics of the studies and the patients

PMID	Study author, year	Country	Study, n	Number of achievement of blood pressure goal	Baseline mean age, years (SD)	Baseline percentage of male patients	Baseline percentage of patients with CKD	Home-based BP telemonitoring	Follow-up periods (months)	Education for pharmacist	Nature of pharmacist intervention
23 463 811	Magid et al, 2013[12]	USA	IG, 162 CG, 164	IG, 88 CG, 58	IG: 60.0 (11.3) CG: 59.1 (10.9)	IG: 61.7 CG: 59.0	IG: 46.3 CG: 50.9 (CKD or DM)	Yes	6	No	Assessment for HTN medication regimen and adherence, and consultation for improvement of lifestyle
23 821 088	Margolis et al, 2013[14]	USA	IG, 188 CG, 182	IG, 135 CG, 104	IG: 62.0 (11.7) CG: 60.2 (12.2)	IG: 54.8 CG: 55.9	IG: 17.1 CG: 14.6	Yes	18	No	Assessment for HTN medication regimen and adherence, and consultation for improvement of lifestyle
25 805 647	Carter et al, 2015[10]	USA	IG, 401 CG, 224	IG, 172 CG, 76	IG (brief): 61.8 (12.4) IG (sustained): 57.8 (11.8) CG: 61.8 (13.7)	IG (brief): 38.7 IG (sustained): 39.6 CG: 40.6	IG (brief): 47.4 IG (sustained): 47.3 CG: 54.0 (CKD or DM)	No	9	No	Assessment for HTN medication regimen and adherence, and consultation for improvement of lifestyle
25 881 226	Cooney et al, 2015[11]	USA	IG, 441 CG, 429	IG, 185 CG, 177	IG: 75.6 (8.2) CG: 75.7 (8.2)	IG: 98.5 CG: 98.0	IG: 100 CG: 100	No	12	Yes	Assessment for HTN medication regimen, and consultation for improvement of lifestyle
27 825 313	Chang, et al, 2016[31]	USA	IG, 24 CG, 23	IG, 13 CG, 13	IG: 64.0 (13.2) CG: 70.6 (9.7)	IG: 37.5 CG: 47.8	IG: 100 CG: 100	No	12	Yes	Assessment for HTN medication regimen and adherence, and consultation for improvement of lifestyle
29 331 037	Anderegg et al, 2018[13]	USA	IG, 227 CG, 108	IG, 77 CG, 23	IG: 61.7 (11.6) CG: 63.1 (12.2)	IG: 37.0 CG: 34.3	IG: 12.3 CG: 13.9	No	9	No	Assessment for HTN medication regimen and adherence, and consultation for improvement of lifestyle

Note: Abbreviations: BP, blood pressure; CG, control group; CKD, chronic kidney disease; DM, diabetes mellitus; HTN, hypertension; IG, intervention group; SD, standard deviation.

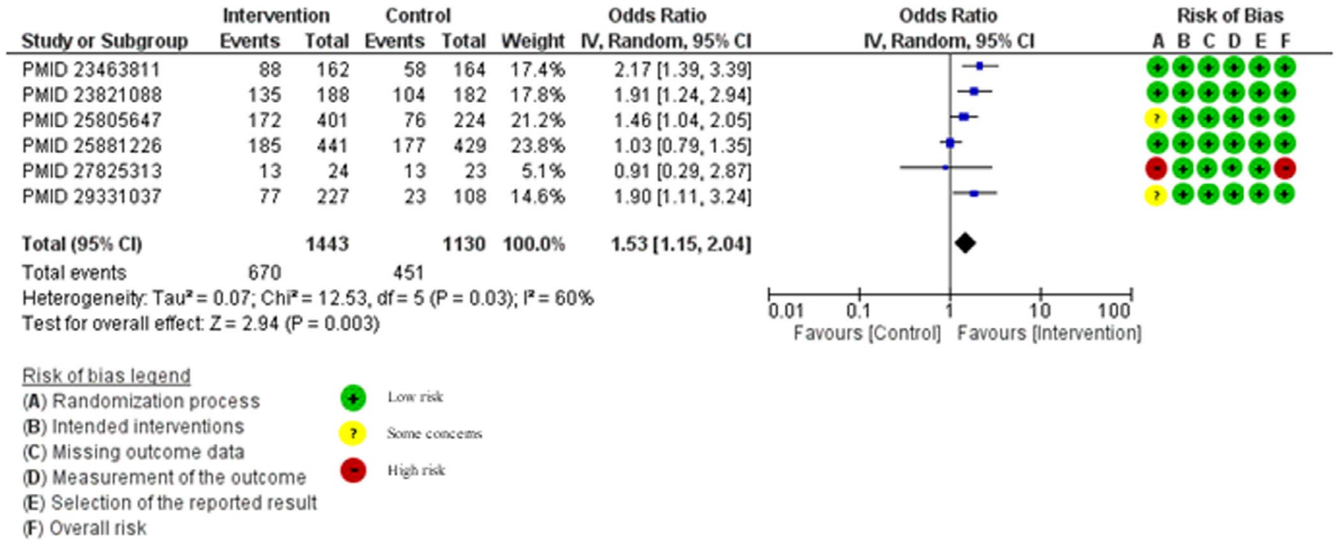

FIGURE 2 Forest plot of pharmacist intervention studies in chronic kidney disease patients with hypertension. In these studies, the total number of patients was 2573, and these pharmacist interventions are significantly superior to control/usual care (OR = 1.53, 95% CI = 1.15-2.04, *P* < .01). The RCTs were assessed by six domains: (A) randomization process; (B) intended interventions; (C) missing outcome data; (D) measurement of the outcome; (E) selection of the reported result; and (F) overall risk

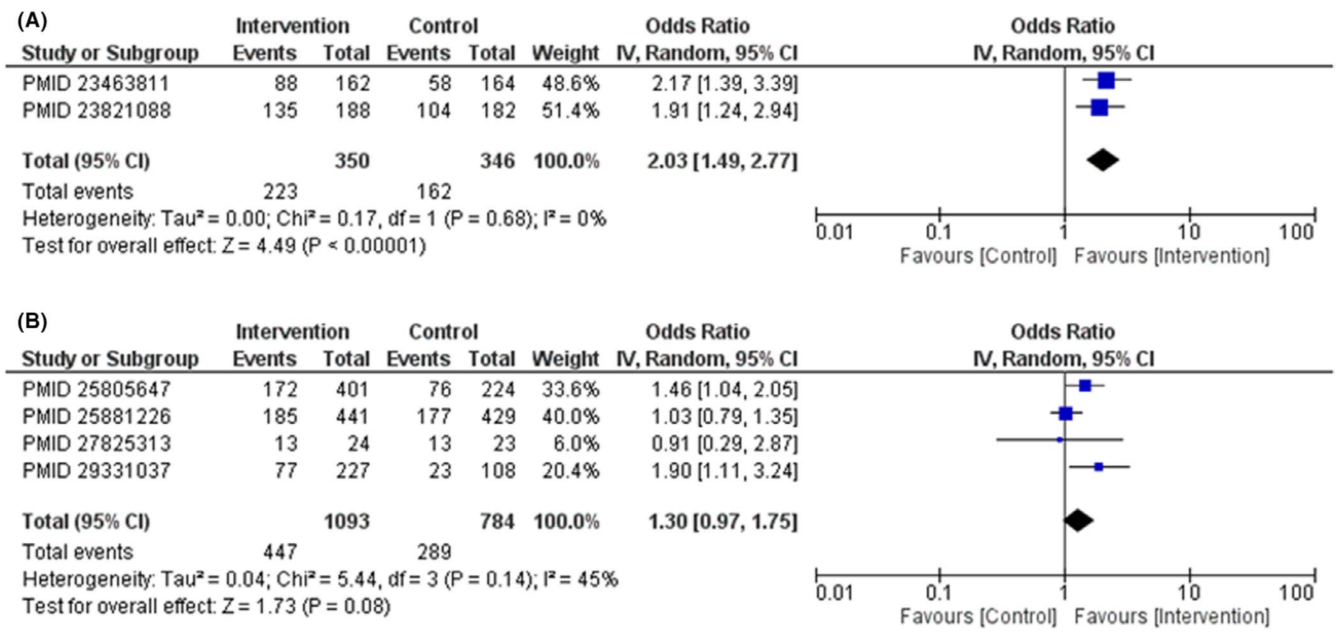

FIGURE 3 Forest plot of comparison between intervention using telemedicine systems or not. A, In studies with home-based BP telemonitoring, the total number of patients was 696, and the interventions with home-based BP telemonitoring were significantly superior to control/usual care (RR = 2.03, 95% CI = 1.49-2.77, *P* < .01). B, In studies without home-based BP telemonitoring intervention, the total sample size was 1879. Although these interventions showed a trend towards better control of BP compared to control/usual care (OR = 1.30, 95% CI = 0.97-1.75, *P* = .08), there was no significant difference

patients and percentage of patients with CKD are shown for both groups in Table 1.

3.2 | Synthesis of results

The summary effects of the six included studies are shown in Figure 2. The total combined sample size was 2573 (mean age 66.0 years and 63.9% male). Pharmacist interventions resulted in significantly improved BP control compared to that with control/usual care (OR = 1.53, 95% CI = 1.15-2.04, *P* < .01). To evaluate the impact of pharmacist intervention with home-based BP telemonitoring, we compared the summary effects of studies with and without home-based BP telemonitoring. In studies with pharmacists with home-based BP telemonitoring (n = 2), the total number of patients was 696, and these interventions resulted in significantly better BP control compared than control/usual care (Figure 3A; OR = 2.03, 95% CI = 1.49-2.77, $P < .01$). The total number of patients in studies without home-based BP telemonitoring was 1877. Although interventions without home-based BP telemonitoring showed a trend towards better control of BP compared to that with control/usual care (Figure 3B; OR = 1.30, 95% CI = 0.97-1.75, $P = .08$), there was no significant difference.

3.3 | Risk of bias assessment and meta-analysis

The summary of risk of bias assessment is shown in Figure 2. One study did not show the randomized allocation process, and thus, this study had higher randomization process bias than other studies.[31] Two studies were evaluated as having some concerns in randomization process.[10,13] Intended intervention bias was low in all studies.

4 | DISCUSSION

Our results suggested that pharmacist interventions with home-based BP telemonitoring improved BP control in this high-risk group with multimorbidity, whereas pharmacist interventions without home-based BP telemonitoring did not significantly improve BP control in this high-risk group.

Because patients with CKD often have many comorbid conditions resulting in the use many medications, these patients may benefit from a pharmacist providing medication therapy management. In this meta-analysis, we focused on the impact of pharmacist intervention in patients with CKD and HTN. In the six RCTs, pharmacists assessed the HTN medication regimen and provided consultation for improved lifestyle. Pharmacist interventions in these RCTs led to improved BP control as defined by each study (Figure 2).

Although our results are consistent with previous reviews evaluating the effectiveness of pharmacist intervention in patients with HTN,[8,32-34] neither previous reviews nor the present study were able to precisely identify the component of the intervention that contributed to BP control. To build a pharmacotherapy care plan, pharmacists need to check medical history, medication use and adherence, laboratory data, and HBP monitoring. These data may be accessible from hospitals or medical clinics. However, there is a barrier in obtaining these data at the community pharmacies. Since all participants were outpatients in the present study, most community pharmacies could not immediately obtain HBP data without home-based BP telemonitoring. A home-based BP telemonitoring system was developed to overcome this barrier, and we hypothesized that home-based BP telemonitoring would be the principal component for improving BP control. In two RCTs, the pharmacists obtained BP values in the pharmacy and shared medical information of the patients with clinic staff.[12,17] Home-based BP telemonitoring supported team-based care for HTN in these studies. In addition, patient self-monitoring with telemedicine devices might enhance patients' abilities to manage their condition by pharmacist instruction.[14] More specifically, home-based BP telemonitoring enhanced the effects of pharmacist interventions on BP goal attainment. These findings supported our hypothesis that home-based BP telemonitoring could play principal roles in achieving BP goal.

There are some limitations to the present study that should be considered when interpreting the results. The follow-up period was different in each RCT (6-18 months). As BP is affected by seasonal variation, [35-39] the ideal follow-up period needs to be more than 12 months. Education and training provided to intervention pharmacists prior to the study were either absent or not reported by four RCTs.[10,12-14] To guarantee the quality of intervention, appropriate training for pharmacists should be required. Two RCTs did not separate the rates of diabetes mellitus and CKD, likely due to their very common co-occurrence.[10,12] In addition, all studies did not show CKD stage of each subject. Although we contacted the authors of these publications, the information was not available. Further meta-analysis needs to use available raw data.

Lastly, there was substantial heterogeneity in our study. To determine the factors of substantial heterogeneity, a subgroup analysis is needed. In addition, the reporting bias needs to be assessed. Since the number of RCTs included in this study was not high enough for these analyses, we were unable to conduct the subgroup analysis and the evaluation of reporting bias.

5 | WHAT IS NEW AND CONCLUSION

The findings of this meta-analysis suggest that pharmacist interventions with home-based BP telemonitoring can improve BP control in patients with CKD.

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CONFLICT OF INTEREST

The author reports no conflicts of interest regarding this work.

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