# Chapter 3: Results

## Literature Search and Abstract Review Process

Results from the searches and the abstract review process were maintained in databases developed in ProCite. A summary of the search results is provided in Table 1. The bulk of the searching was completed in January and February 2001, with a final search of PubMed® completed March 23, 2001. Hand searching of journals was conducted of issues published before May 31, 2001. Hand searching of key references was completed in July 2001.

Of the 6,194 citations retrieved by the search methods, 4,852 were uniquely identified; that is, not previously included in the Blood Pressure Citations database. Of the 4,852 citations, 902 (19 percent) were classified as eligible for second level abstract review. Citations were excluded at this level if they did not address any of the research questions (37 percent), met any exclusion criteria (26 percent) or a combination of the above. Reviewers did not need to agree on what exclusion criterion applied. The most frequent exclusion criterion applied was that the article did not include ABP or SMBP (used by one or both reviewers to delete 1,256 citations). Other major exclusion criteria were a sample size of less than 20 patients (963 citations) and no original data provided (348 citations).

The 902 citations deemed eligible from the first abstract review were imported into a new database and the 35 citations identified by the hand searching efforts were added. Of the 937 citations reviewed at the second level abstract review, 596 (64 percent) were deemed eligible for full article review. As for the first review, the reviewers did not need to agree on a reason for deleting the citation. Of the 341 citations deleted, reviewers agreed that 186 (55 percent) citations included less than 50 patients, that 29 (8 percent) described cross-sectional studies that addressed only question #2 or #3 and did not contain comparison to clinic measurement, that 28 (8 percent) did not address any of the research questions, and that 24 (7 percent) described cross-sectional studies with outcomes other than left ventricular mass or proteinuria/albuminuria. The remainder of the citations were deleted for other reasons or based on a combination of reasons.

## Article Review Process

From the abstract review process, 596 citations were identified for inclusion in the article review phase. We were unable to retrieve, and, therefore, unable to complete article review of three articles. [18-20]

Of the 593 articles reviewed, one article described two studies. Each study was assessed and abstracted separately so there were 594 studies for which a review was completed. An initial scan was completed to identify articles with less than 100 patients. These 223 citations were excluded from the general review but were reviewed, as appropriate, for the study questions addressing reproducibility (#1a-c), prediction of clinical outcomes (#2b and #3b – prospective studies) and effect of treatment guided by self or ambulatory blood pressure measurement (#2d and #3d – trials); the minimum sample

size for the reproducibility studies was 20, while the minimum sample size for the prospective studies and clinic trials was 50.

## General Review

After the exclusion of 223 articles with under 100 patients, there were 370 articles (representing 371 studies) included in the general review. At the article review level, 252 (68 percent) articles were excluded (representing 253 studies). The primary reasons for exclusion were that the article addressed question #1 only and clinic blood pressure measurement used in analyses was completed on one day only (24 percent of excluded articles) and that the article did not include formal comparison of measurements (14 percent). (See Table 2 for list of exclusions.)

The articles determined to be eligible for review were tagged as addressing the following questions: comparison of readings (question #1) 33 studies, association of SMBP with LV mass or proteinuria/albuminuria (question #2a) one study, and association of ABP with LV mass or proteinuria/albuminuria (question #3a) 27 studies.

As part of the general review process articles were tagged if they addressed issues not being covered in this evidence report and if they addressed any of the other questions being reviewed in separate processes. Articles were tagged as addressing the following issues not included in this review: incremental gain of SMBP (question #2c) (0 studies) or ABP (question #3c) (0 studies) over clinic BP, and the association of dippers with left ventricular mass (six studies) or proteinuria/albuminuria (three studies).

## Reproducibility

Thirteen studies were identified through the general review as addressing reproducibility and an additional 50 studies were identified from the articles with less than 100 patients. Most of the 63 studies were excluded (53 studies (84 percent)) as not applicable to the research question which focused on reproducibility of WCH or reproducibility of the difference between ABP (or SMBP) and clinic BP. The vast majority of these studies focused on reproducibility of ABP, SMBP and/or clinic BP. Two studies each were excluded because the study included exclusively children, contained fewer than 20 patients or addressed the prevalence of dipping only. Finally, one study was excluded because data were not presented in an abstractable format. Two studies were identified as addressing reproducibility of white coat hypertension. One study was determined to address reproducibility of the absolute differences between clinic BP and ABP.

## Prospective Studies

From the general review, five studies were identified as addressing the prediction of clinical outcomes using self measurement of blood pressure, 25 studies were identified as addressing prediction of clinical outcomes using ambulatory blood pressure measurement. An additional 13 studies were tagged as prospective studies addressing the prediction of clinical outcomes from the articles with less than 100 patients. From the total number of studies (43), 27 were excluded. The reasons for exclusion were: article did not address research question (15 studies), duplicate

publication (five studies), data not presented in abstractable format (four studies), less than 50 patients (two studies), and no outcome of interest (one study).

### Trials

From the general review 22 studies were tagged as addressing the effect of treatment guided by SMBP or ABP. An additional seven studies were identified as addressing this issue from the articles with less than 100 patients. From the total number of studies (29), 15 were excluded. The reasons for exclusion were: study not a randomized controlled trial (seven studies), did not address research question (four studies), data not presented in abstractable format (two studies), study population exclusively pregnant women (one study), and study had less than 50 patients (one study).

## Description of the Literature

The identified literature addressing BP measurement outside of the office setting was vast and heterogeneous. Most ABP and SMBP studies have been published in specialty journals, primarily those in the field of hypertension. From the 596 articles that were eligible for review, the following journals published ten or more articles (ordered from highest to lowest number of publications): *Journal of Hypertension* (71 articles), *American Journal of Hypertension* (67 articles), *Journal of Human Hypertension* (51 articles), *Hypertension* (48 articles), *Blood Pressure Monitoring* (36 articles), *Journal of Hypertension - Supplement* (33 articles), *American Journal of Cardiology* (11 articles), and *Clinical/Experimental Hypertension* (11 articles). In contrast, publications in general medical journals were relatively uncommon. For example, the *Annals of Internal Medicine* published just two articles, the *Archives of Internal Medicine* five articles, and the *Journal of the American Medical Association* nine articles.

Of these 596 articles, the vast majority of articles (445 articles, 75 percent) were published between 1990 and 1999; 72 articles (12 percent) were published in 2000 or 2001, and another 73 articles (12 percent) between 1980 and 1989. A similar pattern of journal types and of publication years was evident for the articles that were abstracted for this report.

For the majority of the studies, a funding source could not be identified. Approximately 20 percent of studies cited a government source of funding. Of the 89 studies abstracted, 18 percent were completed in the United States, while 54 percent were completed in European countries.

## Question #1

*Comparison of clinic, ambulatory, and SMBP readings*:
*Question #1a. What is the distribution of the BP differences between clinic, ambulatory, and SMBP readings?*

A total of 18 studies addressed the distribution of BP differences among clinic BP, ABP, and SMBP and met the inclusion criteria, which included a minimum sample size of 100 and a requirement for at least 2 visits of clinic BP measurements. Among these, six studies compared clinic BP and SMBP,[21-26] 12 studies compared clinic BP and ABP,[22,25,27-36] and 3 studies compared SMBP and ABP.[25,37,38] One study compared all three types of BP measurements.[25]

Of the 18 studies, a subset of studies displayed in Evidence Table 1, 10 studies were single center,[21-23,25,27-30,35,38] five were multi-center;[26,31-33,37] in the remaining three studies, the number of centers was unclear.[24,34,36] The source of funding was not reported or was unclear in 13 studies; of those reporting the source of funding, two studies were funded by industry,[33,37] two by government[27,36] and one by both government and industry.[32] Twelve studies provided a basic set of patient characteristics (age, gender, and percent on anti-hypertensive medication). Only three studies documented that the clinic BP observer was trained.[22,30,38] Of the eight studies that obtained SMBP measurements, six studies documented that participants received training in SMBP. Of the 14 studies that obtained ABP measurements, only four studies mentioned that participants received training on how to wear an ABP device.[29,31,36,37] A measure of statistical variability (SE, SD, 95% CI or p-value) was reported in all studies.

The sample sizes ranged from 100 to 1651, and mean age ranged from 33 to 75 years (Evidence Table 2). Most studies either targeted hypertensives as the study population or included them as part of a general population; only two studies excluded hypertensive individuals.[29,35] One study targeted only men.[31] Just one study reported that blacks were included in the study sample.[27]

As displayed in Evidence Table 3, the vast majority of studies measured clinic BP in the seated position. Of the 16 studies that obtained clinic BP, all studies had more than one day of blood pressure measurement (range:2 to 4 days); the total number of measurements ranged from 2 to 12. Eight studies used a mercury devices,[21,22,25,27,29,30,34,35] two studies used automated devices[24,26] and one used an aneroid.[23] Of the 12 studies that reported the type of observer, a physician measured BP in six studies, a nurse in four studies, and a technician in two studies.

Of the eight studies that measured SMBP, all studies used an electronic or automated device to record SMBP except for one study which used an aneroid device.[23] (See Evidence Table 4.) Just three studies used a validated device.[22,25,38] Six studies documented that the patient recorded BP;[22-26,37] in two studies this information was not provided.[21,38] The number of measurement-days ranged from two to 14, while the total number of readings ranged from two to 28. In all instances, BP was recorded in the morning and evening; in two studies patients also measured BP in the afternoon.[21,24]

Fourteen studies compared ABP readings to clinic BP (12 studies ) or SMBP (three studies). As displayed in Evidence Table 5, nine studies used a validated device. A majority of studies

used fixed time intervals to define daytime and nighttime ABP; only one study used patient reported times to define awake and asleep ABP.[25]

Six studies compared clinic BP and SMBP (Evidence Table 6). All studies reported lower mean SMBP than clinic BP. The mean differences between clinic BP and SMBP ranged from 5.4 to 17.7 mmHg for systolic BP and from 1.5 to 6.3 mmHg for diastolic BP. All differences were highly significant ($p<0.01$) except for the systolic and diastolic BP differences in one study.[24]

Twelve studies compared clinic BP and ABP (Evidence Table 7 for systolic and Evidence Table 8 for diastolic). For systolic BP, clinic BP exceeded daytime ABP in eight of nine studies (range of differences: -3.8 to 21.9 mmHg, $p<0.001$ in each of eight reports that reported p-values), exceeded nighttime BP in each of three studies (range: 19 to 23.9 mmHg, $p<0.001$ in the two reports with p-values) and exceeded 24 hour ABP in five of six studies (range: -7 to 17 mmHg, $p<0.05$ in the four reports with p-values). For diastolic BP, clinic BP exceeded daytime ABP in each of nine studies (range: 1.9 to 11.8 mmHg, $p<0.05$ in each of six reports with p-values), exceeded nighttime BP in each of three studies (range: 18.9 to22 mmHg, $p<0.001$ in the two reports with p-values) and exceeded 24 hour ABP in each of four studies (range: 3 to 14 mmHg, $p<0.05$ in the four reports with p-values).

Two studies reported gender-stratified analyses.[28,33] For both men and women, clinic BP exceeded daytime and 24 hour BP, but the differences appeared somewhat greater in women than men. The same pattern was evident for both systolic and diastolic BP.

Only three studies compared SMBP and ABP (Evidence Tables 9 and 10). There were no significant differences between SMBP and daytime ABP for either systolic or diastolic BP. In contrast, for both systolic and diastolic BP, SMBP was substantially greater than nighttime ABP in the one study that reported differences and was also greater than 24 hour BP in two studies.

In summary, for both systolic and diastolic BP, clinic BP measurements exceed SMBP, daytime ABP, nighttime ABP and 24 hour ABP. Few studies compared SMBP and ABP levels.

*Question #1b. What is the prevalence of WCH as defined by SMBP?*
*Question #1c. What is the prevalence of WCH as defined by ABP measurement?*

We identified 4 studies that determined the prevalence of WCH using SMBP (Evidence Table 11)[21,38,45,52] and 16 articles that determined the prevalence of WCH using ABP (Evidence Table 12). [36,38-51] Two studies included estimates of the prevalence of WCH using both ambulatory and home BP monitors.[38,45] Thus, a total of 18 articles were identified for review. The majority of studies (n = 11) were conducted at a single clinical center, six were multi-center and for one article the category could not be determined.[49] No funding source was identified for 11 studies. Of those for whom a funding source could be identified, four were funded whole or in-part by a government agency[36,40,50,51] and three were funded whole or in-part by industry[43,50,52] and one by a non-governmental, non-industry source.[47] Most studies (n = 14) reported eligibility criteria in enough detail to replicate the study design and 16 provided basic descriptive characteristics of the study population (age, gender, percent on anti-hypertension medications). However, two studies provided insufficient information on eligibility and baseline characteristics of the study population.[36,41] Observers were masked to other modes of BP measurement in 11

studies. Only three studies specifically indicated that observers were trained in the measurement of clinic BP.[38,43,46] Participants were trained in the use of ABP monitors in eight of sixteen studies utilizing ABPM, and trained in SMBP in two of four studies that utilized home monitors. (See Evidence Table 1.)

As shown in Evidence Table 2, the characteristics of the study populations targeted varied considerably across the studies. A minimum sample size of 100 was required for consideration in this review. The largest sample size was 1,414.[47] Most studies recruited participants from hypertension or specialty referral clinics (n = 10). Four studies were conducted among participants drawn from a general medical clinic;[43,50,52,53] for four studies the population from which the study sample was drawn could not be determined.[36,42,47,51] No studies were conducted in settings that could be described as coming from the general population. Because persons with WCH must, by definition, have an elevated clinic blood pressure, all studies targeted persons with hypertension based on clinic BP. Persons taking anti-hypertensive medications were specifically excluded in 11 of the 18 studies identified. All studies included both men and women, with the percent of men ranging from 38-65 percent. No study reported results according to the race/ethnicity of the study population.

In 10 studies, a mercury sphygmomanometer was used to measure clinic BP. (See Evidence Table 3.) For the remainder, the measurement device was not specified. Physicians or nurses were the observers in 10 studies; in the four other studies, the observer of clinic measurements was not specified. According to the inclusion criteria for this question, all reviewed studies had clinic blood pressure measurements taken on more than one day. The total number of clinic measurements included in the analysis ranged from 2 to 9.

In 9 of the16 studies utilizing ABP measurements, a Spacelab monitor was employed. (See Evidence Table 5.) The remainder used a variety of monitors. The definition of "daytime" was not uniform among studies. In 38 percent of studies, the definition of "daytime" could not be determined or was defined by each participant within the study and thus was not standardized for the study population. When specified the start of "daytime" ranged from 6 a.m. to 10 a.m. and the end of "daytime" ranged from 8 p.m. to 12 p.m.

As shown in Evidence Table 4, the Omron 705c automated device was used in three of the four studies utilizing SMBP to define WCH.[38,45,52] In one study, the device was not specified.[21] For two of the four studies, the observer was specified as the participant, and not another individual.[38,52] For the remaining two studies, the observer was not explicitly stated.[21,45] For three of the four studies, both morning and evening blood pressure readings were included. In one study, the time of BP measurement was not stated.[52] All studies used the average of several readings obtained on different days in the analysis.

The definition of WCH differed within and between studies. For studies utilizing ABP (Evidence Table 12), the mean daytime and/or 24-hour BP was used for comparison to clinic BP measurements. Moreover, different cut-points were used within and between studies to define ABP-determined hypertension, as well as clinic-determined hypertension. Three studies [43,47,50]used a common cut-point for ABP-hypertension proposed by Verdecchia, et al.[54] However, the definition of clinic-hypertension was not uniform between studies. Nevertheless, the prevalence of WCH in these three studies ranged from 18.9 percent to 35 percent. Generally, as expected, the higher the cut-point for ABP-hypertension, the lower the prevalence of WCH.

For studies using ABP monitoring as the method for comparison to clinic BP, the prevalence of WCH ranged from 11 percent to 67 percent. The exceptionally high prevalence of WCH seen in the latter study is noteworthy for several reasons.[46] The study sample was composed of persons receiving medication for the treatment of hypertension. Thus, the extent to which individual blood pressure medications and/or their dosing schedules influenced the results is unknown. Moreover, the participants in this study were enrolled from a tertiary referral center for management of drug resistant hypertension, a population that may exhibit a higher prevalence of WCH. Excluding the highest and lowest estimates for the prevalence of WCH, the prevalence of WCH ranged from 11.9 to 39 percent. The largest study estimated the prevalence of WCH at 19 percent.[47] The study that utilized the greatest number of clinic BP measurements (n=9) for use in comparison to ABP estimated the prevalence of WCH at 23 percent.[39] Finally, in each study that presented prevalence estimates by gender, the prevalence of WCH was higher in women compared to men. In one study, the prevalence of WCH was statistically higher in women than in men, but no gender-specific prevalence estimates were provided.[45]

As shown in Evidence Table 11, in studies using SMBP for comparison to clinic BP, the prevalence of WCH ranged from 13 to 33 percent. However, these studies also used different definitions to define both clinic hypertension as well as SMBP. In two of the four studies, WCH as defined by ABP was available for comparison.[38,45] Within each study, the prevalence of WCH as determined by ABP and self- blood pressure monitoring techniques were similar (11 and 13 percent respectively)[38] and (25.9 and 25.9 percent respectively).[45] However, the prevalence of WCH between studies was more disparate (approximately 8 percent versus 26 percent).

In summary, the prevalence of WCH is difficult to ascertain due the lack of standard definitions for both clinic and non-clinic blood pressures. Most studies were relatively small and the populations studied were quite heterogeneous. Nevertheless, the prevalence of WCH from the available evidence is estimated to be between 11 and 69 percent. However, the largest study and the study that utilized the greatest number of clinic blood pressure measurements in its analysis, place the estimate closer to approximately 20 percent. A similar range was observed for WCH as determined by SMBP. Finally, in studies that examined prevalence of WCH by gender, women consistently had a higher prevalence of WCH than men.

*Question #1a-c. Reproducibility of differences in readings and WCH*

Only two studies provided data on the reproducibility of WCH. One study was a multi-center study [55] and the other was a single center study[56] (Evidence Table 1). Both studies provided eligibility criteria in sufficient detail to replicate the study design. Both studies reported that clinic blood pressure was measured using a standardized technique; however, neither study reported that the observer for clinic BP was trained. For ABP, both studies reported that patients received instructions prior to wearing the ABP device.

Both studies included only untreated hypertensive patients who had previously been identified as having WCH (Evidence Table 2). Only one study provided all three of the basic descriptive characteristics of the study population (age, gender and percent of anti-hypertensive medication).[55] The participants in the study by Palatini et al.[55] were slightly younger than the participants in the study by Verdecchia et al.,[56] 33 years vs. 44.3 years.

As shown in Evidence Table 3, the methods used to assess clinic BP varied across the two studies. In the study by Palatini et al ,[55] the type of device and the type of observer were not reported. One study measured clinic BP in the supine position, [55] while the other measured clinic BP in the sitting position. [56] Both studies assessed clinic BP using more than one day of measurements; however the total number of clinic BP measurements was larger in the study by Palatini et al.[55]

For determination of ABP, both studies used more than one device. As shown in Evidence Table 5, the study by Palatini et al.[55] used the SpaceLabs 90207 and the TM 2420 while the study by Verdecchia et al.[56] used the SpaceLabs 90207 and the SpaceLabs 90202. All of these devices had been validated. Fixed intervals were used to determine daytime and nighttime BP. For daytime BP, the interval between measurements ranged from 10-15 minutes, and for nighttime BP the interval ranged from 15-30 minutes.

The sample sizes of the two studies were similar; the sample size in the study by Verdecchia et al.[56] was 83, while the sample size in the study by Palatini et al. was 90 [55] (Evidence Table 13). For both studies, WCH was determined by clinic BP and ABP; however, these two studies used different definitions of WCH. In the study by Verdecchia et al., WCH was defined as office systolic BP > 140 mmHg and/or diastolic BP > 90 mmHg and ABP < 131/86 mmHg for women or <136/87 mmHg for men.[56] Conversely, Palatini et al. defined WCH as office systolic BP 140-159 or diastolic BP 90-99 and ABP<130/80 mmHg. [55] Additionally, the interval between repeated sets of ambulatory and clinic BP measurements differed substantially between the two studies, three months [55] vs. 2.5 years. [56]

As shown in Evidence Table 13, in the study by Verdecchia et al, 63 percent of the population initially defined as white-coat hypertensive, remained white-coat hypertensive when reassessed 2.5 years later.[56] In the study by Palatini et al, 23.7 percent of the initial population remained white-coat hypertensive when reassessed after three months, while the remaining 76.3 percent became sustained hypertensives.[55]

## Question #2

*The relationship of mean blood pressure levels and WCH as defined by SMBP to clinical events.*

*Question #2a. Is SMBP more or less strongly associated with BP-related target organ damage than clinic BP measurements?*

Only one study that compared the association of target organ damage with self-measured and clinic blood pressure fulfilled our inclusion criteria.[22] This study described in detail the eligibility criteria and baseline characteristics of study participants, and the study personnel collecting clinic blood pressure measurements were masked to self measurements and to relevant clinical data (Evidence Table 14). In addition, clinic blood pressure measurements were taken by trained personnel using an appropriate cuff size. At least 2 minutes separated clinic BP measurements. The study subjects also received written instructions and individual guidance on how to perform self measurements correctly.

The study was a cross-sectional assessment of newly diagnosed, moderate to severe untreated hypertensives, 35 to 54 years of age, referred to the study clinic from the primary and occupational health services in the metropolitan area of Turku, Finland. The authors screened 252 patients. After excluding patients with coronary artery disease, cerebrovascular disease, insulin-treated diabetes mellitus, significant valvular disease and pregnant women (Evidence Table 15), the authors studied 239 eligible patients and present data on 233 subjects with complete clinic, SMBP, and ABP measurements.

As shown in Evidence Table 16, clinic BP was measured by a trained nurse using a mercury sphygmomanometer, after the patient sat for at least 15 minutes. Clinic BP was recorded twice in each visit, and measurements were obtained at 4 separate visits within 3 weeks. The reported clinic BP was the average of these 8 measurements.

Self-measurements of blood pressure (Evidence Table 17) were performed at home with a semiautomatic oscillometric device (Omron HEM 705C) that has been validated according to the BHS and AAMI standards. The cuff size was selected as a function of the patient's arm circumference. Patients were instructed to follow the same preparations to measure their blood pressure as in the clinic and to have their blood pressure self-measured twice at a 2-minute interval every morning between 6 and 9 a.m. and every evening between 6 and 9 p.m. on 7 consecutive days. The reported self-measured blood pressure was the average of these 28 measurements.

Left ventricular mass was measured by two-dimensionally controlled M-mode echocardiography (Aloca SST-860) and a 3.5 MHz transducer. Measurements were performed according to the American Society for Echocardiography recommendations[58] and the equation developed by Devereaux et al.[59] was used to estimate the left ventricular mass. The average left ventricular mass index (LVMI) of study participants was 111 $g/m^2$ (SD 25) of body surface area. (See Evidence Table 18).

As shown in Evidence Table 19, the correlation of SMBP with LVMI was greater than that of clinic BP. The correlation coefficients of SMBP and clinic BP with LVMI were 0.47 and 0.44, respectively, for systolic BP, and 0.40 and 0.37, respectively, for diastolic BP. In multivariate stepwise models, gender and home blood pressure were the only significant predictors of LVMI in models that also considered age, gender, clinic, and ambulatory blood pressure measurements.

The same study also compared the association of albuminuria with SMBP and clinic BP. Albumin excretion was determined by nephelometry in 24 h. urine collections. (See Evidence Table 20). The average urinary albumin in the study participants was 25.7 mg/24 hour (SD 39.3). As shown in Evidence Table 21, self-measured and clinic BP showed a similar correlation with log-transformed urinary albumin. The correlations of SMBP and clinic BP with log-albumin were 0.32 and 0.34, respectively, for systolic BP and 0.28 and 0.25, respectively, for diastolic BP.

In summary, only a single study compared SMBP and clinic BP with target organ damage. In this study, SMBP was a better predictor of left ventricular mass than clinic BP. Correlations of albumin excretion with SMBP and clinic BP were similar. Although the study was methodologically sound, the added prognostic information provided by self-measured blood pressure with respect to clinic measurements on target organ damage remains uncertain. No

study compared the levels of target organ damage in normotensives, white coat hypertensives, and sustained hypertensives as determined by self-measured blood pressure.

*Question #2b. Does SMBP predict subsequent clinical outcomes?*

Two articles, both published from the same prospective observational study, addressed the issue of whether SMBP can predict subsequent BP-related events.[60,61] In one article, the outcome variables were total mortality and CVD mortality.[60] In the other article, fatal and non-fatal stroke was the outcome.[61]

As displayed in Evidence Table 22, the cohort study was a single center study partially supported by government and other sources. The description of eligibility was adequate in both reports, but a complete set of core baseline characteristics (age, gender, percent on medications) was not reported in one article.[61] Participants received training on recording SMBP. Follow-up data were available in greater than 80 percent of participants for both reports.

The cohort study was a population-based survey of adults, ages 40 and older, conducted in one region in Japan. Participants included non-hypertensive persons as well as hypertensive persons, some of whom were on medication (Evidence Table 23). The study did not measure standard BP in the office or clinic setting. Rather, survey staff measured BP at home, using an automated device (Evidence Table 24); hence, for this section, the term 'clinic BP' applies to home measurements by survey staff. Clinic BP was the average of 2 measurements obtained at one visit. Self-measured BP was the average of daily morning measurements recorded over 28 days. The device used for SMBP was not validated according to AAMI or BHS guidelines because baseline data were collected prior to publication of these guidelines. The mean number of measurements contributing to the average SMBP exceeded 20 in both reports. (See Evidence Table 25.)

As shown in Evidence Table 26, the size of the cohort was less than 2000 persons. The difference in sample sizes between the two reports reflects the additional exclusions of prior stroke and atrial fibrillation in one article.[61] Over follow-up, there were 52 CVD deaths, 160 total deaths, and 39 strokes (non-fatal or fatal). Analyses were adjusted for several CVD risk factors (age, gender, smoking, and prior CVD events) but not cholesterol or diabetes. In one paper, risk estimates were presented as the relative risk (RR) per mmHg.[60] In the other paper, the risk estimates were presented for quintiles of BP with different reference categories;[61] hence, risk estimates were re-calculated so that the lowest quintile of BP was the reference group.

Neither clinic systolic BP nor clinic diastolic BP was significantly associated with any of the three outcomes in a progressive, dose-response fashion. However, for stroke, the RRs associated with the highest quintile of clinic systolic and diastolic BP were significant. For SMBP, the RR associated with the fifth quintile of diastolic was significant.[61] In the original publication, the relationship between systolic SMBP and stroke was non-linear, that is, J-shaped.[61] For CVD mortality and for total mortality, systolic SMBP but none of the other BP measurements was significantly associated with these outcomes.[60]

Neither study explicitly tested whether SMBP was superior to clinic BP for predicting outcomes or whether SMBP provided additional prognostic information (incremental gain) beyond that of clinic BP.

In summary, the published literature is insufficient to provide a definitive answer to this research question. The only cohort study that has assessed whether SMBP can predict outcomes documented a linear, progressive relationship of systolic SMBP with total and CVD mortality but a non-linear, J-shaped relationship with stroke. Neither study reported comparative analyses on risk prediction by SMBP and clinic BP.

*Question #2c: What is the incremental gain in prediction of clinical outcomes from use of self-measurement devices beyond prediction from clinic BP alone?*

Please see discussion for Question #2b.

*Question #2d. What is the effect of treatment guided by SMBP in comparison to treatment guided by clinic BP.*

A total of 12 trials assessed the effects of SMBP interventions on BP or hypertension control.[62-73] As displayed in Evidence Table 28, one was a multi-center trial, nine were single center trials, and two trials did not provide this information. Seven trials had partial or adequate descriptions of eligibility criteria, only one trial provided a sample size justification, and seven trials had partial or adequate descriptions of the randomization process. Nine trials provided an adequate description of the BP outcome variable, five explicitly stated or had methods that ensured blinding of the outcome, and seven reported between group p-value. In ten trials, participants received training to use SMBP devices, but just five described the approach to adjusting BP therapy based on the SMBP results.

All 12 trials had a parallel group design (eight with two groups, two with three groups, one with four groups, and one with five groups). In nine of the trials, SMBP was the only component of the active intervention arm, except for BP reports to patients and/or physicians in three studies. Other dimensions of the active intervention groups were an activated significant other (trained and encouraged to measure in BP) in one trial, telephone evaluation of adherence in one trial, and a multi-component behavioral treatment program in one trial. Two of the 12 trials used telemetry as part of the active intervention program.[66,70] One trial used ABP as the outcome variable while all others used clinic BP measurements.[70]

The sample size of the trials ranged from 62 to 622. (See Evidence Table 29.) Participants were drawn from a general population in two trials, general clinics in five trials, hypertension clinics in one trial, screening events in one trial, and rehabilitation hospital in one trial; the setting was not specified in one trial. All trials enrolled hypertensive individuals, and three trials focused on individuals with poorly controlled hypertension. Trials typically enrolled both men and women (range of percent men: 22.8 to 98 percent). Five trials reported that blacks were enrolled (range of percent African-Americans in these five studies: 10.5 to 76.2 percent]. Mean age in the trials ranged from 41.2 to 76.5 years.

As displayed in Evidence Table 30, seven trials used an electronic or automated device , two used a mercury manometer and three did not specify the device. In eight trials, the manufacturer and/or specific device was provided. Nine trials provided the frequency of SMBP measurements, which ranged from once per week to three times each day.

The outcome variable in these trials is poorly described (Evidence Table 31). The device used to measure BP is mentioned in just two trials;[62,70] of these, ABP was the BP outcome measurement technique in one trial.[70] Of the 11 trials that did not use ABP, the position of the participant is mentioned in three trials, and the number of days of follow-up measurements is mentioned in six trials. Of these six trials, follow-up BP was measured on just one day in five trials and on three days in the other trial.

The SMBP interventions led to significant changes in BP, either systolic or diastolic BP, in seven trials (reduced BP in six trials[63-66,70,71] and increased BP in one trial[62]). (See Evidence Table 32.) In the other five trials, BP was either unchanged, or the significance test was not reported. In both of the trials that included telemetric transmission of BP, the interventions significantly reduced diastolic BP but not systolic BP.[66,70] Three trials reported or commented on gender differences; in one trial, reductions in BP from the SMBP intervention were similar by gender,[70] while in two studies results were better in women compared to men.[71,73] One trial reported that the SMBP intervention significantly improved mean arterial pressure in blacks.[70]

Initiation and use of medication was reported in three trials. In two trials,[62,68] including the one trial in which BP rose, medication use at the end of follow-up was higher in the control group compared to the SMBP group. In one other trial, medication use was similar.[69] One trial, that included SMBP as well as telemetric transmission of data and a multi-factorial intervention, documented improved adherence in this group.[66] One trial documented that SMBP reduced costs of hypertension care.[71]

The interpretation of SMBP trial results is complex. First, because SMBP is a diagnostic technology used to assist in BP management, the impact of SMBP is indirect, that is, mediated through changes in BP therapies, both pharmacologic and non-pharmacologic. Hence, an evaluation of SMBP must include an assessment of the approach to therapy in both active and control groups. Unfortunately, none of the papers explicitly stated whether and how SMBP guided therapy. Second, SMBP can be used to adjust BP medications for two distinct problems, that is, to improve BP control in those with inadequately controlled hypertension or to reduce the intensity of BP therapy in persons with apparently low BP. Hence, the lack of BP reduction from SMBP in some studies may reflect a mixed effect, namely, downward titration of medications in some patients and upward titration of medications in other patients. Third, while all trials used SMBP, many of the trials combined SMBP with other interventions, often as a means to improve adherence with therapy. Fourth, SMBP technology is undergoing rapid advances that should influence its effectiveness, specifically, the development of integrated systems that not only synthesize SMBP readings but also can transmit reports to patients and physicians with feedback including advice on therapy. While such advances should, in general, improve the utility of SMBP, there is the potential for inadvertently recording and synthesizing data from multiple individuals (e.g., spouse).

In summary, interventions that included SMBP improved BP control in six of 12 trials. In view of major design limitations, particularly suboptimal measurement of the outcome variable, it is possible that additional studies would have documented benefits had they used a more satisfactory outcome measurement technique. Few published trials used contemporary technologies that automatically synthesize SMBP data over time and that allow for telemetric

transmission of SMBP measurements. Of the two trials that used this technology, both documented reduced BP from intervention that included this technology.

## Question #3

*The relationship of mean levels and WCH as defined by ABP measurement to clinical events. Question #3a. Is ABP more or less strongly associated with BP-related target organ damage than clinic BP measurements?*

A total of 27 papers (Evidence Table 33) fulfilled our selection criteria and provided data to compare the association of clinic BP and ABP with target organ damage (left ventricular mass in 22 studies, or urinary albumin/protein excretion in nine studies).[22,30,39,43,47,50,53,74-93] These papers originated from 25 different studies (two studies published their findings in two separate reports each[43,50,53,92]). As in other sections in this report, the percentages describing the evidence will refer to the number of studies rather than the number of papers, unless explicitly indicated. The majority of studies (64.0 percent) were single-center, and 24.0 percent were multicenter. In 12.0 percent of studies, the number of centers involved could not be determined. The source of funding was also unclear for 60.0 percent of studies. Of the nine studies (35.7 percent) that documented a source of funding, five were funded by government, three by industry, and five by other sources (non-exclusive categories).

As shown in Evidence Table 33, most studies (92.0 percent) reported the eligibility criteria with enough detail to replicate the study design, and all studies provided basic descriptive characteristics of the sample participants (gender, age, and percentage of patients on antihypertensive medication). However, limitations in the quality of blood pressure determinations were widespread. For clinic measurements, only four studies (16.0 percent) stated that the persons who took the clinic blood pressure determinations were trained, and only 11 studies (44.0 percent) reported some effort at standardizing the measurement techniques, such as following standard guidelines, using appropriate cuff sizes, or waiting some period of time between repeated measurements. Clinic BP measurements were masked to other study data in 56.0 percent of studies. Only 11 studies (44.0 percent) reported that they had provided some kind of instructions to participants when they wore an ABP device.

The characteristics of the study populations targeted varied considerably (Evidence Table 34). Although all studies included hypertensive patients, most of them (84.0 percent) either excluded patients on anti-hypertensive medications or discontinued treatment for a variable period of time prior to study measurements. Two notable exceptions are the studies by Myers et al.[30] and by Cuspidi at al.[74] that specifically targeted treated hypertensives as part of the study population. The proportion of hypertensives in the studies ranged from 34.6 to 100 percent, with 10 studies (40.0 percent) including only hypertensive participants.

Most studies (60.0 percent) did not report who had taken the clinic blood pressure determinations (Evidence Table 35). Of the 10 studies that reported the observers, six used physicians exclusively, three nurses exclusively, and one physicians and nurses. Among the 16 studies that reported the device used, 14 used mercury sphygmomanometers (two with random zero), one study used an automated device, and one study used multiple devices. All studies

reporting information on the total number of measurements used multiple determinations (ranging from 2 to 9), although no study took more than three measurements per day, and only the study of Jula et al. took them on more than three different days.[22] Only two studies used trained observers, followed a standard technique, and took BP on three or more days.[22,43]

Although there was a wide representation of manufacturers of ABP devices across studies, SpaceLabs devices were most frequently used (Evidence Table 36). Also, most studies (92.0 percent) established a distinction between day and night periods for ABP measurements, usually using fixed time periods (19 studies) rather than periods defined by the patients' activities (4 studies).

A total of 22 studies compared the associations of clinic blood pressure and ABP with LV mass (Evidence Table 37), although the reporting of LV mass determinations differed across studies. If several different measures were available in a study, we abstracted LV mass indexed against the body surface area (16 studies). Five studies indexed LV mass by different powers of height, and the rest used other methods of adjustment for height and/or weight, or did not report the adjustment method. The studies were also highly variable in the criteria for diagnosing left ventricular hypertrophy; in fact, of the six studies that reported these criteria, no two studies shared the same definition. The percentage of patients with left ventricular hypertrophy in these studies ranged from 14 to 36 percent.

The correlation coefficients of LV mass index with clinic BP and ABP were compared in 14 studies (Evidence Table 38). The correlation coefficient of clinic systolic BP with LV mass index ranged from 0.03 to 0.52. In all groups studied the correlation coefficient of 24 hour systolic BP was higher than that of clinic systolic BP, except in men in the study of Martinez et al. [43]and in normotensives in the study of Verdecchia et al. [89] The findings were similar when daytime or nighttime systolic BP, rather than 24 hour systolic BP, were compared to clinic systolic BP, although the correlations of nighttime systolic BP and LV mass index tended to be lower than those of 24 hour or daytime systolic BP.

For each type of BP measurement assessed (clinic, 24 hour, daytime, or nighttime), the correlations of diastolic BP with LV mass index were in general lower than those of systolic BP with LVMI. Twenty four hour diastolic BP correlations with LV mass index were consistently higher than clinic diastolic BP correlations, with the exception of the normotensive group in the study by Schulte et al. [93] Also, daytime and nighttime diastolic BP measurements tended to correlate better with LV mass index than clinic diastolic BP, although not as strongly correlated as 24 hour diastolic BP.

Most studies based the comparisons between clinic and ABP determinations in unadjusted correlations. As noted in Evidence Table 38, studies included different types of determinants in stepwise regression models to elucidate which factor was a more significant determinant of LV mass index. However, substantial differences in statistical methods and the presentation of results precluded firm conclusions. The observed heterogeneity in the use of multivariate modeling methods is partly a reflection of the fact that there is no single "correct" way of modeling these data, and partly a reflection of different modeling objectives in many of the studies (i.e., most studies tried to establish the set of variables with significant associations, while this review was attempting to determine the added value of ABP if clinic BP measures are already in the model).

Ten studies compared the LV mass index of white coat hypertensives with that of normotensives and/or sustained hypertensives (Evidence Table 39). In most of these studies, the cutoffs for clinic hypertension were blood pressures of 140/90mmHg, but the cutoffs for hypertension based on ABP were less consistent. Four studies used 135/85mmHg,[43,77,80,82] one study each used 135/90mmHg,[53] 130/85mmHg,[78] 137/87mmHg,[39] one study used diastolic ABP as cutoffs,[85] and two studies did not report the cutoffs used for defining hypertension on ABP.[30,47] The proportion of white coat hypertensives in these studies ranged from 13.4 to 77.4 percent of participants. Except in the study by Myers et al,[30] sustained hypertensives had higher LV mass index than white coat hypertenvises, with differences of up to 28.3 g/m$^2$. Likewise, white coat hypertensives had higher LV mass index than normotensives in all studies except in Hoegholm et al.,[53] with differences of up to 26.0 g/m$^2$. For LV mass, WCH appears to be an intermediate condition between normotension and sustained hypertension.

As shown in Evidence Table 40, the association of ABP with albuminuria was assessed in 9 studies. Six studies used 24 hour samples, one used spot urine samples, one used three 8 hour urine samples, and one study did not report the type of sample collection. Of the eight studies reporting criteria for microalbuminuria, five used 30 mg/24 hour as cutoff.

The correlation of albuminuria with clinic BP versus ABP was compared in 6 studies (Evidence Table 41). The correlation coefficient of clinic systolic BP with albumin excretion ranged from 0.09 to 0.34. In the study of Jula et al.[22] and in the normotensive group of Hoegholm et al.,[92] clinic systolic BP and diastolic BP were more strongly correlated with albuminuria than 24 hour, daytime or nighttime systolic BP and diastolic BP, respectively. In all other subgroups studied, however, ABP measurements were stronger determinants of albumin excretion than clinic BP, often with marked increases in the correlation coefficients. For instance, in the study by Redon et al.,[86] the correlation coefficients for 24 hour ABP (systolic/diastolic) and clinic BP with albumin excretion were 0.34/0.34 and 0.10/0.16, respectively. Overall, protein excretion is more closely associated with ABP than with clinic BP. As with left ventricular mass index, several studies used multivariate models to assess the strongest determinants of albuminuria/proteinuria, but the methodology and the reporting of the models were inconsistent.

Seven papers from five studies compared the albumin/protein excretion of white coat hypertensives with that of normotensives and/or sustained hypertensives (Evidence Table 42). The results of these studies were fairly consistent. In all of them, albumin/protein excretion of sustained hypertensives was significantly higher than that of white coat hypertensives. The differences between normotensives and white coat hypertensives, however, were small, and not significant in all studies except in Martinez et al.[43] While there is a clear impact of sustained hypertension on renal function, the impact of WCH is unclear.

Although the correlation of LV mass and protein excretion with BP tended to be larger for ABP (particularly 24 hour and daytime) than for clinic BP, the poor quality of clinic BP determinations in the majority of studies precludes a satisfactory comparison with clinic BP as recommended by guidelines. The impact of WCH, as determined by ambulatory monitoring, on target organ damage was also evaluated. White coat hypertensives had intermediate levels of LV mass between normotensives and sustained hypertensives as determined by ABP. However, normotensives and white coat hypertensives had similar levels of protein excretion, and only

sustained hypertensives had clearly elevated values. These studies were also limited by the poor overall quality of clinic BP measurements, and by the lack of adjustment for potential confounders when comparing normotensives, white coat, and sustained hypertensives.

*Question #3b. Does ABP predict subsequent clinical outcomes?*

A total of 14 articles from 10 prospective observational studies addressed the issue of whether ABP can predict subsequent BP-related events.[32,94-106] Of the 10 studies, one study published three articles that covered different aspects of this research question,[98-100] two other studies each published two relevant articles,[32,95,104,105] and the remaining seven studies published only one article. Unless otherwise stated, this section will report and enumerate by 'study' rather than by 'article'.

As displayed in Evidence Table 43, all of the studies were single center except for one multi-center study.[32,95] Government partially funded three studies (corresponding to six articles); in all other instances, the source of funding was uncertain. In seven studies, there was an adequate description of eligibility criteria. A complete set of core baseline characteristics (age, gender, percent on medication) was reported in each study. In terms of clinic BP measurements, only one article documented that the clinic BP observer was trained,[103] only 3 studies documented that the clinical observer was masked to other BP measurements,[32,95,98-100,104,105] and only four studies documented use of standard measurement technique.[94,99-102] Only two articles mentioned that participants received training on how to wear an ABP device.[94,106] Outcome ascertainment was masked in only three studies.[32,95,98-100,104,105] Follow-up data were available on greater than 80 percent of participants in all but one study,[97] and a measure of statistical variability (SE, SD, 95% CI or p-value) was reported in all studies.

The sample size in the studies ranged from 57 to 2010; in eight studies, the sample size was greater than 1000 persons (Evidence Table 44) . One study enrolled hemodialysis patients;[94] another study enrolled type 2 diabetics.[97] In the other studies, the participants were drawn from unselected populations, clinical trial participants, or drawn from general medical clinics and/or hypertension clinics. Except for one study,[101] the mean age was greater than 50 years; two studies focused on older aged individuals.[32,95,103] All studies included both genders (range of percent men: 29.1 to 63 percent). None reported enrollment of African-Americans. Several studies focused exclusively on hypertensive individuals. In one study that reported observational analyses within a placebo-controlled trial, only those assigned to placebo were used in analyses.[32]

All but one study documented the type of ABP device that was used.[97] A SpaceLabs device was used in six studies,[32,94,95,102,104-106] a Diasys device in one study,[96] a Nippon Colin device in two studies,[98-100,103] and a Remler device in one study.[101] Accordingly, the most common technique to record BP was oscillometric. In six studies, the ABP devices had been validated according to criteria of the BHS or the AAMI.[32,94-96,102,104-106] In three other studies, the devices had undergone validation studies prior to widespread use of the BHS or AAMI criteria.[98-101,103] In most studies, a fixed time period was used to define 'daytime' and 'nighttime' BP, while in one study,[98-100] 'awake' and 'asleep' were defined by actual participant reports. The interval between

readings ranged from 15 to 30 minutes (4 readings to 2 readings per hour) for daytime BP and from 15 to 60 minutes (4 readings to 1 reading per hour) for nighttime BP.

Limited information is available on the type and number of clinic BP measurements. Four of the ten studies did not provide any information on clinic measurements.[94,96,97,106] Of the remaining six studies, four used a mercury device,[94,101,102,104,105] one used an automated device,[98-100] and one additional study did not mention the type of device.[95] In four studies, the type of observer was mentioned; a technician or nurse measured clinic BP in three studies, while a physician measured BP in one study.[104,105] Clinic BP was recorded on just one day in three studies[98-100,103-105] and on three days in another three studies.[32,95,101,102] In these six studies, the total number of BPs contributing to average clinic BP ranged from two to nine. In one study, 'clinic' BP measurements were taken at home by medical personnel.[98-100]

As displayed in Evidence Table 45, the outcomes of interest included total mortality (four studies[32,98,99,106]), CVD mortality (four studies[32,94,98,99]), CVD morbidity and mortality (nine studies [32,95,96,101-106]), stroke (three studies[32,95,100]), dialysis (one study[97]) and cardiac morbidity and mortality (one study[32]). The period of follow-up ranged from 1 to 6.4 years. The number of clinical events ranged from 4 to 120. In 11 reports, analyses were adjusted for potential confounders; however, the methods and extent of adjustment procedures varied considerably across reports and occasionally within the same report.

Evidence Tables 46 and 47 present risk estimates as the relative risk, or hazard ratio, of the outcome by change in BP (a continuous variable, mmHg) or by category of BP. Cutpoints for the categories of BP were conventional cutpoints (e.g., systolic BP of 140 mmHg), convenience values, or values of the BP distribution (e.g., quintiles). For this report, the reference category was the lowest level of BP. Because these studies commonly displayed risk relationships in other formats, relative risk estimates were, in several instances, calculated from data presented in the articles,[95,99,101,104,106] including an article in which the reference category was not the lowest BP category.[99]

As displayed in Evidence Tables 46 and 47, a total of eight prospective studies (nine articles) reported the relationship between absolute levels of systolic ABP and subsequent outcomes,[32,94,96,99-103,105]while four studies (five articles) reported corresponding relationships for diastolic ABP.[94,99-101,103] For systolic BP, at least one study outcome was significantly related to clinic BP in two of five articles,[101,105] to daytime ABP in four of seven articles,[32,100-102] to nighttime ABP in four of five studies,[32,94,100,103] and to 24 hour ABP in five of six articles.[32,96,100,103,105] For diastolic BP, at least one study outcome was significantly related to daytime ABP in two of five articles,[100,101] nighttime ABP in two of four articles, [100,103]and 24 hour ABP in one of three articles.[103] Clinic diastolic BP was significantly associated with outcomes in the anticipated direction in one of five studies[101] and in an inverse direction in another study;[94] the latter finding may have resulted from the study population, namely, dialysis patients in whom a lower diastolic BP may be related to excess risk. Overall, absolute level of ABP (mean daytime, nighttime or 24 hour BP, systolic or diastolic) predicted outcomes in each of eight studies that examined this issue, while clinic BP predicted outcomes in two of five studies.

Three articles from two prospective studies examined WCH as a predictor of outcomes (Evidence Table 48).[95,104,105] Both studies documented that the risk associated with WCH was

less than that of sustained hypertension. In one of these studies, the risk associated with WCH was similar to that of non-hypertensives.[104]

Six articles from five studies examined dipping status as a predictor of outcomes (Evidence Table 48). In each instance, the reference category was dippers (that is, those with the usual pattern of lower nighttime BP than daytime BP). In both studies that examined the risk associated with reversed or inverse pattern (that is, higher nighttime than daytime BP), this pattern was associated with a significantly greater risk of outcomes than that of dippers.[97,98] A non-dipping BP pattern (that is, lack of nighttime BP reduction) was associated with a significantly increased risk of outcomes in three of four studies. In one study, non-dipping was a significant predictor of BP events in women but not in men.[104]

The findings are summarized by type of outcome for each potential predictor (clinic BP; daytime, nighttime and 24 hour ABP; WCH and non-dipping status) in Table 3.

Nine of 14 articles compared prediction of outcomes by ABP to prediction by clinic BP. Of these nine studies, just two studies[32,101] assessed 'incremental gain', that is, whether ABP provided additional information that was predictive of risk beyond that of clinic BP. To assess incremental gain, one study used a residual method to determine whether ABP predicted the residual variance left after regression of outcomes on clinic BP,[101] and one presented regression analyses with both clinic BP and ABP in the same model.[32] The other seven studies compared prediction by clinic BP and ABP without determining whether ABP provided additional information beyond clinic; of these, six studies used stepwise regression techniques[97,99,100,102,103,105] and one used discriminant function analyses.[96] ABP was a better predictor of outcomes than clinic BP in each of the seven studies that compared prediction of outcomes by clinic BP and ABP. In the two other studies, ABP provided incremental gain in information beyond that of clinic BP.

In summary, ABP predicted BP-related clinical outcomes. In each of ten prospective studies (14 articles), at least one dimension of ABP predicted one or more clinical outcomes. Absolute ABP levels (mean daytime, nighttime or 24 hour BP, systolic or diastolic) predicted outcomes in each of eight studies, WCH predicted a reduced risk of outcomes compared to sustained hypertension in each of two studies, and non-dipping or inverse dipping predicted an increased risk in four of five studies.

However, available data were insufficient to compare prediction of outcomes by ABP and clinic BP. Absolute clinic BP levels predicted outcomes in two studies in the anticipated direction, in one study in an unanticipated opposite direction, and did not predict outcomes in two other studies; five studies did not report whether clinic BP predicted outcomes. Although ABP was a better predictor of outcomes than clinic BP in most studies and even provided 'incremental gain' in outcome prediction in two studies, measurement of clinic BP and the types of comparative analyses were suboptimal. Hence, it is unclear whether the apparent superiority of ABP over clinic BP resulted from a better estimate of usual BP from ABP or a suboptimal measurement of clinic BP.

*Question #3c. What is the incremental gain in prediction of clinical outcomes from use of ambulatory devices beyond prediction from clinic BP alone?*

Please see discussion regarding Question #3b.

*Question #3d. What is the effect of treatment guided by ABP in comparison to treatment guided by clinic BP.*

Two trials, both of which were multi-center studies, tested whether BP management guided by ABP has similar effects on BP and other outcomes in comparison to management guided by clinic BP.[107, 108] (See Evidence Table 49.) In each trial, the eligibility criteria, the approach to BP therapy, and the description of the BP outcome were adequately described; in both studies, the between group p-values were provided. In one study, the description of randomization was adequate, and blinding of the outcome assessors was explicitly stated.[107] Neither study reported whether participants received instructions on how to facilitate ABP measurements.

Both trials were conducted in Europe, one in Germany[108] and the other in several European countries.[107] The sample size in the trial by Schrader was 1298 with a mean follow-up period of 56.4 months,[108] while the sample size in the trial by Staessen was 419 with a median follow-up period of 6 months.[107](See Evidence Table 50.) Both studies enrolled men and women with hypertension; the mean age was over 50 years in both studies. In both studies, mean baseline systolic BP exceeded 160mmHg.

Both trials used ABP to titrate medications, that is, either increase medication use if BP was inadequately controlled or decrease medication use if BP was below the target range. Both trials explicitly described the schedule of BP measurements, the medications used to control BP, and the BP thresholds used to titrate medications. In the trial by Schrader, ABP was obtained annually and in the setting of elevated clinic BP; in the control group, clinic BP was measured one, three, nine and 12 months after randomization and then annually. In Schrader's trial, the thresholds for increasing medications were clinic BP > 140/90mmHg in the control group and daytime BP >135/85 mmHg in the ABP group. In the trial by Staessen, BP in each group was measured at one, two, four and six months after randomization; the target range was a diastolic BP of 80 to 89 mmHg in each group. (See Evidence Table 51.)

In the trial by Schrader, follow-up clinic BP was obtained in both groups (the average of six readings, that is, three readings one each of two days).[108] In the trial by Staessen, both clinic BP and ABP were outcomes; in this trial, clinic BP was the average of three readings obtained on one day.[107](See Evidence Table 52.)

In both trials, there were non-significant increases in clinic BP in the ABP group, net of change in the control group (Evidence Table 53). In the trial by Staessen, which also reported the effects on ABP as an outcome variable, the ABP group had significantly higher 24 hour systolic BP, 24 hour diastolic BP and daytime systolic BP (Evidence Table 54).

In both trials, ABP was used to titrate medications in a fashion that would lead to more aggressive use of medications in persons with elevated ABP and less aggressive medication use in persons with apparently low ABP. In the trial by Staessen, there was less use of medications in the ABP group compared to control group, while in the trial by Schrader medication use was similar, perhaps as a result of enrollment procedures. Specifically, in this trial, persons with WCH were excluded post-randomization in the ABP group but not the control group. Had these

individuals with WCH been included in both groups, not just the control group, overall medication use might have been less in the ABP group.

During follow-up, BP related end-organ disease, as assessed by LV mass, was similar in the ABP and control groups in the trial by Staessen. In the trial by Schrader, clinical cardiovascular events and deaths were less common in the ABP group than the control group, despite similar mean levels of clinic BP in both groups. This pattern of findings occurred despite the fact that the ABP group in this trial was enriched with a relatively high risk group, sustained hypertensives, while the control group included 'white coat hypertensives'. The reduction in clinical cardiovascular events in the ABP group may have resulted a differential approach to persons with high ABP, specifically, those in the ABP group received upward titration of medications whereas those with high ABP remained undetected in the control group.

In summary, the availability of just two trials limits inferences about the utility of ABP to guide BP management. The dearth of studies might be related to several factors, including historical lack of reimbursement for ABP, difficulties in obtaining repeat ABP, and the perception that SMBP is a more suitable alternative to ABP for management. Still, it is noteworthy that there was no apparent excess in BP-related end organ damage in both trials and potentially even a reduction in clinical events, despite the fact that BP medications were sometimes titrated downward.

## Question #4

*Does the evidence for the above questions vary according to a patient's age, gender, income level, race/ethnicity, and clinical subgroups?*

As discussed previously, the vast majority of studies included both men and women. However, few studies reported results separately by gender. Also, studies rarely documented enrollment African-Americans; accordingly, race-stratified data was extremely unusual. The remainder of this section documents reports of individual studies that provided subgroup findings. Except for the prevalence of WCH, it is impossible to draw distinct conclusions for separate subgroups.

*Research Question 1*

One study reported differences between SMBP and clinic BP by gender.[26] For both systolic and diastolic BP, clinic BP was greater than SMBP in women and men. Another two studies reported BP differences between ABP and clinic BP, separately by gender.[28,33] For both men and women, clinic BP exceeded daytime and 24 hour BP, but the differences appeared somewhat greater in women than men. The same pattern was evident for both systolic and diastolic BP.

The only apparent subgroup difference was the prevalence of WCH by gender. Specifically, in each study that presented WCH prevalence estimates by gender, the prevalence of WCH was higher in women compared to men.[39,40,43,49,51,53]

*Research Question 2*

No observational study presented SMBP risk relationships separately by gender. In contrast, three trials that evaluated the effects of SMBP reported or commented on gender differences. In one trial, reductions in BP from the SMBP intervention were similar by gender,[70] while in two studies results were better in women compared to men.[71,73] One trial reported that the SMBP intervention significantly improved mean arterial pressure in blacks[70]

*Research Question 3*

In one cross-sectional study,[43] correlations of left ventricular mass with BP appeared higher in women than in men. In the same study, left ventricular mass in sustained hypertensives was greater than that of individuals with WCH, for both men and women. In one prospective study,[104] non-dipping status was significantly associated with a greater risk of CVD morbidity and mortality in women but not in men.