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REVIEW SERIES

Significance of white-coat and masked hypertension in chronic kidney disease and end-stage renal disease

José Boggia, Ricardo Silvariño, Leonella Luzardo and Oscar Noboa

Hypertension is a frequent and modifiable cardiovascular risk factor with a cyclic relationship with chronic kidney disease (CKD). The diagnosis, treatment, monitoring and control of high blood pressure are all mandatory not only in CKD but also in end-stage renal disease (ESRD). As demonstrated by studies using population and hypertensive patients, white-coat hypertension (WCHT) and masked hypertension (MHT) carry a particular degree of risk. The advantages of ambulatory techniques in the management and prognostic stratification of patients with CKD and ESRD have also been recognized. However, most of the evidence underlines the importance of nocturnal hypertension and neglects WCHT and MHT. The absence of specific reports involving untreated and treated patients hinders the ability to significantly discriminate WCHT from the white-coat effect and MHT from masked uncontrolled hypertension. The heterogeneous definitions that are used add additional difficulty in translating experimental evidence into clinical practice. Reaching a consensus in definitions is mandatory for designing future research. Cross-sectional studies underscore the frequency of misdiagnosis, potentially leading to undertreatment (MHT) and overtreatment (WCHT) in renal disease. The divergent prevalence of WCHT and MHT reported in CKD could be related to the diverse definitions of hypertension and the heterogeneity of the pathologies pooled under the CKD definition. Even in the absence of randomized clinical trials specifically addressing this issue, the scarce longitudinal studies confirm that WCHT carries a risk close to that of sustained normotension, whereas MHT is associated with a risk close or identical to that of sustained hypertension.
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INTRODUCTION

Hypertension is present from the very early stages of chronic kidney disease (CKD), and it is also a major problem in patients reaching end-stage renal disease (ESRD).[1–5] The prevalence, severity and ability to control blood pressure (BP) worsen with the progression of renal disease. Hypertension and CKD are highly prevalent, reaching 20–40% and 10–15% of the general population, respectively,[6,7] and these percentages are projected to increase in the near future.[6,8] Both disorders behave as aggregate risk factors:[9] on the one hand, sustained hypertension causes renal impairment and the progression of CKD and, on the other hand, renal disease interferes with BP, from impairing control in the preclinical stages[10] to the extreme of being considered a cause of secondary hypertension in established CKD.[11] This close relationship is supported by higher rates of hypertension among CKD patients independent of race, sex and age,[12–16] and by a progressive increase in the incidence and prevalence of hypertension from early to advanced stages of CKD.[17–19] However, race, sex and age disparities in the prevalence and rate of BP control have also been described.[20]

Cardiovascular (CV) disease is one of the main causes of death and nonfatal complications in patients with CKD and ESRD, and these patients have higher rates of CV complications than the general population, mainly because of the major contributions of hypertension.[5,17,18,21,22] The current charts for the stratification of total CV risk are based on BP and also include CKD as a synergistic condition with an inverse relationship between the estimated glomerular filtration rate (eGFR) and CV risk.[11] Systolic BP (24-h ambulatory BP) accounts for a major proportion of the explained CV risk in comparison with eGFR (CKD-EPI).[3] Furthermore, BP reduction in CKD, independent of drug class, is an effective strategy in preventing the occurrence of cardiovascular events[23] and the progression to ESRD.[5] For these reasons, the diagnosis, treatment, monitoring and control of high BP are mandatory in CKD.[1]

The diagnosis and control of hypertension are critically dependent on accurate BP measurements.[24] In the 1960s, Sokolow *et al.*[25] observed that 'a substantial proportion of cases in which casual (office) BPs were considerably elevated, yet hypertensive complications did not develop, as well as cases in which complications occurred although arterial pressures were only moderately increased' and raised this question: 'to what extent are the discrepancies between casual BP and clinical course due to the possibility that casual pressures fail to represent the usual BP of the

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patient?'[25] From this pioneering research[25,26] to the present,[27–32] the superiority of out-of-office techniques for BP measurement (ambulatory BP monitoring (ABPM) and self/home BP measurement) over conventional (office) BP measurement has been largely documented and reviewed elsewhere.[33,34] Ambulatory techniques not only result in better diagnostic accuracy but also in more precise prognostic prediction. In the general population, the ABPM thresholds for the diagnosis of hypertension were initially derived from different approaches in cross-sectional studies using the office BP thresholds for reference.[35–39] Ohasama researchers[40] and, more recently, IDACO investigators[41] provided ABPM thresholds based on a prognostic criterion and the 10-year equivalent risk, respectively. Thus, ABPM is an accurate technique with well-defined thresholds and better performance for risk stratification than office BP. In most cases, both techniques are concordant in identifying normotensives and hypertensives. However, the categories of discrepancy emerging from the cross-classification of ambulatory and office BP measurements also carries a particular degree of risk, as documented in cross-sectional and longitudinal studies.[42–44] White-coat hypertension (WCHT) is defined as an elevated office BP with normal ambulatory BP and should be differentiated from the white-coat effect.[45] Masked hypertension (MHT) is defined as normal BP in the office with elevated ambulatory measurement.[46] IDACO investigators, based on long-term follow-up of four cohorts and more than 7000 people, recently showed that the risks conferred by WCHT and MHT were intermediate compared with those associated with normotension and sustained hypertension.[30] However, the discrepant categories of the cross-classification (WCHT and MHT) are asymmetrical in terms of their associated risks. MHT carries a risk equivalent to sustained hypertension, whereas WCHT carries a risk almost identical to normotension.[30] Thus, ambulatory techniques can help refine the diagnosis and risk stratification in the general population as well as in studies of hypertensive patients.[47] We will address whether we have evidence that supports the hypothesis that ambulatory techniques improve BP measurement in the diagnosis and risk stratification of patients with chronic renal disease. We will focus on WCHT and MHT.

Renal disease is a heterogeneous condition from both a pathogenic point of view and a clinical perspective. We will differentiate two conditions of major clinical relevance: the progression through CKD stages and patients with ESRD under renal replacement therapies. We will analyze the usefulness of a diagnosis of WCHT or MHT in these two clinical conditions. Because of the high prevalence of hypertension in CKD and ESRD, most of the studies include a large proportion of patients under antihypertensive treatment (Table 1). In those cases, the terms white-coat effect and masked uncontrolled hypertension would be more appropriate. However, the published data do not discriminate the results by treatment status, generating another limitation in the interpretation of the evidence. For that reason, in this review, we will use the terms WCHT and MHT to represent either untreated or treated patients, but the reader should be familiar with the difference.

WCHT AND MHT IN CKD

The diagnostic and prognostic superiority of ABPM over office BP measurement in CKD patients has also been documented in cross-sectional and longitudinal studies[14,15,48–60] and was also confirmed by a meta-analysis.[61] Most of the studies address changes in the circadian pattern of BP, with the analysis centering on nocturnal hypertension or nighttime BP dipping.[48,49,56–60] However, some studies also report the prevalence and prognostic relevance of the categories that emerge when office and ambulatory BP measurements are used in combination (Table 1).[14–16,54,55,62–69] A recent analysis of the Chronic Kidney Disease-Japan Cohort Study (CKD-JCS),[70] which includes almost 3000 CKD Asian patients,[69] showed that, based solely on office BP, 31.6% of all participants were diagnosed as having hypertension. However, based on 24-h ambulatory BP, the proportion of hypertensive patients rose to 56.9%, with 30.9% of patients having MHT and 5.6% having WCHT (Figure 1). Using a multiple regression approach, the authors analyzed the clinical factors associated with the differences between office and ambulatory BP measurements. Age, diabetes, antihypertensive treatment and lower eGFR (MDRD-4 adjusted for Japanese), but not proteinuria, all significantly contributed to the observed variance between office and ambulatory measurements in the multiple regression analysis.

The prevalence of the concordant categories (sustained normotension (SNT) and sustained hypertension (SHT)), as well as the discrepant categories (WCHT and MHT), is highly variable among studies (Table 1). There is a multitude of potential factors that may contribute to the discrepancies in the prevalence between the categories of the cross-classification in CKD. First, different ABPM parameters were used in the definitions of WCHT and MHT. Even when the classical descriptions of WCHT and MHT were based on daytime BP, in many published studies, it was replaced by either 24-h BP[15,54,55,62,69] or nighttime BP[16,67,68] (Table 1). Other studies used self/home blood pressure measurement as the out-of-office technique.[64,65] Second, variable and arbitrary cutoffs were used to define hypertension in CKD patients during office and ambulatory measurements. Although most population-based studies used 140/90 mm Hg as the systolic/diastolic cutoff for office BP, most of the studies based on CKD patients used 130/80 mm Hg. This disparity in office BP thresholds between studies results partly from the absence of a consensus on the arbitrary limit to define high BP in CKD patients. Recently, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[1] established 130/80 mm Hg (systolic and diastolic BP, respectively) as the limit at which antihypertensive drug treatment should be initiated, independent of the presence or absence of proteinuria. Japanese guidelines suggest an even lower cutoff in cases of significant proteinuria.[71] However, the National (British) Institute for Health and Clinical Excellence (NICE) guidelines[72] recommend a 140/90 mm Hg threshold for CKD in the absence of proteinuria and a 130/80 mm Hg cutoff for proteinuric CKD. Furthermore, the recent joint guidelines of the European Society of Hypertension and European Society of Cardiology (ESH-ESC)[11] recommend 140/90 mm Hg as the threshold for CKD patients, independent of proteinuria. The prevalence of MHT in studies that used a stricter definition (clinic <130 mm Hg, ambulatory $\geqslant 130$ mm Hg) was lower (5.3%, confidence interval (CI) 3.4–7.2%) compared with studies that used a higher cutoff for office BP measurements (19.8%, CI 16.1–23.6%).[61] The opposite was true for WCHT.[61] In several published studies, there are also disparities in the thresholds for ABPM parameters even for the 24 h, daytime or nighttime values. Third, the ethnicity, age, associated comorbid conditions and other baseline characteristics of the study participants could be additional sources of variation.[73] Fourth, CKD, as defined by eGFR and proteinuria,[74] can result from a wide spectrum of pathologic conditions. Some of these conditions are limited to the kidney, whereas others are manifest from systemic diseases (for example, diabetic nephropathy); still others cause severe nephritis that demands the use of steroids, calcineurin inhibitors and other drugs (for example, systemic lupus erythematosus) that could potentially interfere with BP control. Only one study was limited to a

Table 1 Summary of studies reporting the prevalence for the categories of the cross-classification of office and ambulatory/self blood pressure measurements

Author/year	*Study*	*CKD/n (%)*	*T/H*	*Age (years)*	*Women (%)*	*Office (mm Hg)*	*ABPM (mm Hg)*	*SBPM (mm Hg)*	*SNT (%)*	*WCHT (%)*	*MHT (%)*	*SHT (%)*
Csiky *et al.*[62]/1999	—	126[a]/126	71/71	~42	33 (26)	140/90	24 h 135/85	—	45 (35.7)	—	10 (8.0)	71 (56.3)
Agarwal *et al.*[51]/2006	—	217[b]/217	199/217	67	8 (3.6)	SBP 130	—	SBP 130	19 (8.7)	16 (7.4)	27 (12.4)	116 (53.5)
Minutolo *et al.*[64]/2007	—	290[c]/290	218/228[a]	~65	118 (41)	SBP: 130	DT-S 130		45 (15.5)	92 (31.7)	17 (5.9)	136 (46.9)
Terawaki *et al.*[65]/2008	Ohasama	708[d]/1365	178/376[a]	63 ± 9	921 (68)	140/90	—	135/85	823 (60.3)	203 (14.9)	175 (12.8)	164 (12.0)
Pogue *et al.*[14]/2009	AASK-CS	617[e]/617	617/617	60 ± 10	234 (38)	140/90	DT 135/85 or NT 120/70	—	112 (18.2)	14 (2.3)	265 (42.9)	226 (36.6)
Kanno *et al.*[66]/2010	Ohasama	164[d]/1023	71/256	~67	~740 (72)	140/90	DT 140/85 and NT 135/85	—	614 (60)	158 (15)	153 (15)	98 (10)
Hermida *et al.*[67]/2012	MAPEC	794[f]/3344	893/1352[a]	52 ± 14	1626 (49)	140/90	DT 135/85 or NT 120/70	—	192 (18.1)	192 (20.6)	99 (28.0)	311 (31.2)
Rios *et al.*[68]/2013	Hygia	1496[f]/3042	3042/3042	64 ± 11	1355 (44)	140/90	DT 135/85 or NT 120/70	—	—	—	317 (20.5)[m]	1229 (79.5)[m]
											205 (13.7)[n]	1291 (86.3)[n]
Gabbai *et al.*[54]/2012	AASK-CS	617[e]/617	616/617	60 ± 10	235 (38)	SBP 130	24 h 125/79	—	105 (17.0)	—	162 (26.2)	350 (56.7)
Shafi *et al.*[55]/2012	—	156[g]/156	156/156	~70	87 (56)	130/80	24 h 130/80	—	10 (6.4)	9 (5.8)	46 (29.5)	91 (58.3)
Gorostidi *et al.*[15]/2013	Spanish Registry	5693[h]/ 14 382	3943/ 14 382[k] 4846/5693[l]	61 ± 14	6813 (47)	140/90	24 h 130/80	—	837 (14.7)	1641 (28.8)	396 (7.0)	2819 (49.5)
Cha *et al.*[16]/2013	APrODiTe	1317[i]/1317		58 ± 11	488 (37)	140/90	DT 135/86 and NT 120/70	—	256 (19.4)	57 (4.3)	447 (34.0)	557 (42.3)
Iimuro *et al.*[69]/2013	CKD-JCS	1075[i]/1075	975/1075	61 ± 12	393 (37)	140/90	24 h 130/80	—	404 (37.6)	60 (5.6)	332 (30.9)	279 (26.0)

Abbreviations: 24 h, 24 h blood pressure; AASK-CS, Afro-American study of kidney disease and hypertension–cohort study; ABPM, ambulatory blood pressure monitoring thresholds for hypertension; Age, mean age in years; APrODiTe, assessment of blood pressure control and target organ damage in patients with chronic kidney disease; CKD, chronic kidney disease; CKD-JCS, chronic kidney disease-japanese cohort study; DT, daytime blood pressure; DT-S daytime systolic blood pressure; MAPEC, *Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares*; MHT, prevalence of masked hypertension; *n*, total number of subjects/patients in the study; NT, nighttime blood pressure; Office, thresholds for hypertension at doctor office; SBP, systolic blood pressure; SBPM, self(home) blood pressure measurement thresholds for hypertension; SHT, prevalence of sustained hypertension; SNT, prevalence of sustained normotension; T/H, treated/hypertensive patients; WCHT, prevalence of white-coat hypertension.
The symbol '–' indicates not available information.
[a]Nonuremic IgA nephropathy.
[b]Estimated glomerular filtration rate (eGFR) modification of diet in renal disease 4 (MDRD-4) $<60\,ml\,min^{-1}$ per $1.73\,m^2$, or eGFR >90 and albumin/creatinine (Alb/Cr) ratio $\geq 30\,mg\,g^{-1}$ Cr.
[c]eGFR (MDRD-4) $<60\,ml\,min^{-1}$ per $1.73\,m^2$.
[d]eGFR (Cockcroft–Gault (CG)) $<60\,ml\,min^{-1}$ per $1.73\,m^2$ with Proteinuria (SU + DS, $30\,mg\,Lt^{-1}$).
[e]GFR (^{125}I-iothalamate clearance): 20–65 $ml\,min^{-1}$ per $1.73\,m^2$.
[f]eGFR (Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)) $<60\,ml\,min^{-1}$ per $1.73\,m^2$, albuminuria ($\geq 30\,mg$ per 24 h or Alb/Cr ratio $\geq 30\,mg\,g^{-1}$ per Cr) or both.
[g]eGFR (MDRD-4) $<60\,ml\,min^{-1}$ per $1.73\,m^2$ or kidney damage (>3 mo).
[h]eGFR (CKD-EPI) $<60\,ml\,min^{-1}$ per $1.73\,m^2$, albuminuria (Alb/Cr ratio $\geq 30\,mg\,g^{-1}$ per Cr).
[i]eGFR (MDRD-4) 15–59 $ml\,min^{-1}$ per $1.73\,m^2$ or eGFR <90 and Alb/Cr ratio $\geq 30\,mg\,g^{-1}$ per Cr.
[j]eGFR (MDRD corrected for Japan) <60 and $>15\,ml\,min^{-1}$ per $1.73\,m^2$.
[k]all participants.
[l]CKD patients.
[m]No CKD patients ($n=1546$).
[n]CKD patients ($n=1496$).

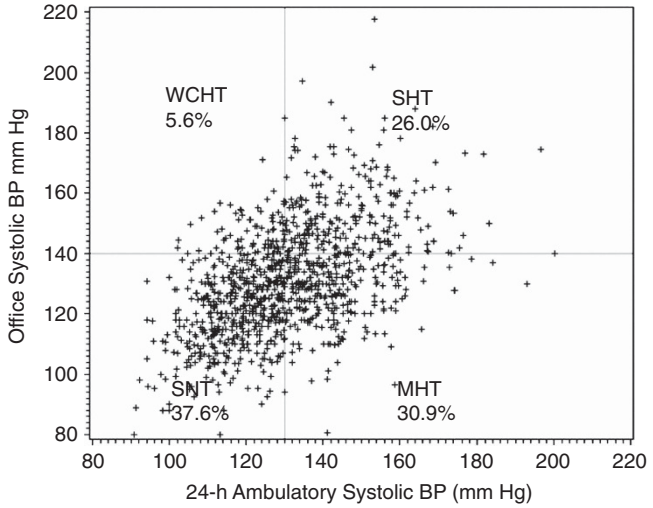


Figure 1 Two-dimensional scattered plot of office systolic BP and 24-h ambulatory systolic BP in 2977 Japanese patients with chronic kidney disease. The cutoff levels for the diagnosis of hypertension were 140/90 mm Hg for office BP and 130/80 mm Hg for 24-h ambulatory BP (from Iimuro *et al.*[69] with permission). BP, blood pressure; MHT, masked hypertension; SHT, sustained hypertension; SNT, sustained normotension; WCHT, white-coat hypertension.

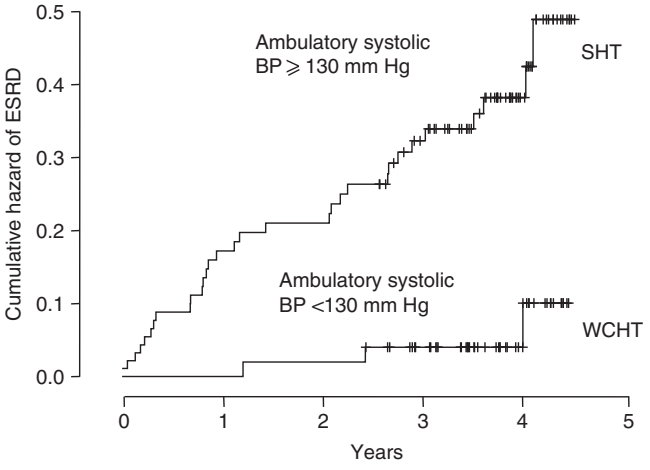


Figure 2 Cumulative risk of end-stage renal disease (ESRD) in patients with chronic kidney disease and elevated systolic clinic blood pressure (BP). None of the patients who had well-controlled standardized clinic BP had ESRD in this study. Those patients with poorly controlled standardized clinic BP (⩾130 mm Hg) but well-controlled awake ambulatory BP (<130 mm Hg)—white-coat hypertension (WCHT)—had fewer ESRD events (lower line) compared with those with poorly controlled standardized clinic BP and poorly controlled ambulatory BP (upper line; $P<0.05$ by log-rank test; from Agarwal and Andersen[51] with permission). SHT, sustained hypertension.

well-defined renal disease (IgA nephropathy),[62] and all of the remaining studies included variable causes of renal disease. Thus, the heterogeneity of renal disease could be a source of variation that significantly explains the differences between the reported prevalences of WCHT and MHT in CKD. Finally, the design of the study (population *vs.* patients, hypertensives or CKD) and the proportion of subjects under treatment could be an additional source of variability. A recent publication from the Spanish ABPM Registry[15] found 5693 (39.5%) patients with the full definition of CKD[74] among a total of 14 382 patients. Among the CKD patients, 3893 (68.4%) patients were in stage 3, and 5152 (90.5%) were in stages 1 to 3. However, some studies either excluded patients with an even moderate decrease in renal function (creatinine $>1.5\,mg\,dl^{-1}$ equivalent to eGFR (CKD-EPI) $\sim 40\,ml\,min^{-1}$ per $1.73\,m^2$ for 50-year-old men) or did not report specific data on this population.

Because of these limitations, the prevalence of WCHT in CKD ranges from 2.3 to 31.7%,[14,64] and the prevalence of MHT in CKD varies from 5.9 to 42.9%.[14,64]

Prognostic information associated with WCHT and MHT in CKD patients is scarce. Most reports, even longitudinal studies,[14,66,69] are based on baseline (cross-sectional) data.

There are very few studies that report data on the prognosis of WCHT and MHT in CKD. Kanno *et al.*[66] evaluated the CKD risk associated with WCHT and MHT as determined by 24-h ABPM in 1023 residents in the general population of Ohasama, Japan. Subjects were categorized using 140/85 mm Hg daytime ABPM and 140/90 mm Hg office BP as thresholds. The odds ratios (ORs) for the prevalence of CKD were calculated using a multiple logistic regression model. Compared with normal BP, the risk of CKD was significantly higher in sustained hypertension (OR, 2.81; 95% CI 1.66–4.75; $P=0.0001$), MHT (OR, 2.29; 95% CI, 1.45–3.63; $P=0.0004$) and WCHT (OR, 1.67; 95% CI, 1.03–2.71; $P=0.0368$). They concluded that WCHT and MHT were significantly associated with CKD. However, data on the prognostic value of these categories were not analyzed. Pogue *et al.*[14] also examined the cross-classification data of a prospective cohort from the AASK study (AASK-CS). MHT was defined by elevated daytime (⩾135/85 mm Hg) or elevated nighttime (⩾120/70 mm Hg) ABPM in those with controlled clinic BP (<140/90 mm Hg). They reported a very high prevalence of MHT. Compared with subjects with controlled clinic BP or WCHT, target organ damage (proteinuria and left ventricular hypertrophy) was more common in subjects with MHT or sustained hypertension when assessed cross-sectionally. They speculated that MHT may account for the disappointing results in the AASK study where, despite excellent in-office BP control, there was still a progression of CKD.

Agarwal *et al.*[51–53,56,75] addressed the issue of the prognostic importance of ABPM in CKD from many perspectives. However, the results of the prognostic relevance of WCHT and MHT are elusive. In a cohort of 217 elderly (67.4 ± 10.9) men (96.3%) with CKD, patients with well-controlled clinic systolic BP measurement did not evolve to ESRD. However, among the patients with poor systolic BP control by clinic measurement, 3/51 (6%) patients with good ambulatory systolic BP (WCHT) reached ESRD, whereas 31/95 (33%) with poor 24-h ambulatory systolic BP (SHT) also reached ESRD (Figure 2).[51] This study showed a significant increase in the cumulative risk for progressing to ESRD in patients with sustained hypertension in comparison with patients with WCHT.[51] The hazard ratios (HRs) associated with an increase of 1 s.d. in systolic BP with respect to the combined end point ESRD and death or ESRD alone showed the superiority of ambulatory (s.d.: 16.3 mm Hg; HR: 1.88 and 3.04, respectively) *vs.* office BP (s.d.: 25.6 mm Hg; HR: 1.6 and 2.75, respectively). However, no specific HRs were reported for the categories of the cross-classification.[51] From another perspective, it has been widely demonstrated that the risk of cardiovascular complications and death increase proportionally with ambulatory blood pressure. In a recent publication[16] of a study using more than 1317 CKD patients, Cha *et al.*[16] demonstrated that 24-h ambulatory BP progressively increases with the categories of SNT to WCHT to MHT to SHT. Thus, WCHT and particularly MHT in CKD patients

seem to attain an increased risk; however, accurate prognostic significance is elusive and should be analyzed using standardized definitions in future studies.

WCHT AND MHT IN ESRD

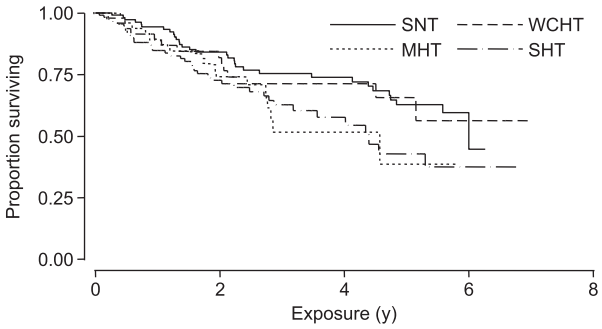
Hypertension is the second most frequent (incident and prevalent) cause of renal disease that requires renal replacement therapy in the United States and Europe, accounting for almost one-third of new cases.[22,76] Among the total number of patients under renal replacement therapy in 2011 (excluding renal transplantation), ~92% of patients in the United States and ~83% of patients in Europe were under hemodialysis therapy.[22,76]

It is noteworthy that 60 to 90% of maintenance hemodialysis patients have hypertension.[22,77,78] Despite the use of multiple medications, high BP in these patients is often poorly controlled.[22,77] There is an elevated prevalence of hypertension in both hemodialysis and peritoneal dialysis; however, it seems more difficult to achieve high BP control in the former.[79] In the patients under hemodialysis, BP is dependent on the volume of the extracellular fluid.[80,81] Other factors such as dialysis dose, residual diuresis, increased activity of the sympathetic system and the renin–angiotensin–aldosterone system, the degree of systemic inflammation and arterial stiffness could also play a role.[79,82–84] Hemodialysis is an intermittent technique with fluctuations (48- to 72-h cycles) in the volume of the extracellular fluid and other parameters.[80] One should expect that, in most cases, BP follows these fluctuations, with a progressive increase from postdialysis to the next predialysis measurement. However, different patterns of BP have been described during the interdialytic interval and during the intradialysis procedure even during the same week.[85,86] Thus, BP has a great variability in patients under hemodialytic therapy. In this context, it is unclear which casual BP measurement is the most representative in terms of diagnosis, control and prognosis in patients under hemodialysis. Predialytic,[78] postdialytic,[78] average or median intradialytic[87,88] BP and the change between pre- and post-dialysis BP have all been considered as potential moments to standardize BP measurements, but no consensus was reached.[87] KDOQI guidelines suggest a predialysis BP goal of $<$140/90 mm Hg and a postdialysis BP goal of $<$130/80 mm Hg of systolic and diastolic BP, respectively.[78]

Because ambulatory techniques cover a long period (24-h ABPM) or even the whole interdialytic period (44-h ABPM), it is reasonable to expect a more accurate estimation of the real BP in comparison with the peridialytic casual measurements.[89] Compared with peridialytic recordings, interdialytic BP measurements are not only more powerful determinants of target organ damage[90,91] but also stronger predictors of all-cause mortality.[92–94] Thus, an accurate diagnosis and control of hypertension in hemodialysis patients should assess interdialytic ambulatory BP recordings.[80]

Moreover, the evaluations of the circadian rhythm of BP in hemodialysis patients demonstrate not only a higher prevalence of nocturnal hypertension but also a major prognostic ability of this condition to predict cardiovascular and all-cause mortality.[95,96] However, similar to what we described in CKD, there are few studies that evaluate MHT and WCHT in patients under hemodialysis. Again, the absence of a consensus in definition is closely related to the scarce and heterogeneous reports.[97]

A recent French study evaluated the prevalence of WCHT and MHT in home BP self-measurement and conventional predialytic measurement of BP in a cohort of hemodialysis patients in two hospitals.[98] BP was recorded using the two methods for 1 week. From the 60 patients who were evaluated, 23 (38%) had sustained uncontrolled hypertension, 13 (22%) had MHT, 8 (13%) had WCHT and 16 (27%) had sustained controlled normotension. Based on data from the general population showing that MHT carries a risk of CV events equivalent to sustained hypertension, the authors concluded that the proportion of patients with MHT should alert clinicians because of the poor cardiovascular prognosis associated with MHT.



Number at risk				
SNT	118	73	41	3
WCHT	51	31	13	3
MHT	53	28	5	0
SHT	120	52	18	1

Figure 3 Kaplan–Meier survival curves for ambulatory systolic blood pressure (BP) and mortality in hemodialysis patients. The numbers below indicate the patients at risk. The mortality of white-coat hypertension (WCHT) was similar to that observed for sustained normotension (SNT). However, the mortality of masked hypertension (MHT) was similar to that of sustained hypertension (SHT). The equality of the survival curves between WCHT and SNT on one hand and MHTN and SHT on the other was tested using the log rank test and found to be significant ($P<0.009$; from Agarwal *et al.*[97] with permission).

However, specific prognostic data for WCHT and MHT in hemodialysis patients are elusive and even more so for peritoneal dialysis. Agarwal *et al.* studied 355 middle-aged (mean 55 years old) patients, mostly black with long-term hemodialysis.[97] Using a threshold of 140/80 mm Hg for median midweek dialysis-unit BP and 135/85 mm Hg for 44-h ambulatory BP, the authors defined four categories of BP: SNT, WCHT, MHT and SHT. The prevalence of SNT was 35%, WCHT 15%, MHT 15% and SHT 35%. The rate of death was higher in MHT and SHT in comparison with SNT and WCHT (Figure 3). Unadjusted and multivariate-adjusted analyses showed that the all-cause mortality increases proportionally with the severity of hypertension. Unadjusted HRs from SNT, WCHT, MHT and SHT were 1.00, 1.12, 1.70 and 1.80, respectively (P for trend $\leqslant$0.01). Adjusted HRs were confirmatory: 1.00, 1.30, 1.36 and 1.87, respectively (P for trend $\leqslant$0.02). When a predialysis BP threshold of 140/90 mm Hg was used to classify patients into BP categories, the prevalence of SNT was 24%, WCHT 26%, MHT 4% and SHT 47%, and the HRs for mortality were similar when compared with the median midweek dialysis-unit BP. In agreement with the evidence in the general population,[30] a significant relationship between increasing levels of hypertension from SNT to WCHT to MHT to SHT and all-cause mortality have been observed. Even though we will most likely need future confirmatory studies, present evidence[97] points to the prognostic significance of MHT and WCHT in patients under hemodialysis.

CONCLUSION

There is convincing evidence supporting the advantages of using ABPM and self/home blood pressure measurement in CKD and

ESRD. The prevalence of WCHT (including the white-coat effect) and MHT (including masked uncontrolled hypertension) in CKD and ESRD is higher than in the general population and in studies of hypertensive patients. Cross-sectional and longitudinal studies emphasize that the degree of risk associated with WCHT and MHT in these patients mirrors that of studies involving the general population and hypertensive cohorts. The risk attributed to WCHT is close to that of SNT and the risk of MHT is as high as that of SHT. However, some uncertainty remains regarding the significance of WCHT and MHT in CKD and ESRD that is because of ambiguous definitions and the absence of specific reports on treatment status. Reaching a consensus in the definitions of hypertension in CKD and ESRD and reporting the treatment status are mandatory for designing future research. In the interim, including patients with renal disease in randomized clinical trials and reporting specific results for renal disease by treatment status will help support the present evidence.

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