Masked Uncontrolled Hypertension in CKD

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ABSTRACT

Masked uncontrolled hypertension (MUCH) is diagnosed in patients treated for hypertension who are normotensive in the clinic but hypertensive outside. In this study of 333 veterans with CKD, we prospectively evaluated the prevalence of MUCH as determined by ambulatory BP monitoring using three definitions of hypertension (daytime hypertension ≥135/85 mmHg; either nighttime hypertension ≥120/70 mmHg or daytime hypertension; and 24-hour hypertension ≥130/80 mmHg) or by home BP monitoring (hypertension ≥135/85 mmHg). The prevalence of MUCH was 26.7% by daytime ambulatory BP, 32.8% by 24-hour ambulatory BP, 56.1% by daytime or night-time ambulatory BP, and 50.8% by home BP. To assess the reproducibility of the diagnosis, we repeated these measurements after 4 weeks. Agreement in MUCH diagnosis by ambulatory BP was 75–78% (k coefficient for agreement, 0.44–0.51), depending on the definition used. In contrast, home BP showed an agreement of only 63% and a k coefficient of 0.25. Prevalence of MUCH increased with increasing clinic systolic BP: 2% in the 90–110 mmHg group, 17% in the 110–119 mmHg group, 34% in the 120–129 mmHg group, and 66% in the 130–139 mmHg group. Clinic BP was a good determinant of MUCH (receiver operating characteristic area under the curve 0.82; 95% confidence interval 0.76–0.87). In diagnosing MUCH, home BP was not different from clinic BP. In conclusion, among people with CKD, MUCH is common and reproducible, and should be suspected when clinic BP is in the prehypertensive range. Confirmation of MUCH diagnosis should rely on ambulatory BP monitoring.


CKD affects 11% (19.2 million) of the United States adult population; among them hypertension occurs in at least 70%. Controlling hypertension is an important strategy to reduce cardiovascular morbidity and mortality and end-stage renal disease. Yet some large randomized trials that have lowered BP have failed to show an improvement in cardiovascular or renal outcomes. One explanation may be that techniques to assess BP in these patients were suboptimal. Whereas non-traditional risk factors may certainly be important, data from the Framingham Heart Study demonstrate that it is the traditional risk factors that mediate the inflammatory state; this in turn impairs vascular function. Thus, it appears appropriate to re-focus our attention on the traditional risk factors—such as blood pressure—and how to better assess and treat hypertension.

Masked hypertension (MHTN), which is defined as normal BP in the clinic but elevated BP at home is seen in 10–20% of the general population that does not receive antihypertensive therapy. A meta-analysis of 36 studies incorporating 25,629 participants reported its prevalence as 17%. People receiving antihypertensive therapy who have hypertension out of office but have normal BP in the clinic are said to have masked uncontrolled hypertension (MUCH). In studies of CKD patients, all of which recruited a limited number of patients, a meta-analysis also found a high prevalence of MUCH. The lack of recognition of elevated BP outside the clinic may lead to inadequate

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treatment of those with normal clinic BP. In the general population, data consistently show that the lack of recognition of high BP outside the clinic—masked hypertension—is associated with increased cardiovascular damage and cardiovascular morbidity and mortality. Although emerging data in CKD also support this concept, whether patients with CKD also have a high prevalence of MHTN, and if so what the determinants of this condition are, and how reproducible this diagnosis is, remains to be demonstrated prospectively in studies dedicated to this purpose. Furthermore, the ability of home BP to diagnose MHTN and its reproducibility remains scarcely studied even in the general population.

In this prospective study, we report the prevalence of masked hypertension, test various definitions on their effect on the prevalence rates of MHTN, determine the value of baseline clinic BP on the prevalence rates of MHTN, and evaluate its reproducibility. Finally, we tested the ability of home BP to diagnose MHTN confirmed by 24-hour ambulatory BP monitoring (ABPM).

RESULTS

An overview of the study design over six visits over a 5-week period is shown in Figure 1.

Baseline characteristics of participants are shown in Table 1. Typical of a veteran population, participants were older, mostly white men, and two-thirds were past smokers. A high prevalence of diabetes mellitus, sleep apnea, and cardiovascular disease was noted. The average eGFR was 44 ml/min per 1.73m² and the median urinary albumin/creatinine ratio was 30 mg/g (interquartile range 6–228 mg/g). All but six participants were receiving antihypertensive drugs for BP control and the average number of antihypertensive drugs used was 3.1.

**Figure 1.** Overview of study design. After a brief history and physical examination, participants had BP measured in a seated position. The technique of HBPM was explained and a self-inflating oscillometric device was dispensed. For one week, each participant recorded home BP twice daily. ABPM was performed over 24 hours. After one month hiatus, the study was repeated as in the initial month. CBP, clinic BP; HBPM, home BP monitoring.

**Bivariate Distribution of Clinic and Ambulatory BP at Baseline and Repeat Visits**

All 333 participants who were recruited had screening clinic measurement of <140/90 mmHg. Of these 333 participants, 38 had inadequate or absent ambulatory BP recordings and were not classifiable, therefore the remaining 295 formed the basis of this report. Over three visits, 33 (11%) participants had an average clinic BP ≥140/90 mmHg at baseline (Figure 2A). Among them, only one (3%) had isolated clinic hypertension defined as well controlled daytime and nighttime hypertension, but 32 (97%) had uncontrolled hypertension (UCH). The distribution of UCH is shown in Figure 2B: one (3%) had isolated daytime hypertension (UCH-D), four (13%) had isolated nighttime hypertension (UCH-N), and 27 (84%) had both daytime and nighttime hypertension (UCH-DN).

At baseline, 262 participants had clinic BP <140/90 mmHg. Of these, 115 (44%) had well controlled ambulatory BP both during the day and during the night (controlled hypertension) whereas 147 (56%) had MUCH (Figure 2A). The distribution of MUCH was as follows: eight (6%) had isolated daytime hypertension (MUCH-D), 77 (52%) had isolated nighttime hypertension (MUCH-N), and 62 (42%) had both daytime and nighttime hypertension (MUCH-DN) (Figure 2B). Repeat measurements 4 weeks later were available in 274 of 295 (93%) participants with classifiable hypertension at baseline. The proportions of participants with isolated clinic hypertension, UCH, controlled hypertension, and MUCH at the repeat visit were similar to those noted at baseline (Figure 2C). Furthermore the categories of UCH and MUCH were also similar (Figure 2D).

**Prevalence of MUCH Using Various Definitions**

Using the conventional definition of MUCH as clinic BP <140/90 mmHg and daytime ambulatory BP ≥135/85 mmHg, 70 (27%) participants had MUCH whereas 192 (73%) had well controlled hypertension (Table 2). Repeat visit revealed prevalence of MUCH as 28% (n=69) and that of well controlled hypertension as 72% (n=177).

In contrast to the above definition, using the 24-hour ABPM threshold of ≥130/80 mmHg to define hypertension revealed a higher prevalence of MUCH: 33% at baseline visit and 37% at repeat visit. Furthermore, by using the most liberal definition of daytime or nighttime hypertension increased the prevalence of MUCH to 56% and 57% at baseline and repeat visit, respectively.

In comparison to ABPM-based definitions, home BP monitoring-based diagnosis revealed the prevalence of MUCH to be about 46% on each of the two occasions.

**Reproducibility of Categories and the Diagnosis of MUCH**

There were 204 pairs of complete datasets available for clinic and ambulatory BP measurements 4 weeks later were available in 274 of 295 (93%) participants with classifiable hypertension at baseline. The proportions of participants with isolated clinic hypertension, UCH, controlled hypertension, and MUCH at the repeat visit were similar to those noted at baseline (Figure 2C). Furthermore the categories of UCH and MUCH were also similar (Figure 2D).

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recordings among participants with controlled clinic BP at both weeks that formed the basis of assessment of reproducibility. Agreement was between 75% and 78% regardless of the definition of MUCH (Table 3). The $\kappa$ coefficient for agreement was between 0.441 and 0.509, which is considered moderate. In contrast to ABPM-based diagnoses, in the case of home BP-based diagnosis of MUCH, the agreement was only about 63% and $\kappa$ coefficient 0.249, which is considered fair.

**Effect of Clinic BP on the Prevalence of MUCH**

After excluding one participant who had isolated diastolic hypertension, the prevalence of controlled hypertension and UCH stratified by baseline clinic systolic BP is shown in Table 4.
Increasing levels of clinic systolic BP was associated with increasing numbers of UCH and reducing numbers of controlled hypertension. Accordingly, the prevalence of MUCH increased with increasing clinic systolic BP. Compared with clinic systolic BP <110 mmHg, increments of 10 mmHg clinic systolic BP were associated with odds ratios of 13.4, 33.8, and 128.3 at baseline visit and 4.3, 13.9, and 28.3 at 4 weeks. Each 10 mmHg increment in clinic systolic BP increased the odds of MUCH by 3.5 (95% confidence interval (95% CI), 2.4–5.0) at baseline visit and 2.7 (95% CI, 2.0–3.8) at 4 weeks. Multivariable adjustments for the following characteristics: age, race, diabetes, smoking, cardiovascular disease (defined as myocardial infarction, stroke, peripheral vascular disease and congestive heart failure), number of antihypertensive drugs, eGFR, MUCH is calculated as UCH×100%/CH+UCH.

Table 2. Prevalence of masked hypertension using different definitions and over two time periods

<table>
<thead>
<tr>
<th>Definition</th>
<th>Baseline visit</th>
<th>Repeat visit at 4w</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CH (n) UCH (n) MUCH (%)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Daytime ABPM</td>
<td>192 70 26.7</td>
<td>21.3–32.1%</td>
</tr>
<tr>
<td>24-Hour ABPM</td>
<td>176 86 32.8</td>
<td>27.1–38.5%</td>
</tr>
<tr>
<td>Daytime and nighttime ABPM</td>
<td>115 147 56.1</td>
<td>50.1–62.2%</td>
</tr>
<tr>
<td>Home BP</td>
<td>140 122 46.6</td>
<td>40.5–52.6%</td>
</tr>
</tbody>
</table>

Figure 2. Bivariate distribution of hypertension categories by visit. (A) Number of participants who had hypertensive clinic BP (left bar) or were normotensive (right bar). If clinic BP was in the hypertensive range, but ambulatory BP was normal isolated clinic hypertension (ICH) was diagnosed, or if ambulatory BP was high, they were said to have uncontrolled hypertension (UCH). If clinic BP was normal and ambulatory BP was normal they had controlled hypertension (CH), or if ambulatory BP was elevated they were diagnosed with MUCH. (B) The reason why participants were diagnosed with UCH or MUCH. UCH during daytime only (UCH-D), daytime or nighttime (UCH-DN), or nighttime only (UCH-N) pie-chart is shown. Similarly MUCH breakdown as a pie chart by ambulatory BP monitoring elevation during daytime (MUCH-D), daytime or nighttime (MUCH-DN), and nighttime alone (MUCH-N) are shown. (C) and (D) Data from repeat measurements at week 4.
and log urinary albumin/creatinine ratio did not remove the statistical significance of increasing clinic systolic BP on the odds of MUCH (Table 4).

**Ability of Home BP to Diagnose Ambulatory BP**

Using the conventional definition of MUCH (elevated day time ambulatory BP (>135/85 mmHg but normal clinic BP <140/90 mmHg), we asked the question whether home BP can detect MUCH and if so what are the diagnostic characteristics of this test. We used receiver operating characteristic (ROC) curves to evaluate the performance of home BP in making a diagnosis of MUCH.

The ROC curve to diagnose MUCH using home systolic BP is shown in Figure 3A and B for baseline visit and week 4 visit, respectively. The area under the curve (AUC) of the ROC curve shown in Figure 3A and B for baseline visit and week 4 visit, much before GFR declines.

**DISCUSSION**

The definition of MUCH has an important bearing on the prevalence of this condition. The original definition proposed by Pickering and colleagues29 and one used by the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) investigators30 do not take into account BP recordings at night. The conventional definition of MUCH used in these studies relies on clinic BP <140/90 mmHg and daytime ambulatory BP ≥135/85 mmHg. Using this definition, among participants with CKD with normal clinic BP, the prevalence of MUCH was 27%. However, some investigators use elevation of either daytime or nighttime BP to diagnose MUCH.23 Using this definition more than doubles the prevalence of MUCH to 56%. This is similar to the prevalence reported in those studies. For example, from a Spanish registry of ABPM, 14,840 subjects with treated and controlled conventional BP, MUCH diagnosed by 24-hour ABPM was prevalent in 31%.31 Nighttime hypertension was the exclusive abnormality in 24%. In comparison, in our study, nearly 95% had nighttime BP elevation, and it was the exclusive abnormality in half the participants. This is not surprising given the observation that non-dipping among patients with CKD is common;35,36 in fact, it antedates the occurrence of albuminuria in type 1 diabetes mellitus33 and much before GFR declines.

A second important observation made in this study is that the prevalence of MUCH is strongly dependent on the level of clinic BP. Thus, those who repeatedly have a low clinic systolic BP (<110 mmHg) are unlikely to have MUCH. However, among those with usual clinic BP of 130–139 mmHg, MUCH is prevalent in two of three and those with usual clinic BP of 120–129 mmHg, MUCH is prevalent in one of three. Even among individuals with clinic BP of 110–119 mmHg, the prevalence of MUCH was approximately one in six. To allow direct comparison among cohorts, future studies on the prevalence of MUCH should report prevalence stratified by levels of clinic BP.

The reproducibility of the diagnosis of MUCH has previously been tested among 50 untreated participants who had borderline hypertension.15 Using daytime ambulatory BP of >135/85 mmHg to define hypertension, the prevalence of masked hypertension at first visit was 54% and a week later was 53%. The high rates likely reflect the higher baseline BP as most participants already had borderline hypertension. Daytime ambulatory BP was concordant in classifying participants 73% of the time but the κ statistic was only 0.47. In a retrospective cohort in which 80% of the participants were being treated and MUCH was present in 25 of 196 (13%) participants, after a mean period of 1.5 years, the κ statistic was only 0.26.36 However, treatment for hypertension could be changed and time elapsed between BP recordings was variable; the standard deviation of elapsed time between recordings was 1.5 years. Among 503 untreated Japanese participants, using morning home BP as the standard for out-of-office

### Table 4. Prevalence of MUCH defined by daytime ABPM stratified by clinic BP

<table>
<thead>
<tr>
<th>Clinic systolic BP (mmHg)</th>
<th>Baseline</th>
<th></th>
<th></th>
<th></th>
<th>Return visit at 4 weeks</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CH (n)</td>
<td>UCH (n) MUCH (%)</td>
<td>OR (95% CI) aOR</td>
<td>CH (n) UCH (n) MUCH (%)</td>
<td>OR aOR</td>
<td>CH (n) UCH (n) MUCH (%)</td>
<td>OR aOR</td>
</tr>
<tr>
<td>&lt;110</td>
<td>66</td>
<td>1.5</td>
<td>1</td>
<td>62</td>
<td>4.4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>110–119</td>
<td>69</td>
<td>16.9</td>
<td>13.4 (1.7–104.7)</td>
<td>9.1 (1.1–74.9)</td>
<td>53</td>
<td>17.2</td>
<td>4.3 (1.1–16.2)</td>
</tr>
<tr>
<td>120–129</td>
<td>39</td>
<td>33.9</td>
<td>33.8 (4.4–262.1)</td>
<td>21.2 (2.6–172.1)</td>
<td>43</td>
<td>40.3</td>
<td>13.9 (4.0–48.7)</td>
</tr>
<tr>
<td>130–139</td>
<td>18</td>
<td>66.0</td>
<td>128.3 (16.4–1001.8)</td>
<td>90.3 (11.1–734.3)</td>
<td>19</td>
<td>57.8</td>
<td>28.3 (7.7–103.9)</td>
</tr>
</tbody>
</table>

aOR, adjusted odds ratio; OR, odds ratio.

Adjustments were for age, diabetes, smoking, cardiovascular disease, number of antihypertensive drugs, eGFR, and log urinary albumin/creatinine ratio.

### Table 3. Reproducibility of masked hypertension using different definitions

<table>
<thead>
<tr>
<th>Concordance statistics</th>
<th>Agreement</th>
<th>κ</th>
<th>95% CI</th>
<th>P level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime ABPM</td>
<td>78.4%</td>
<td>0.441</td>
<td>0.305–0.577</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-Hour ABPM</td>
<td>76.5%</td>
<td>0.474</td>
<td>0.339–0.609</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Daytime and nighttime ABPM</td>
<td>75.5%</td>
<td>0.509</td>
<td>0.372–0.645</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Home BP</td>
<td>62.8%</td>
<td>0.249</td>
<td>0.112–0.386</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Figure 2. Nighttime and Daytime BP Distribution**

**Figure 3. ROC Curve**

**Table 4. Prevalence of MUCH defined by daytime ABPM stratified by clinic BP**

- aOR, adjusted odds ratio; OR, odds ratio.
- Adjustments were for age, diabetes, smoking, cardiovascular disease, number of antihypertensive drugs, eGFR, and log urinary albumin/creatinine ratio.

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**Figure 5. Concordance statistics**

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- aOR, adjusted odds ratio; OR, odds ratio.
- Adjustments were for age, diabetes, smoking, cardiovascular disease, number of antihypertensive drugs, eGFR, and log urinary albumin/creatinine ratio.
Our study used 24-hour ABPM, the gold-standard method to diagnose MUCH/MHTN diagnosed by home BP monitoring is independent of the definition of MUCH using ABPM (46% versus 27%). In contrast to daytime ambulatory hypertension (135/85 mmHg) at baseline visit (A) and after 1 month (B). The area under the curve (AUC) for clinic and home BP monitoring were similar (P=0.38 and 0.14, respectively) at each of the two visits.

Figure 3. Receiver operating characteristic (ROC) curves for the diagnosis of MUCH. ROC curves for the diagnostic test performance of systolic clinic and home BP in predicting MUCH diagnosed by daytime ambulatory hypertension (135/85 mmHg) at baseline visit (A) and after 1 month (B). The area under the curve (AUC) for clinic and home BP monitoring were similar (P=0.38 and 0.14, respectively) at each of the two visits.

measurement, k coefficient for agreement was 0.58 at 6 months.37 Our study is the largest specifically to test the reproducibility of MUCH after 4 weeks. Our study had a high completion rate with 295 participants completing the first set of visits and 274 participants completing the second set 4 weeks later. We found agreement of between 75% and 78% and k of 0.44–0.51 similar to that reported in those with MHTN in a cohort of people with untreated borderline hypertension. The observed concordance in the diagnosis of MUCH suggests that MUCH is more than a statistical phenomenon and may have a biologic basis.

In this cohort, home BP monitoring detected a prevalence of MUCH that was nearly 70% more than that of the standard definition of MUCH using ABPM (46% versus 27%). In contrast to ambulatory BP-based definitions, home BP-based diagnosis had lower agreement and poor k suggesting only fair reproducibility. Furthermore, home BP measurements were no better than clinic BP in making a diagnosis of MUCH. Numerically, the AUC under ROC curves was greater for clinic BP than home BP in diagnosing MUCH. Thus, there is little reason to suspect lack of statistical power as a reason for failure of home BP over clinic BP in diagnosing MUCH. It is possible that a larger sample size might have demonstrated that clinic BP significantly outperforms home BP. Taken together, these findings extend the observations of Viera et al. who also pointed out the inadequacy of home BP monitoring in detecting MHTN.35 In contrast to daytime ambulatory BP recordings, many of which may be taken during activity, home BP recordings are always made during rest. Given that activity generally increases systolic BP it is surprising that home BP found a higher prevalence of MUCH.36 However, the act of home BP measurement may be stressful, and readings during the first few hours after waking may be higher than during the rest of the day.39 This might explain why the prevalence of MUCH detected by home BP recordings was higher. Prior studies which suggested the usefulness of using home BP for diagnosing MUCH likely ignored the independent contribution of clinic BP for diagnosing this condition. Nonetheless, our study does not discount the importance of home BP monitoring. MUCH diagnosed by home BP monitoring is associated with an increased risk of cardiovascular events in elderly treated patients with essential hypertension.9 Among those with CKD, MUCH diagnosed by home BP monitoring is associated with an increased risk of ESRD.20,40 An individual level meta-analysis reported by investigators of the International Database of Home Blood Pressure in relation to Cardiovascular Outcomes, from five populations in 5008 participants, suggests that home BP monitoring can refine cardiovascular risk assessment above and beyond clinic BP.41 This is particularly true when clinic BP is in the normal range (i.e., among those with MHTN or MUCH). Accordingly, a more logical explanation of our findings is that home BP monitoring-diagnosed MUCH may detect a different phenotype.

Our study has limitations. Participants in our study were restricted to veterans who are older and are predominantly men. Whether our findings apply to younger people and women will need future studies. There are several strengths of our study: our study used 24-hour ABPM, the gold-standard method to diagnose out-of-office hypertension. Our study was prospective, it carefully phenotyped the BP pattern in each individual using several BP monitoring methods, used multiple clinic visits to define clinic hypertension, had a high completion rate, and it assessed reproducibility of MUCH using an adequate sample size for this purpose.

The three clinical implications of our findings are as follows: (1) Among patients with CKD, nearly all of whom were taking antihypertensive medications, MUCH is likely to be seen in as many as one of six if clinic BP is 110–119 mmHg, twice as many (one in three) if clinic BP is 120–129 mmHg, and four times as many (two of three) if the usual clinic BP is 130–139 mmHg. Only if clinic BP is <110 mmHg, is the likelihood of MUCH low (<5%). (2) The use of home BP monitoring to diagnose MUCH in CKD is not supported by our study, however we recognize that home BP monitoring may detect a different phenotype and that MUCH/MHTN diagnosed by home BP monitoring is independently associated with cardiovascular outcomes. (3) The short-term reproducibility of MUCH diagnosed by ambulatory BP measurement regardless of the definition is between 75% and 78%; therefore MUCH may be more than a statistical
phenomenon and have a biologic basis. Future studies will define the biologic basis of MUCH and the long-term outcomes associated with this common disorder.

CONCISE METHODS

This is a prospective study of CKD patients stages 2 to 4 (eGFR defined using the Modification of Diet in Renal Disease (MDRD) equation < 90 ml/min per 1.73 m² but > 15 ml/min per 1.73 m²). For those with stage 2 CKD, albuminuria (A2 or ≥ 300 mg/g creatinine) was required for inclusion in the cohort. Those with an initial clinic BP of 140/90 mmHg or less were considered eligible and studied further. Detailed inclusion and exclusion criteria are shown in the supplemental Appendix. After obtaining a clinical history, performing a physical examination, and obtaining basic laboratory tests, measurements of BP in the clinic (average of three visits), home (one week average) and by 24-hour ambulatory monitoring (24 hour average) were performed (for details on measurements, please see supplemental Appendix). BP measurements were repeated after one month to assess their reproducibility. Only those diagnoses confirmed by physician review of the electronic chart of the patient are reported here.

Classification of Hypertension

Masked hypertension is a term reserved for people not receiving antihypertensive medications. Given that there were only six participants in our study who were not receiving antihypertensive therapy, we used the term masked uncontrolled hypertension (MUCH) to define participants who had controlled clinic BP (< 140/90 mmHg on average of three clinic visits by oscillometric BP measurement) but elevated ambulatory BP. Elevated ambulatory BP was defined three different ways: (1) elevated daytime (≥ 135/85 mmHg); (2) elevated 24-hour (≥ 130/80 mmHg); and (3) either elevated daytime or elevated nighttime (≥ 120/70 mmHg) ambulatory BP. To define daytime and nighttime we used patient diaries as noted in the supplemental Appendix. The average weekly home BP was used to define home hypertension if BP was ≥ 135/85 mmHg. The prevalence rates of MUCH for each of these definitions and their 95% CIs are reported.

Determination of Sample Size

Estimation of Sample Size for Prevalence of Hypertension

In our preliminary study we found the prevalence of masked hypertension by standardized measurements of clinic BP to be 26% (95% CI, 13–39%). We estimated that a sample size of 300 subjects with controlled hypertension in the clinic will allow us to estimate the prevalence of MHTN with a 3.8% margin of error and 95% CI when the true prevalence is as low as 13%, and with a 5.5% margin of error if the true prevalence is as high as 39%.

Estimation of Sample Size for Reproducibility

We estimated that approximately 78 patients (26% of 300) will have masked hypertension in a sample of 300 patients who complete both visits. At one month we sought a diagnosis of MHTN by repeating the study. We defined reproducibility to be modest if 60–79% were diagnosed with MHTN and excellent if 80–100% were diagnosed with MHTN. We calculated that if 78 patients had MHTN it would allow us to estimate reproducibility with a 10.2% margin of error when the true reproducibility rate was 70%. This sample size of 78 patients would also give us a 95% CI to estimate an excellent reproducibility with a 6.7% margin of error when the true reproducibility rate was 90%.

Statistical Analysis

Software for data entry at front end was designed for manual and electronic import. For example, home BP and ambulatory BP data were electronically imported. Stored in a relational database, data were queried for accuracy of data entry and quality. Means, standard deviations, counts and proportions were calculated for baseline data. Prevalence rates of MUCH and their 95% CIs were calculated. Reproducibility was evaluated by using percentage agreement and k statistic. Ordinal logistic regression was used to evaluate the association of declines of systolic clinic BP with the diagnosis of MUCH. Logistic regression was used to evaluate the association of each 10 mmHg increase in clinic systolic BP with the odds of MUCH. Multivariate adjustments were made based on a careful review of the literature accounting for variables associated with MUCH. The ability of clinic and home BP to detect MUCH was evaluated using receiver operating-characteristic curves. All statistical analyses were done with Stata 13.1 (StataCorp., College Station, TX). Nominal level of statistical significance was taken as a two-sided P value of 0.05.

ACKNOWLEDGMENTS

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DISCLOSURES

R.A. has consulted for several pharmaceutical companies that make antihypertensive drugs including Merck, Takeda, Novartis, Daiichi Sankyo, Abbvie, Bayer, and Johnson and Johnson. The other authors have nothing to declare.

REFERENCES


11. Bangash F, Agarwal R: Masked hypertension and white-coat hyperten-


17. Fagard RH, Cornilissen VA: Incidence of cardiovascular events in white-coat, masked and sustained hypertension versus true normo-


31. Agarwal R: Regulation of circadian blood pressure: from mice to as-

32. Lurbe E, Redon J, Kesani A, Pascual JM, Tacones J, Alvarez V, Batlle D: Increase in nocturnal blood pressure and progression to mi-


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Appendix

Participants
Consecutive patients attending the Renal Clinic or a general medicine clinic at the Roudebush VA Medical Center at Indianapolis were recruited if they met the following criteria.

Inclusion criteria
1. Chronic kidney disease from stages 2 through 4 (Estimated GFR <90 mL/min/1.73 m² but >15 mL/min/1.73 m²). For those with stage 2 CKD, albuminuria (A2 or >300 mg/g creatinine) was required.
2. Age >18 years but <90 years.
3. Clinic systolic blood pressure >90 mm Hg but <140 mm Hg. Those with very low systolic blood pressure in the clinic are unlikely to have masked hypertension at home. Clinic systolic blood pressure will be the average of three separate visits.
4. Clinic diastolic BP of <90 mmHg.

Exclusion Criteria
1. Planning to move or unable to make 5-6 visits in the next 4-6 weeks.
2. Morbid obesity (BMI of 40 kg/m² or more)—difficult to perform ambulatory BP monitoring in the morbidly obese subjects.
3. Six or more irregular heart beats per minute, including atrial fibrillation—these events make BP measurement difficult by any technique.
4. Renal transplantation or end-stage renal disease requiring dialysis.
5. Advanced coexisting illness (e.g. terminal cancer, advanced heart failure or advanced liver cirrhosis).
6. Nursing home resident.
7. Non-English speaking.
8. Pregnant or nursing mothers.
9. Unable or unwilling to learn home BP monitoring.

BP measurement methods

Ambulatory Blood Pressure Monitoring
Ambulatory blood pressure (ABP) monitoring was performed in all patients at baseline and at the end of the four week follow-up using the Spacelabs 90207 monitor which has been shown to be accurate by two protocols: the British Hypertension Society (BHS) and the Association for the Advancement of Medical Instruments (AAMI) 1. In all study patients, appropriately sized cuffs, with bladder sizes that encircled 80–100% of arm circumference and widths that are at least 40% of arm circumference were placed on the non-dominant arm and patients were instructed in the use of the ABP monitor 1. Measurements were taken every 20 minutes from 06:00 – 22:00 and every 30 minutes.
from 22:00 – 06:00 based upon a prior protocol. The patients recorded their awake and sleep times into diaries that were used to help calculate daytime and nighttime ABP. The patients were told to pursue normal activities during the data collection. ABP monitoring was considered adequate if there were at least 14 daytime readings and at least 7 night time readings. Blood pressures were averaged by the hour in which the blood pressure was taken and then by awake or asleep state.

**Clinic blood pressure**

Clinic oscillometric blood pressures were obtained in triplicate by a trained technician using the non-dominant arm. With the arm and the forearm supported at the level of the heart, oscillometric blood pressure measurements were taken using a digital sphygmomanometer (Model HEM-907, Omron Healthcare, Vernon Hills, IL) with an appropriate cuff size after 5 minutes at rest. Following the oscillometric measurements, auscultatory blood pressures were measured using methodology recommended by the European Society of Hypertension. The monitor was set to manual mode which allowed the automatic sphygmomanometer to be used as a manual recorder. The first Korotkoff’s sound (K1) and the last (K5) were used as systolic and diastolic blood pressure, respectively. There was a 30 second pause between readings. The average of the three oscillometric readings was used as the visit BP. The clinic BP was calculated by averaging the visit BP from three visits on day 1, 7, and 8. For purposes of this study, auscultated measurements were ignored.

**Home blood pressure**

Each patient was dispensed a home digital sphygmomanometer with an automatic inflator (Model HEM790IT, Omron Healthcare, Inc, Vernon Hills, IL) with a cuff size appropriate for arm size. This monitor stores up to 200 measurements in memory that can be retrieved. Subjects were asked to record their blood pressure after 5 minutes of seated rest in triplicate twice daily for one week. All patients were given instructions in use of the monitor prior to participation in the study. Data from subjects with <9 readings at home were not used.

**Reference List**
