Implications of Ambulatory Blood Pressure Monitoring Substudies on the Interpretation of Clinical Trials in Hypertension: Should the Threshold for Drug Therapy Be Lower in Older Patients?

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In the modern era of blood pressure (BP) measurement, a reading of 140/90 mm Hg has been recognized as the dividing line between normal BP and hypertension. Concern about the quality of manual BP measurement in the office/clinic led to the development of standard guidelines for using devices such as the mercury sphygmomanometer. Intensive campaigns to promote these guidelines were undertaken by organizations such as the American Heart Association, but these efforts seem to have met with limited success.[1]

There appears to be a hierarchy for BP readings recorded in different settings using different techniques (Table I). Manual BP measured in routine clinical practice generates, on average, the highest values when compared with the awake ambulatory BP.[2–6] Research-quality manual BP readings recorded as part of a formal research study are about 10/5 mm Hg lower than routine manual BP readings. Ambulatory BP, a gold standard for determining future cardiovascular risk in relation to BP, is associated with even lower BP readings. Most population studies and hypertension guidelines[1,7] equate a manual clinic BP of 140/90 mm Hg for defining hypertension with an awake ambulatory BP of 135/85 mm Hg. Some authors have proposed even lower values (eg, 130/85 mm Hg) or have used the term *optimum* BP for readings <130/80 mm Hg while defining *normal* BP as <135/85 mm Hg.[7] Data from clinical trials appear to favor a lower cutpoint for the awake ambulatory BP, such as 130/85 mm Hg.[8]

If one accepts that a research-quality manual BP is not the same as a manual BP taken in routine clinical practice, then extrapolation of research studies to define cutpoints for hypertension needs to be re-evaluated. A simplistic approach would be to use a correction factor to account for the higher readings in routine clinical practice. However, this approach would not improve the quality or accuracy of routine manual BP. Manual BP recorded in routine clinical practice is not only higher but also correlates poorly with the awake ambulatory BP, whereas research-quality BP exhibits both lower readings and a significantly stronger correlation.[2,9] Applying a simple correction factor would not distinguish between individuals with a white-coat effect and those whose BP is less affected by the setting or measurement technique.

Greater use of out-of-office BP measurement with 24-hour ambulatory BP monitoring (ABPM) has been recommended by clinical practice guidelines to avoid overdiagnosis and overtreatment of hypertension in the community.[10] However, guidelines for treatment using ABPM are not supported by the robust data from clinical trials using manual BP measurements, which form the basis for treating hypertension. A possible solution to this conundrum may be found in the results of clinical trials that included both manual BP readings and a 24-hour ABPM substudy (Table II).

THE HOT STUDY

The Hypertension Optimal Treatment (HOT) study[11] examined the reduction in clinical cardiovascular outcomes when hypertensive patients were treated to 3 different target diastolic BP levels: <90 mm Hg, <85 mm Hg, and <80 mm Hg. The demographics of 297 patients enrolled into an ABPM substudy[12] were similar to the 18,790 patients in the entire HOT study, with the mean age of the patients being 62 years. In the ABPM subgroup, a baseline mean (±standard deviation) office BP recording using a mercury sphygmomanometer was 170±14/105±3 mm Hg compared with a mean awake ambulatory BP of 148±18/90±10 mm Hg (Table II). The office BP in the entire HOT study population was similar (170±14/105±3) to the ABPM study group. Thus, research-quality manual BP readings were on average 22/15 mm Hg higher than the awake ambulatory BP.

SYST-EUR TRIAL

The Systolic Hypertension in Europe (Syst-Eur) trial[13] randomized 4695 patients aged 60 years and older with systolic hypertension to either drug therapy or placebo. As part of the study, 808 patients underwent 24-hour ABPM at baseline.[14] The ABPM subgroup had similar demographic characteristics as all Syst-Eur trial participants, with a mean age of 69.6±6 years and mean manual BP 173±11/86±6 mm Hg (Table II). The mean awake ambulatory BP in the 808 patients was 151±16/84±10 mm Hg, which was 22/2 mm Hg lower than the mean manual BP.

THE HYVET INVESTIGATION

The Hypertension in the Very Elderly Trial (HYVET)[15] enrolled 3845 aged 80 years and older (mean age, 84 years) with predominantly systolic hypertension (173/91 mm Hg). Manual BP was recorded using a mercury sphygmomanometer. Data on the first 50 patients in HYVET who participated in an ABPM

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TABLE I. Mean Blood Pressure (BP) Readings Taken Manually in Routine Clinical Practice by the Patient's Physician, Readings Taken as Part of a Research Study Using a Mercury Sphygmomanometer, and the Mean Awake Ambulatory BP

		Type of BP Measurement, mm Hg				
Study	No.	Routine Clinical Practice	Difference	Research-Quality Office	Difference	Mean Awake Ambulatory
Myers et al[2]	147	146/87	6/4	140/83	8/5	132/78
Owens et al[3]	1350	178/106	10/8	168/98	16/5	152/93
Brown et al[4]	611	161/95	9/10	152/85	13/3	139/82
Gustavsen et al[5]	420	165/104	9/4	156/100	9/4	147/96
Myers et al[6]	309	152/87	12/7	140/80	6/3	134/77

TABLE II. Mean Blood Pressure (BP) Values From Clinical Trials With 24-Hour Ambulatory BP Monitoring (ABPM) Substudies

	Patients, No.		Manual Clinic BP, mm Hg			
	Entire Study	ABPM Substudy	Entire Study	ABPM Substudy	Mean Awake Ambulatory BP, mm Hg	Difference Between Clinic BP and Awake Ambulatory BP in Substudy, mm Hg
Hypertension Optimal Treatment (HOT) study	18,790	297	170/105	170/105	148/90	22/15
Systolic Hypertension in Europe (Syst-Eur) trial	4695	808	174/86	173/86	151/84	22/2
Hypertension in the Very Elderly Trial (HYVET)	3845	50	173/91	174/91	134/77	40/14

substudy have been reported.[16] At baseline, mean office BP was 174/91 mm Hg compared with a mean awake ambulatory BP of 134/77 mm Hg, a difference of 40/14 mm Hg. The mean age in the ABPM subgroup was not reported. Results of the entire ABPM subgroup in HYVET have yet to be published, although the findings were presented at the 23rd Scientific Meeting of the International Society of Hypertension and were similar to the published data.

INTERPRETATION OF ABPM SUBSTUDIES

Based on an analysis of population data from 5682 patients, a mean awake ambulatory BP value of 130 mm Hg to 135/85 mm Hg is equivalent to a research-quality manual BP of 140/90 mm Hg, traditionally used to define hypertension.[8] The difference in BP of 5 mm Hg to 10 mm Hg is much smaller and not consistent with the difference between manual clinic BP and awake ambulatory BP reported in the ABPM substudies of the above clinical trials. In these studies, differences in systolic/diastolic BP were between 22–40 mm Hg/2–15 mm Hg, depending on the age of the population studied and the type of hypertension, such as isolated systolic or combined systolic/diastolic. The Syst-Eur and HYVET populations had mostly patients with systolic hypertension, whereas the patients in the HOT trial had combined systolic and diastolic hypertension.

The most striking finding is the marked difference between the mean manual clinic BP and awake ambulatory BP seen in HYVET (40/14 mm Hg). The systolic BP in HYVET was similar to corresponding values in HOT (170 mm Hg) and Syst-Eur (173 mm Hg) and yet the decrease in BP using ABPM is almost double that seen in the other two studies. Although the patients in Syst-Eur were relatively old (mean age, 70 years), the participants in HYVET were considerably older (mean age, 84 years). The percentage of female participants in HYVET (60.5%) was also relatively high and similar to the percentage in the Syst-Eur trial (62%). Other studies[17,18] have shown that older women with predominantly systolic hypertension tend to exhibit a greater white-coat effect, which is consistent with the findings in these two trials.

IS HYVET THE FIRST CONTROLLED TRIAL IN BORDERLINE/MILD HYPERTENSION?

A noteworthy finding in HYVET is the baseline mean awake ambulatory BP at entry, which was only 134/77 mm Hg. Assuming a normal distribution of BP, about one half of the HYVET patients would be diagnosed as normotensive, making HYVET the first placebo-controlled clinical trial in borderline hypertension. Other important aspects of HYVET are the mean age of the patients (84 years) and the decision by the Data Safety Monitoring Board to stop the trial early because of a significant decrease in total mortality in the treatment group. These findings are particularly noteworthy given that the HYVET investigators were initially concerned about treating these older patients and selected a target systolic BP of <150 mm Hg as a precaution to avoid harm from decreasing BP too low.

In reality, the ambulatory systolic BP in the HYVET patients being treated with drug therapy was even lower, almost certainly <130 mm Hg.

IMPLICATIONS OF THE ABPM SUBSTUDIES

What would be the implications for treating patients older than 80 years with high office BP readings if the results of the HYVET ABPM substudy are indeed representative of the entire HYVET population? One interpretation of the results would be to opt for no treatment based on the relatively low baseline mean ambulatory BP reading since ABPM is the best predictor of future cardiovascular events. The problem with this interpretation is that treating the elderly hypertensive population in HYVET for only 2 years resulted in a significant decrease in total mortality. Clearly treating these patients was beneficial despite any preconceived concerns that reducing BP in a very old population might cause harm.

The data from these ABPM substudies, especially HYVET, should lead to new clinical trials of hypertension with cardiovascular outcomes using 24-hour ABPM as the basis for making treatment decisions. In view of the relatively low awake ambulatory BP at baseline in the HYVET substudy, BP entry criteria for such studies should be somewhat lower than in the past, with an awake ambulatory BP of 130 mm Hg to 135/85 mm Hg being the threshold for enrollment, especially for older patients. Meanwhile, the approach to diagnosing and treating older patients needs to be re-evaluated, especially now that manual BP measurement is being replaced by ABPM, home BP, and more recently automated office BP in routine clinical practice.

All three types of automated BP measurement reduce the white-coat response resulting in systolic BP readings substantially lower than those with manual BP.[1,9] The results of these studies, especially HYVET, suggest that treating older patients with hypertension, defined as a BP ≥135/85 mm Hg with these automated devices, would be beneficial in reducing future cardiovascular events. As always, decisions on drug therapy are best made on an individual patient basis.

The HYVET investigation is unique in several aspects, which included a very old patient population, antihypertensive therapy reducing total mortality, and a dramatic difference between manual BP and awake ambulatory BP. The publication of the complete results of the HYVET ABPM substudy would provide further evidence to support changes in how older patients with hypertension are managed in the era of automated BP measurement.

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