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Home Blood Pressure Monitoring: How Good a Predictor of Long-Term Risk?

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Abstract

Most management decisions for the diagnosis and treatment of hypertension are made using blood pressure (BP) measurements made in the clinic. However, home BP recordings may be of superior prognostic value. In this review, we show that home BP recordings are generally superior to clinic BP measurements in predicting long-term prognosis. Home BP has been shown to significantly predict important end points including all-cause mortality, progression of chronic kidney disease, and functional decline in the elderly. In addition, home BP recordings significantly and strongly predict cardiovascular events. These findings are robust, as they concur despite having been studied in disparate populations, using heterogeneous methods of clinic and home BP recordings are not due solely to a larger number of measurements, and they extend to the elderly, patients with chronic kidney disease, and those on hemodialysis. Because home BP recordings combine improved accuracy with the advantages of low cost and easy implementation, most patients with known or suspected hypertension should have their BP assessed and managed by means of home BP recordings.

Keywords

BP measurement; Home BP; Clinic BP; Comparative study; Prognosis; Chronic kidney disease; Hemodialysis

Introduction

Hypertension affects one third of the American population and is a consistent and independent risk factor for cardiovascular and renal disease [1–4]. However, despite the expenditure of a great deal of time and resources, hypertension is still underdiagnosed and undertreated [5]. It cannot be controlled without accurate and practical methods for blood

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pressure (BP) measurement. Over the past century, conventional clinic-based BP measurement performed by a medical professional has been the method most commonly used to manage hypertension [6]. However, there is a growing understanding that office BP measurement can be misleading, owing to the phenomena of white-coat hypertension, which are estimated to be prevalent in 15%–20% of patients, and masked hypertension, estimated to occur in 10%–15% of patients [7]. Clinic-based BP also is less reliable because of inherent BP variability and observer bias [8, 9]. On the other hand, 24-hour ambulatory BP monitoring is considered the gold standard for the diagnosis and management of hypertensive patients [8], but it is not widely used because it is costly, requires trained clinic staff and specialized equipment, and may interfere with patients' usual activities and sleep [9].

Home blood pressure monitoring (HBPM) offers an attractive alternative. HBPM is distinct from both clinic-based BP measurement, which is performed by a health-care professional at a medical office or facility, and from ambulatory BP monitoring, which is performed using an automated cuff that measures BP at frequent intervals while a patient wears it for 24 h or longer. Instead, HBPM is performed by the patient outside of the setting of a health-care facility, typically using a validated oscillometric device that records pressure from the brachial artery [10].

Evidence regarding the usefulness of HBPM for therapeutic compliance and BP control has continued to accumulate over the past three decades [11–13]. Additionally, multiple cross-sectional studies have reported that target organ damage is more strongly correlated with home BP measurements than with clinic BP measurements [14–16]. However, despite these seeming advantages and the low cost, high availability, and easy application of HBPM, the diagnosis and treatment of hypertension are still based mainly on clinic-based BP values, probably at least in part because outcome data on the prognostic significance of home BP have been limited. The goal of this review is to present and summarize the current evidence examining the use of HBPM as a predictor of long-term cardiovascular and renal risk.

HBPM as a Prognostic Marker in the General Population

Among the first studies that highlighted the prognostic significance of HBPM was one from Japan. As can be seen from the summary of studies in Table 1, this cohort has been thoroughly and repeatedly analyzed and provides a large body of evidence to support the use of HBPM for prognostication. Starting in 1987, Ohkubo and colleagues assembled a cohort of 1,789 subjects from the rural Japanese community of Ohasama, all of whom were at least 40 years old, and compared the prognostic significance of HBPM compared with clinicbased screening BP [17]. Whereas the screening BP consisted of two measurements by a health-care professional, the HBPM consisted of a morning home BP measurement every day for 4 weeks, with a mean of over 20 measurements collected per patient. The home BP values were analyzed as both the average of all measurements per subject at home and as the average of the initial two measurements at home. The mean follow-up duration was 6.6 years. Only the home systolic BP (SBP) had a significant relation to the risk of cardiovascular mortality, with a 1 mm Hg rise in home SBP conferring an increased risk of 2.1% (95% CI, 0%–4.2%), supporting the assertion that multiple home BP measurements are better able to predict cardiovascular mortality than clinic-based BP measurement. The investigators also evaluated the minimum number of home BP recordings required to provide prognostic information. To do so, the investigators entered the screening BP and the initial two home BP values simultaneously in the same statistical model. They found that neither BP method was significantly related to the risk of cardiovascular mortality. They therefore concluded that HBPM was superior to clinic-based BP measurement only when three or more measurements were considered [17].

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A subsequent study of the same Ohasama cohort [18] included 1,913 subjects who had at least three home BP values at baseline. These patients now had a mean duration of followup of 8.6 years. The authors found that isolated systolic hypertension, defined as average home SBP \geq 137 mm Hg and diastolic BP (DBP) <84 mm Hg, significantly increased risk by 135% (95% CI, 41%–290%) for cardiovascular death as compared with normotension. Similarly, systolic-diastolic hypertension, defined as average home SBP \geq 137 mm Hg and DBP \geq 84 mm Hg, increased the risk of cardiovascular death by 85% (95% CI, 7%–221%). Interestingly, the authors also analyzed the influence of increasing home pulse pressure on cardiovascular mortality risk, and they found that each 10 mm Hg increase in home pulse pressure corresponded to a 37% increased risk (95% CI, 14%–65%). Thus, this was the first study to demonstrate the significant and independent relationship between cardiovascular mortality and pulse pressure as assessed by HBPM, a relationship that had been previously established for clinic-based measurements of BP [19].

Several follow-up studies of the Ohasama cohort have examined the comparative prognostic value of HBPM and clinic BP and the risk of stroke and the subtypes of strokes. One study analyzed the 1,491 participants without a history of stroke. With a mean follow-up duration of 10.6 years, the risk for an incident cerebrovascular event increased significantly with increasing home BP (P<0.0001 for linear trend), but there was no significant relationship with the clinic BP [20]. Interestingly, consideration of the first home BP value alone showed more utility than the mean of two clinic BP values. This finding was in contrast to the earlier finding that at least three home BP recordings are required for prognostication. The investigators demonstrated that when both the screening BP and the single initial home BP were analyzed simultaneously in the same statistical model, only the single home SBP value had a significant relation to the risk of an incident cerebrovascular event, with a 10 mm Hg increase in the single home SBP value increasing the risk by 18% (P=0.002) [20]. A similar and contemporaneous analysis of the Ohasama cohort examined the relationship between HBPM and subtypes of stroke, finding that an increase of 10 mm Hg in home SBP significantly increased the total stroke risk by 29% and increased the risk of ischemic and hemorrhagic stroke by 30% and 32% respectively [21]. By comparison, the same analysis found that an increase of 10 mm Hg in the clinic-based BP value significantly raised the total stroke risk by only 9% and the risk of ischemic stroke by 11%; there was no significant relationship with the risk of hemorrhagic stroke [21].

Two additional studies of the Ohasama cohort examined the relationship between BP and stroke risk when patients were categorized by levels of hypertension, as recommended by the Joint National Committee 7 [22] or by the European Society of Hypertension–European Society of Cardiology 2003 guidelines [23] for both clinic-based BP and home BP. When patients were categorized according to the recommendations of the Joint National Committee, both clinic BP and home BP showed a significant linear trend for increasing stage of hypertension being associated with increased risk of stroke [22]. However, for each category of BP as classified by the Joint National Committee, the hazard ratio for risk of stroke was markedly higher for home BP than for clinic BP. When patients were similarly categorized according to the European guidelines, both clinic BP and home BP again exhibited a significant linear trend associating increasing grade of hypertension with increased risk of stroke, but under this categorization, the hazard ratios for clinic BP and home BP and home BP were similar across the categorize of BP [23].

A more recent cohort study compared clinic BP and HBPM in predicting risk of stroke in an expanded Ohasama cohort of 2,369 patients at least 35 years of age and without prior history of stroke; recruitment for the expanded cohort started in 1992 [24]. In a multivariate adjusted analysis, an increase in home SBP by one standard deviation was associated with an increase in the risk of stroke of 48% (95% CI, 28%–70%), whereas the risk of stroke

increased by only 19% (95% CI, 5%–34%) for a single standard deviation increase in clinic SBP [24].

The Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) Study was a cohort study comparing clinic BP and HBPM in the general population; this study recruited 2,051 subjects aged 25–74 years from Monza (a suburb of Milan), Italy, starting in 1990 [25]. At baseline, all patients had clinic BP measurements performed in triplicate by auscultation. Over the following day, they performed HBPM twice: a single home BP measurement in the morning and a single measurement in the evening. During the mean follow-up period of 10.9 years, both clinic BP and home BP were significantly related to the risk for both allcause and cardiovascular mortality. For any given BP level, however, the hazard ratios for both mortality categories were always higher for home BP than for clinic BP [25]. A subsequent analysis of the PAMELA cohort of 2,051 subjects examined the risk of whitecoat hypertension, masked hypertension, and overall hypertension, as compared with normotension (defined as clinic BP <140/90 mm Hg and home BP <135/83 mm Hg) [26]. The authors found a significant and increasing trend in risk of cardiovascular death (P=0.015) with the progression from normotension to white-coat hypertension, masked hypertension, and finally overall hypertension, even after adjusting for other traditional cardiovascular risk factors. There was no significant trend between these BP categorizations and all-cause mortality, however [26].

Stergiou and colleagues conducted a cohort study to compare clinic BP and HBPM in the general population by recruiting 665 adults from the village of Didima in southern Greece, starting in 1997 [27]. At baseline, all patients had their clinic BP measured in triplicate by a physician using the auscultatory method on two separate clinic visits, and these BP values were averaged for analysis. HBPM was performed using an oscillometric device to measure BP twice in the morning and twice in the evening for 3 days, and these BP values were subsequently averaged for analysis. During the mean follow-up duration of 8.2 years, 67 patients had at least one cardiovascular event. After adjustment for traditional cardiovascular risk factors, HBPM did not have a significant relationship with cardiovascular events. Only clinic-based diastolic BP had a significant relation to cardiovascular events, with a 1 mm Hg rise in BP corresponding to a 3.4% (95% CI, 0.8%–6.1%) increase in risk [27]. Of all the studies reviewed here, this is the only one that found clinic BP to be a superior prognosticator to HBPM.

Most recently, the Finn-Home study was a cohort study that evaluated the comparative prognostic significance of clinic BP and HBPM in the general population by recruiting 2,081 subjects aged 45–74 years from across Finland, starting in the year 2000 [28••]. All patients had clinic BP measured by a nurse using the auscultatory method to gather two BP values, which were averaged for the analysis. HBPM was performed using an oscillometric device to measure BP twice in the morning and twice in the evening for 7 consecutive days, and these values were subsequently averaged for the analysis. The average number of home BP measurements collected was over 26 per patient. During the mean follow-up duration of 6.8 years, both clinic BP and home BP were significantly and independently related to cardiovascular events. Rises in home BP conferred a greater risk of cardiovascular events, with a 10 mm Hg rise in home SBP corresponding to a 23% increase in risk (95% CI, 13%-34%), compared with only a 13% increase in risk (95% CI, 5%–22%) with a 10 mm Hg rise in clinic SBP. After adjustment, only home SBP was significantly related to all-cause mortality. Moreover, when both clinic BP and home BP were entered into the same multivariate model, only home BP remained a significant predictor of cardiovascular events (*P*<0.001).

In contrast to the prior studies, which recruited across multiple age groups, Fagard and colleagues examined the prognostic value of clinic BP and HBPM in the elderly; their cohort study enrolled 391 patients at least 60 years of age and without a history of myocardial infarction or stroke, recruited from a single primary care clinic in Flanders, Belgium, starting in 1990 [29]. At baseline, all patients had their BP measured in the clinic and in the home setting by a physician who used the auscultatory method to record the BP in triplicate; the three BP values were then averaged for analysis. This study was therefore different from others in that even the home BP measurements were made by the physician. Over the mean follow-up period of 10.9 years, an increase in home SBP of one standard deviation was associated with a 32% increase in independent risk of cardiovascular events (95% CI, 6%–64%). In contrast, clinic BP had no significant relationship to risk for cardiovascular events [29]. It appears from this study, therefore, that the location of measurement and not the operator is related to the superior prognostic information contained in HBPM.

Nishinaga and colleagues compared clinic BP and HBPM in elderly patients by conducting a cohort study of 461 subjects at least 75 years of age and without atrial fibrillation from the community of Kahoku Town, Japan, starting in 1992 [30]. HBPM was performed by the patients twice in the morning and twice in the evening for 5 consecutive days at baseline. During 9 years of follow-up, there were 125 deaths, of which 53 were due to cardiovascular causes. Of the survivors at 9 years, 118 had experienced a loss of functional independence, defined as a score of less than 20 of a possible 21 on a self-administered questionnaire about activities of daily living. When patients were categorized based on their average home BP values, no relationship was found between BP and cardiovascular or total mortality after adjustment for baseline factors. However, both average home SBP \geq 15 mm Hg were independent predictors of loss of functional independence at 9 years, even after multivariate adjustment (including adjustment for nonfatal stroke), suggesting that home BP predicted functional decline independent of the impairment caused by a stroke [30].

Bobrie and colleagues performed another cohort study comparing clinic BP and HBPM in an elderly population, the Self-Measurement of Blood Pressure at Home in the Elderly: Assessment and Follow-up (SHEAF) study, which is the largest study of its type to date [31]. In total, 4,939 patients, all at least 60 years of age and with a diagnosis of hypertension, were recruited from French primary care sites. The protocol called for all patients to have clinic BP measured in triplicate by a physician using the auscultatory method on two separate clinic visits 2 weeks apart, and all patients were to perform HBPM using an oscillometric device three times in the morning and three times in the evening for 4 consecutive days. After a mean follow-up of 3.2 years, home BP remained significantly and independently associated with cardiovascular events: a 10 mm Hg increase in home SBP increased risk by 17.2% (95% CI, 11.0%–23.8%); clinic BP had no significant relationship to cardiovascular events. However, both home BP and clinic BP had no significant relationship to either total mortality or cardiovascular mortality in this analysis. Additionally, the authors noted that 9% of their population had a controlled clinic BP but an elevated home BP, defined as average clinic BP less than 140/90 mm Hg and average home BP of 135/85 mm Hg or higher. This population with masked hypertension had a risk of cardiovascular events similar to those patients with uncontrolled hypertension when measured by both clinic BP and home BP; their risk increased by 106% (95% CI, 22%-337%) compared with those whose hypertension was controlled. Conversely, the 13% of patients with white-coat hypertension (elevated clinic BP but controlled hypertension with HBPM) had a risk for cardiovascular events that did not differ significantly from that of patients whose BP was well controlled when measured by both methods [31].

HBPM as a Predictor for Progression of Chronic Kidney Disease

Clinic BP is a recognized major determinant of progressive renal insufficiency, with higher BP posing the greatest long-term risk [32]. Prospective studies assessing the predictive ability of HBPM in the setting of kidney disease are limited. The earliest such study was a cohort study conducted by Rave and colleagues, which compared clinic BP to HBPM in predicting progression of renal disease [33]. Starting in 1985, this study recruited 77 patients from a clinic in Germany; these patients had diabetes mellitus type I, diabetic nephropathy, a diagnosis of hypertension, and serum creatinine less than 4 mg/dL. In contrast to the studies in the general population, these patients did not just have clinic BP and home BP measures performed at baseline, but rather, these measures were performed longitudinally. Clinic BP was measured using the auscultatory method an average of 2.6 times per year during the follow-up period. After training by clinic personnel, home BP was self-measured using the auscultatory method. Blind patients performed HBPM using an oscillometric device. All patients were initially encouraged to perform HBPM once in the morning and once in the evening every day, but unfortunately the average number of measurements per patient was not reported. For analysis, all clinic BP and home BP values were first converted to mean arterial pressures and then averaged over the duration of follow-up. During the mean followup period of 6.2 years, the average estimated glomerular filtration rate (eGFR), derived from serum creatinine using the Cockroft-Gault formula, declined from 74 mL/min to 52 mL/min. After adjustment for baseline patient characteristics, both clinic mean arterial pressure and home mean arterial pressure significantly correlated with the yearly decline in eGFR, but home BP had a stronger correlation (r=0.42, P<0.001) as compared with clinic BP (r=0.33, P < 0.004). Moreover, replacing home BP with clinic BP in the statistical model to predict decline in eGFR resulted in a decrease in the goodness of fit for the model [33].

Suzuki and colleagues compared the ability of clinic BP measurements and HBPM to predict progression of renal disease when they performed an uncontrolled interventional study of 113 patients with chronic kidney disease and hypertension, who were recruited from a renal clinic in Saitama, Japan [34]. All patients had clinic visits every 2 weeks for the 36-month study duration, and at these visits patients had clinic BP measured in duplicate using the auscultatory method. HBPM was performed using an oscillometric device, and patients were instructed to take their home BP at least twice per week. Using a study protocol based on therapy with amlodipine and benazepril, all patients had their medication regimen adjusted to achieve a goal clinic BP of less than 130/85. The average serum creatinine for this study population with renal disease was 1.87 mg/dL, and the average baseline urinary protein excretion was 1.2 g per 24 h. During the study duration of 3 years, the average eGFR for the population reportedly decreased significantly, but unfortunately it is unclear whether this was estimated based only on the monthly serum creatinine values or with the additional use of monthly 24-hour urinary creatinine excretion values. Although all average clinic BP and home BP values were significantly correlated to the yearly decline in eGFR, home SBP measured in the morning had the strongest correlation (r=0.64) with the yearly decline in eGFR, stronger than clinic SBP (r=0.43) [34].

Most recently, our group compared the ability of clinic BP and HBPM to predict mortality or progression of renal disease in a cohort study of 217 veterans with chronic kidney disease who were recruited from the renal and general medicine clinics of the Veterans Affairs Medical Center in Indianapolis, Indiana, starting in the year 2000 [35]. At baseline, all patients had a single baseline clinic BP measurement by the clinic nurse, using an oscillometric device, as well as a standardized clinic BP measured in triplicate on two separate visits with the same oscillometric device by a nurse trained in BP measurement according to published guidelines [36]; the average of the six standardized clinic BP values was used in the analysis. Additionally, each patient performed HBPM using an oscillometric

device to record home BP once each in the morning, afternoon, and evening over 7 consecutive days; the first day's results were discarded, and the remaining values were averaged for the purposes of analysis. During the median follow-up duration of 3.5 years, 75 patients experienced the combined end point of end-stage renal disease (ESRD) or death, with 39 of these patients dying prior to ESRD. SBP independent of technique was significantly predictive of ESRD, death, or the combined end point of the two, except that routine clinic SBP did not significantly predict death. However, for each end point, the risk was highest for home BP, then for standardized clinic BP, and lowest for routine clinic BP. For example, the increase in risk for ESRD associated with an increase in BP of one standard deviation was 210% for home BP (95% CI, 117%-341%), compared with an increase of 175% for standardized clinic BP (95% CI, 87%-304%) and only 70% with routine clinic BP (95% CI, 24%-134%). The significant association between home SBP and death, ESRD, or the combination of the two end points remained even after adjustment for risk factors for ESRD and after adjustment for either method of clinic BP measurement [35]. In the same cohort, our group analyzed the relationship of BP measurement type with the combined end point of myocardial infarction, stroke, and all-cause mortality. Compared with BP measured in the clinic, home BP was more strongly related to the composite outcome [37].

Collectively, the studies discussed above support the stronger prognostic value of HBPM among patients with chronic kidney disease.

HBPM as a Prognostic Marker in Hemodialysis Patients

The assessment and management of BP in hemodialysis (HD) patients presents a unique challenge, as BP values can fluctuate widely in relation to the timing of HD and interdialytic periods. HBPM is an attractive method to address the variability of pre-HD and post-HD BP values, but as in the setting of patients with chronic kidney disease who have not started dialysis, the evidence base examining HBPM and long-term prognosis in this population is limited. Our group has explored this relationship in two studies of a cohort of HD patients from Indianapolis, Indiana. The first study recruited 150 adult patients on thrice-weekly HD for at least 3 months from the four HD units in Indianapolis, starting in 2003 [38]. At baseline, all patients had routine pre-HD and post-HD measurements of BP by the oscillometric device attached to the HD machine, over six consecutive HD sessions; routine pre-HD and post-HD BP values were analyzed as an average of the six readings. Similar to our group's study of HBPM in veterans with chronic kidney disease, all patients also had standardized clinic BP measurements performed in triplicate by a trained nurse using an oscillometric device both before and after HD over six consecutive sessions, and the average of these pre-HD and post-HD values over six sessions was used in the analysis. HBPM was performed using an oscillometric device to measure home BP every morning, afternoon, and evening for 7 consecutive days, and the average of these home BP values wa used in the analysis. During the median follow-up period of 2 years, an increase of one standard deviation in any clinic BP, whether measured with the routine or standardized method, was not significantly associated with all-cause mortality. However, post-HD clinic SBP, measured either routinely or by the standardized method, was significantly associated with an increased risk of cardiovascular mortality. An increase in home SBP of one standard deviation was associated with a 35% increase in risk for all-cause mortality (95% CI, 1%-84%) and a 47% increase in risk for cardiovascular mortality (95% CI, 2%–119%), but these findings are of marginal statistical significance. However, a one standard deviation increase in home DBP was associated with a significant 40% increase in risk of all-cause mortality (95% CI, 3%–93%) and a significant 63% increase in the risk of cardiovascular mortality (95% CI, 9%-146%). Additionally, when the BP values were divided into quartiles, increasing quartiles of clinic BP by any method had no significant relationship to all-cause

mortality, whereas increasing quartiles of home BP had a significant linear trend associated with increasing mortality (P=0.05) [38].

Most recently, our group performed a study of the same cohort expanded to 326 patients recruited from the same HD units and using the same recruitment criteria [39••]. All patients had routine clinic BP recorded before and after HD for six consecutive sessions by the oscillometric device attached to the HD machine, and patients performed HBPM three times daily over 7 consecutive days. Over a median follow-up duration of 2.4 years, there were 102 deaths. When BP values were divided by quartiles, there was no significant relationship between any clinic BP and all-cause mortality, but there was a significant relationship between home BP and mortality (log rank p=0.023). Additionally, a statistical model was created to predict all-cause mortality from all available BP measurements in the study. When the clinic BP values were removed from the model, there was no significant decrease in the goodness-of-fit for the model. This suggests that clinic BP (measurements in the dialysis unit) add no further prognostic information to home BP measurements [39••].

Summary

Except for a single study [27], HBPM has been found to be equal to or superior to clinic BP measurements in predicting long-term prognosis in each of the studies reviewed. In an aggregate of thousands of patients followed for tens of thousands of patient-years at risk, home BP has been shown to significantly predict important end points including all-cause mortality [25, 28••, 35, 38, 39••], progression of chronic kidney disease [33–35], and functional decline in the elderly [30], but the most frequent finding is that home BP significantly and strongly predicts cardiovascular events [17, 18, 20–24, 28••, 29, 31, 37, 38]. These findings are robust, as they concur despite having been studied in disparate populations, using heterogeneous methods of BP measurement, and using varied methods of statistical analysis. The superiority of HBPM over clinic BP measurement persisted even when there were more clinic BP measurements than home BP measurements [20], suggesting that the advantages of HBPM are not due solely to a larger number of measurements.

There may be several reasons for the superiority of HBPM over clinic measurements. First, HBPM may more closely reflect the true level of intra-arterial pressure over time; measurements in the clinic, on the other hand, may not reveal this pressure appropriately because of white-coat and masked hypertension effects. Second, HBPM may allow for a greater number of recordings, smoothing out the variation in BP. This phenomenon is probably most important among HD patients dialyzed three times weekly. Blood pressure increases slowly and continuously from post-HD to pre-HD readings. Sampling BP at various times throughout this period may more accurately capture the true intra-arterial pressure. Third, the measurement of home BP may be particularly important among smokers. Because patients typically are not allowed to smoke in medical facilities, the smoking-induced rise in BP may be masked. Especially among heavy smokers, the effect of smoking in increasing BP may be better captured by home BP recordings.

Conclusions

The preponderance of the currently available evidence supports the assertion that HBPM is a significant predictor of long-term risk and that it is superior to clinic BP measurement for this purpose. Thus, HBPM combines improved accuracy with the advantages of low cost and easy implementation. These findings support American [8] and European [9] guidelines recommending that all patients with known or suspected hypertension should have their BP assessed and managed by means of HBPM. Although beyond the scope of this review, a

recent meta-analysis performed by our group shows that BP management guided by home BP measurements results in better blood pressure control, especially when combined with a plan to treat elevated BP readings [40].

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Study	Reference	Country	Population	z	Follow-up (years)	Outcomes
Ohasama	Ohkubo et al. [17]	Japan	General	1,789	6.6	All-cause mortality, CV mortality
Ohasama	Hozawa et al. [18]	Japan	General	1,913	8.6	CV mortality
Ohasama	Ohkubo et al. [20]	Japan	General	1,491	10.6	Stroke
Ohasama	Ohkubo et al. [21]	Japan	General	1,702	10.6	Stroke
Ohasama	Asayama et al. [22]	Japan	General	1,702	11.0	Stroke
Ohasama	Asayama et al. [23]	Japan	General	1,702	11.0	Stroke
Ohasama	Inoue et al. [24]	Japan	General	2,369	11.7	Stroke
PAMELA	Sega et al. [25]	Italy	General	2,051	10.9	All-cause mortality, CV mortality
PAMELA	Mancia et al. [26]	Italy	General	2,051	12.3	All-cause mortality, CV mortality
Didima	Stergiou et al. [27]	Greece	General	665	8.2	CV events
Finn-Home	Niiranen et al. [28••]	Finland	General	2,081	6.8	All-cause mortality, CV events
Flanders	Fagard et al. [29]	Belgium	Elderly	391	10.9	CV events
Nishinaga	Nishinaga et al. [30]	Japan	Elderly	461	9.0	Loss of functional independence
SHEAF	Bobrie et al. [31]	France	Elderly	4,939	3.2	All-cause mortality, CV mortality, CV events
Rave	Rave et al. [33]	Germany	Diabetic nephropathy	LL	6.2	Decline in eGFR
Suzuki	Suzuki et al. [34]	Japan	CKD	113	3.0	Decline in eGFR
Agarwal	Agarwal and Andersen [35]	USA	CKD	217	3.5	All-cause mortality, ESRD
Agarwal	Agarwal and Andersen [37]	USA	CKD	217	3.4	All-cause mortality, CV events
Alborzi	Alborzi et al. [38]	USA	Hemodialysis	150	2.0	All-cause mortality, CV mortality
Agarwal	Agarwal [39••]	USA	Hemodialysis	326	2.4	All-cause mortality

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CKD chronic kidney disease; CV cardiovascular; eGFR estimated glomerular filtration rate; ESRD, end-stage renal disease