Review

Methods of Blood Pressure Assessment Used in Milestone Hypertension Trials

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Keywords

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Abstract

In the present review, we summarized the blood pressure (BP) measurement protocols of contemporary outcome trials in hypertension. In all these trials, clinic BP was used for the diagnosis and therapeutic monitoring of hypertension. In most trials, BP was measured in the sitting position with mercury sphygmomanometers or automated electronic BP monitors by trained observers. BP readings were taken on each occasion at least twice with a 30-to-60-s interval after 5 min of rest. Details regarding the arm side, cuff size, and the timing of BP measurement were infrequently reported. If clinic BP continues being used in future hypertension trials, the measurement should strictly follow current guidelines. The observers must be trained and experienced, and the device should be validated by automated electronic BP monitors. On each occasion, BP readings should be taken 2–3 times. The time interval between successive measurements has to be 30–60 s, and the resting period before the measurement should be at least 5 min in the supine or seated position and 1–3 min standing. BP should usually be measured in the seated position. The higher arm side and an appropriate size cuff should be chosen and noted. BP should be measured at defined trough hours. Automated office BP measurement has recently been used and seems to have less white-coat effect. The out-of-office BP measurement, either ambulatory or home BP monitoring, was only used in a subset of study participants of few hypertension trials. Future trials should consider these novel office or out-of-office BP measurements in guiding the therapy and preventing cardiovascular events.

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Introduction

Accurate blood pressure (BP) measurement is critical for the clinical management of hypertension and for clinical trial research in hypertension as well. The methodology of BP measurement therefore has to be carefully chosen to assure the accuracy of BP measurement in a hypertension trial. Indeed, small discrepancies in BP measuring protocols may have substantial impact on the recorded BP levels and subsequent therapeutic decisions during a trial, and sometimes on the results of the whole trial.

In principle, the methods of BP measurement used in a hypertension trial should stringently follow most recent guideline recommendations [1–3]. If the results of such a trial would be clinically relevant for clinical practice and used for guideline recommendations, the corresponding methods of BP measurement may also be used to formulate recommendations on BP measurement in clinical practice.

Over the years, dozens of clinical trials in hypertension had been conducted with various BP measuring techniques and protocols. Because the technology and knowledge for BP measurement have been advancing rapidly, the BP measuring techniques and protocols changed from the early to the most recent trials in hypertension. In this review article, we will summarize the BP measurement protocols used in the milestone hypertension trials [4–60] and explore the clinical relevance and implications for the management of hypertension.

Methodological Issues of BP Assessment in Milestone Hypertension Trials

A literature search limited to outcome clinical trials published in English between January 1, 1990, and April 1, 2017, was performed using PubMed with the keywords “hypertension” or “blood pressure,” “randomized controlled trial”, and “cardiovascular event.” Additional relevant trials were included from the references of the identified studies. Selected studies were randomized controlled outcome trials with a blinded or open design. We excluded studies of a surrogate outcome measure or in patients with congestive heart failure, end-stage renal disease on dialysis, or acute stroke (<30 days after onset). Relevant information was also obtained from prior publications related to the trial design of the individual studies.

We selected 36 milestone hypertension trials that formed the basis for the past and current hypertension management guidelines. Although ambulatory BP monitoring was performed in a subset of randomized patients in some of these trials, such as the Hypertension Optimal Treatment (HOT) [16], Systolic Blood Pressure Reduction Trial (SPRINT) [58], and Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trials [38], clinic or office BP measurement was used in all these milestone hypertension trials. We evaluated 9 different aspects of BP measurement (Table 1) in terms of the accordance with recent BP measurement guidelines [1–3].

Observers

Physicians measured BP in most of the earlier trials [6–8]. However, non-physician health professionals, such as nurses, were increasingly involved in many of the recent trials [22, 29–32]. In addition to the increased use of automated BP monitors in clinical practice and research, several other reasons drove this shift. Although physicians are usually adequately trained to measure BP, they do not often measure BP in complete compliance with the standards of BP measurement guidelines [61]. When an auscultatory device (mercury, aneroid, or hybrid) is used, they often have reading bias, in other words, digit preference and commonly round BP readings to 0 or 5. In addition, the white-coat effect may also dilute the validity and usefulness of BP measured by physicians. Therefore, some experts recommended that physi-

Table 1. Methodology of blood pressure measurement in major hypertension trials

Study acronym [ref], year of publication	Observer	Device description	Measurements, <i>n</i>	Time interval between measurements	Resting period	Position(s)	Arm	Cuff	Drug timing ^a
SHEP [4, 5], 1991	Trained, certified technician	Random-zero sphygmomanometer	Average of 4 readings (twice at each of the 2 visits)	30 s	After 5 min of seated rest and 1–3 min of standing	Seated and standing	Right arm	Appropriate size	–
STOP-H [6, 7], 1991	Nurse or doctor	Mercury sphygmomanometer	Average of 2 readings	–	After 5 min in supine position and 1–3 min standing	Supine and standing	–	Appropriate size	–
MRC old [8], 1992	Nurse and/or doctor	Random zero sphygmomanometer	Average of the 2nd and the 3rd of 3 readings	–	–	Seated	–	–	–
TOMHS [9, 10], 1993, 1991	Trained, certified, and monitored observer	Random zero sphygmomanometer	Average of 2 readings	30 s	After 5 min of rest	Seated	Right arm	Appropriate size	Morning blood pressure 1–4 h after medication
SYST-EUR [11, 12], 1997, 1991	–	Mercury sphygmomanometer	Average of 6 sitting and 6 standing readings (2 in each position at each of the 3 visits)	–	After 2, 5, and 2 min of rest in supine, seated, and standing positions, respectively	Seated, supine, and standing	–	–	–
SYST-China [13, 14], 1998	Physician	Mercury sphygmomanometer	Average of 6 readings (twice at each of the 3 visits)	1 min	After 5 and 2 min of rest seated and standing, respectively	Seated	–	–	At trough ^b
HOT [15, 16], 1998, 2001	–	Oscillometric semiautomatic device	3 readings	–	After 5 min of rest	Seated	–	–	–
NICS-EH [17], 1999	–	–	–	–	–	–	–	–	–
CAPP [18], 1999	–	Mercury sphygmomanometer	Average of 3 readings	–	–	Supine	–	Appropriate size	–
NORDIL [19], 2000	–	–	Single reading at each of at least 2 visits	–	After 10 min of rest	Seated	–	–	–
INSIGHT [20, 21], 2000	–	Mercury sphygmomanometer	Average of 3 readings	–	After 5 min of rest	–	–	–	At trough ^b
PROGRESS [22, 23], 2001, 1996	Trained observer	Mercury sphygmomanometer	Average of 2 readings	2 min	After 5 min of rest	Seated	–	–	–
IDNT [24], 2000	–	–	–	–	–	Seated	–	–	–
HOPE [25, 26], 2001, 2000	–	Mercury sphygmomanometer	Average of 2 readings on each arm	–	–	–	Arm with higher BP	–	–

Table 1 (continued)

Study acronym [ref], year of publication	Observer	Device description	Measurements, <i>n</i>	Time interval between measurements	Resting period	Position (s)	Arm	Cuff	Drug timing ^a
LIFE [27, 28], 2002, 1997	-	Validated, calibrated manual manometer	Average of 2 readings	1 min	After 5 min of rest	Seated and standing	Right or left arm	Appropriate size	At trough (22–26 h)
ALLHAT [29, 30], 2002, 2001	Trained observer	-	Average of 2 readings	30 s	-	Seated	-	-	-
ANBP 2 [31, 32], 2003, 1997	Trained study nurse	Mercury sphygmomanometer	Average of the 2nd and 3rd of 3 readings if blood pressure difference <10/6 mm Hg between readings	-	After 5 min of rest	Seated	-	Appropriate size	-
SCOPE [33, 34], 2003, 1999	-	-	Average of the 2nd and the 3rd of 3 readings	1 min	After 5–10 min of rest	Seated and standing	-	Appropriate size	-
INVEST [35, 36], 2003, 1998	-	Mercury sphygmomanometer, calibrated aneroid manometer, or validated electronic device	Average of 2 readings; additional readings if difference >5 mm Hg between readings	2 min	After 5 min of rest	Seated	Right or left arm	Appropriate size	-
VALUE [37], 2004	-	-	-	-	After 5 min of rest	Seated	-	-	At trough (24 h after the dose)
ASCOT-BPLA [39, 40], 2005, 2001	-	Semiautomated device (Omron HEM 705CP)	Average of the 2nd and 3rd of 3 readings	-	After 5 min of rest	Seated	-	-	All drugs taken no more than 24 h before study visits
FEVER [41], 2005	-	Mercury sphygmomanometer	Average of 3 readings	1 min	After 5 and 2 min of rest seated and standing, respectively	Seated and standing	-	Appropriate size	-
E-COST [42], 2005	-	-	Average of readings	-	-	Seated	-	-	At trough ^b
ADVANCE [43], 2007	-	Standardized automated (Omron HEM-705CP)	Average of 2 readings	-	After 5 min of rest	Seated	-	-	-
AVOID [44], 2008	-	Mercury sphygmomanometer	Average of 3 readings	2 min	After 5 min of rest	-	-	Appropriate size	At trough ^b
ONTARGET [45, 46], 2008, 2004	-	Semiautomatic validated device (OMRON HEM-757)	Average of 2 readings	-	After 3 min of rest	Seated	-	-	-
ACCOMPLISH [47, 48], 2008, 2004	-	-	Average of 3 readings	2 min	After 5 min of rest	Seated	-	-	-

Table 1 (continued)

Study acronym [ref], year of publication	Observer	Device description	Measurements, <i>n</i>	Time interval between measurements	Resting period	Position(s)	Arm	Cuff	Drug timing ^a
JATOS [49], 2005	-	Sphygmomanometer	Average of at least 2 readings per visit	-	After 5–10 min of rest	Seated	-	-	-
CASE-J [50], 2008	-	-	Average of 2 readings	-	-	Seated	-	-	-
HJCREATE [51], 2009	-	Mercury sphygmomanometer	-	-	After 5 min of rest	Seated	-	-	-
ACCORD BP [52, 53], 2010, 2007	-	Automated blood pressure monitor (Omron 907)	Average of 3 readings	-	-	Seated	-	-	-
COPE [54], 2011	Physician	-	Average of 2 stable readings	1–2 min	After 5 min of rest	Seated	-	-	-
OSCAR [55, 56], 2012, 2009	-	Mercury or automatic sphygmomanometer	Single reading at 2 different visits	-	-	Seated	-	-	-
NAGOYA HEART [57], 2010	-	-	Single reading at each of at least 2 visits	-	-	-	-	-	-
SPRINT [58], 2017	Unattended	Automated manometer (Omron 907)	Average of 3 readings	1 min	After 5 min of rest	Seated	-	Proper cuff size –	-
HOPE-3 [59, 60], 2016	-	Automatic blood pressure monitor (Omron HEM-711DLXCAN) or mercury sphygmomanometer	Average of 2 readings	At least 1 min	After 5 min of rest	Seated	Right arm	Evenly tight	-

^a Timing of the blood pressure measurement in relation to the last medication dosage. ^b "Trough" usually refers to blood pressure measured 20–26 h after the last study medication was taken.

cians should not measure BP themselves but should rely on BPs measured by trained observers or using validated automated devices to improve the quality of care of hypertensive patients in general and the accuracy of BP assessment in clinical research in particular [61].

However, people believe that even though BP is measured by nurses, other “trained observers,” or automated devices, the white-coat effect is still possible in clinic BP measurement. Many patients still become anxious in the clinical setting even in the absence of physicians. The presence of a nurse or other trained observers may lead to conversation and therefore increase BP. That is the rationale for establishing unattended BP measurement facilities. Such an unattended BP measurement was used in the recent Systolic Pressure Reduction Intervention Trial (SPRINT) [58]. In SPRINT, clinic BP was measured automatically 3 times with a validated oscillometric device with the patient being quiet and isolated in a room [62]. This methodology has been labelled as automated office BP measurement (AOBP). This so-called AOBP used in the SPRINT trial had 2 key elements. First, everybody except the patient him/herself was out of the room during measurements and the resting period prior to measurements. Second, the BP measurement device (Omron 907, Kyoto, Japan) was preset to wait for 5 min before measurements were started. BP was measured 3 times at a 1-min interval.

This unattended BP measurement is considered superior to conventional office BP measurement because it reduces the white-coat effect and shows a better correlation with ambulatory BP and target organ damage than conventional office BP [63, 64]. This approach to measuring BP is, in some researchers’ opinion, probably better than conventional office BP measurement methods. However, systolic BP, assessed by unattended measurements, is lower than measurements in the presence of a physician or nurse [65, 66]. According to some researchers, the blood-pressure levels attained in the SPRINT intensive treatment group (systolic BP <120 mm Hg) might correspond to a conventional office systolic BP <136 mm Hg, which is more or less the same as the currently recommended therapeutic target of adequate BP control (systolic BP <140 mm Hg) [65].

The 2005 recommendations on BP measurement do not mandate who should measure BP but do require that the observer be properly trained [1, 2]. AOBP was recommended in the 2013 European Society of Hypertension guidelines for the management of hypertension as a superior method to improve reproducibility and to make office BP values closer to daytime ambulatory and home BP [67].

Devices

Before electronic BP monitors became readily available in clinical practice a few decades ago, mercury sphygmomanometers were the major instrument for BP measurement in earlier clinical trials, including the Hawksley random-zero sphygmomanometer [4, 8]. However, even in the era of electronic BP measuring devices, both aneroid and mercury sphygmomanometers had been used in parallel with automated and semiautomated electronic devices in the International Verapamil SR-Trandolapril Study (INVEST) [35, 36]. In fact, this multiple-device approach was also seen in several other multicenter clinical trials, such as the recent Heart Outcomes Prevention Evaluation-3 (HOPE-3) trial [59, 60], and even in the single-center Olmesartan and Calcium Antagonists Randomized (OSCAR) trial [55, 56].

The standard sphygmomanometer has been the mainstay of clinic BP measurement since BP could be measured noninvasively. This technique usually requires a mercury manometer. It has been removed from clinical practice in several countries and will eventually be eliminated from BP measurement in all countries not before long because of serious environmental concerns about mercury pollution. In addition, manual auscultatory BP measurement is prone to observers’ error or bias. For these reasons, manual BP measurement is gradually being supplanted by automated techniques.

Currently, the most widely used mercury-free devices are automated oscillometric BP monitors [68]. Some professional oscillometric devices allow consecutive repeated automated measuring and averaging and simultaneous two-arm measurements, with some optional functions, such as associated auscultatory BP measurement mode, detection of irregular heart beat or specifically atrial fibrillation, automated memory, and computer link or blue-tooth transfer of readings. The use of oscillometric devices for office BP measurement is still debatable in the presence of atrial fibrillation. However, the results of recent studies suggested that in atrial fibrillation, oscillometric BP monitors had similar accuracy in both systolic and diastolic BP measurements as the repeated auscultatory method [69].

Whatever devices are used, they should be regularly calibrated. When automated BP monitors are used, they should be validated. In the latter case, mercury column-based sphygmomanometers, although being phasing out in office BP measurement, are still critical for evaluating the accuracy of algorithm-based electronic devices [1].

Body Position and Resting Period

Most studies reported seated BP levels, and the resting time before the initial measurement varied from 3 to 10 min, with the most frequent resting period being 5 min. In several early studies (before 2000), BP was measured in the supine position [18] or in both the supine and standing positions [7], usually after 5 min rest in the supine position. In some other studies, BP was measured in both the seated and standing positions [4, 27, 33, 41]. In the standing position, BP was usually measured after 1–3 min.

Number of BP Readings and Time Interval

In most trials, multiple (2–6) BP readings were obtained. However, the ultimately recorded value varied from the lowest of a number of readings to an average of 2 or 3 readings or the last 2 of 3 readings. The time interval between consecutive readings ranged from 30 to 120 s (Table 1).

Arm Side and Cuff Size

BP was measured on the upper arm in almost all trials, although this was rarely acknowledged explicitly. The arm side for BP measurement was also infrequently noted. However, most commonly it was the right arm or the arm with the higher BP value. The actual protocol used to determine the correct cuff size was rarely stated. However, an “appropriate size” was frequently delineated. Other aspects, such as whether the brachial artery was positioned at the “heart level” as per guideline, could not be assessed in most trials.

Timing of BP Measurement

“Trough” BP levels were most commonly obtained although indicated in only a minority of trials, and the trough time is usually at 20–26 h after the last antihypertensive medication dosage.

The BP measurement guidelines do not mandate timing of BP measurement. However, for the purpose of comparability between trial groups and over time, BP should be measured at “trough” effect hours in all comparison studies. This is indeed mandatory for the approval of any medication by the US Food and Drug Administration [70]. For a claimed once-daily medication, the trough efficacy of BP lowering must be at least 50% of the peak effect [70]. However, the timing in relation to the last medication dosage is rarely discussed in the guidelines [1–3].

Summary of Recommendations for Optimal BP Measurement

There is no specific guideline for BP measurement in hypertension trials. In general, BP measurement should strictly follow the current recommendations or guidelines [1, 2].

Taking into account accuracy as well as practicability, the best scenario for the 9 aspects of BP measurements in hypertension trials would be as follows: (1) the observers are trained and experienced; (2) the device should be automated electronic BP monitor and should have been previously validated and regularly calibrated; (3) on each occasion, BP should be measured 2–3 times, and an average of 2 or 3 readings should be taken; (4) the time interval between successive measurements has to be 30–60 s; (5) the resting period before measurement has to be at least 5 min in the supine or seated position and awake, and 1–3 min standing; (6) BP should usually be measured in the seated position, and under some circumstances in the supine or standing position; (7) the higher arm side should be chosen and noted; (8) an appropriate size cuff should be chosen, and the size of the cuff should be noted; and (10) BP should be measured at trough hours, which should be defined, and the exact time of BP measurement should be noted.

In all hypertension trials, these aspects have to be defined a priori in the protocol and recorded in the case report forms. The application can be monitored during the execution of the trial.

Clinical Implications

Office BP measurement has been used for the diagnosis and therapeutic monitoring of hypertension for more than a century. Office BP still has a role in the screening, diagnosis, and follow-up of hypertension, despite its apparent drawback of overdiagnosis and underdiagnosis of hypertension because of the white-coat and masked hypertension, respectively [71].

AOBP seems to be a superior office BP measurement method. However, it should be recognized that although the BP values of AOBP may be more strongly associated with hypertension-related target organ damage, there is no evidence to date that treatment decisions based on AOBP yield better cardiovascular outcomes than the conventional office BP measurement [72]. More research, especially outcome trial research, is needed before a universal recommendation can be made on the use of AOBP in clinical practice. A lower cutoff value of 135/85 mm Hg has been proposed when AOBP is used for the diagnosis of hypertension, as compared with the conventional office BP measurement of 140/90 mm Hg [72, 73]. The results of a recent study in 3,627 participants also suggested that 135/85 mm Hg may be an appropriate threshold for the diagnosis of hypertension in older subjects using AOBP [74].

As compared with any office BP measurement, out-of-office BP measurement, such as ambulatory and home BP monitoring, has apparent advantages. It is devoid of the white-coat effect, and by comparing with office BP, it may identify white-coat hypertension. It may help in the diagnosis of masked hypertension, including nocturnal hypertension [75]. It may also improve cardiovascular prediction by measuring nocturnal dipping, morning BP surge, and reading-to-reading BP variability [76]. Nonetheless, the superiority of ambulatory and home BP monitoring over office BP in guiding antihypertensive therapy, in terms of cardiovascular disease prevention, has not yet been fully proven by randomized controlled trials [77], needless to say that its availability in both high- and low-income settings is still limited.

Future randomized clinical trials should consider the use of these novel office or out-of-office BP measurements in the guidance of antihypertensive therapy and prevention of cardiovascular events.

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