



# Twenty-Four-Hour Ambulatory Blood Pressure Monitoring in Hypertension: An Evidence-Based Analysis

Health Quality Ontario

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# List of Abbreviations

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<b>ABPM</b>	Ambulatory blood pressure monitoring
<b>ABP</b>	Ambulatory blood pressure
<b>ADBP</b>	Diastolic blood pressure measured by an ambulatory device
<b>ASBP</b>	Systolic blood pressure measured by an ambulatory device
<b>BP</b>	Blood pressure
<b>CBP</b>	Conventionally measured blood pressure
<b>CBPM</b>	Conventional/clinic/office blood pressure monitoring
<b>CDBP</b>	Conventionally measured diastolic blood pressure
<b>CEA</b>	Cost-effectiveness analysis
<b>CI</b>	Confidence interval(s)
<b>CSBP</b>	Conventionally measure systolic blood pressure
<b>CHD</b>	Coronary heart disease
<b>CVD</b>	Cardiovascular disease
<b>DBP</b>	Diastolic blood pressure
<b>HMI</b>	Hypertension Management Initiative
<b>HQO</b>	Health Quality Ontario
<b>HRQOL</b>	Health-related quality of life
<b>HSFO</b>	Heart and Stroke Foundation of Ontario
<b>ICER</b>	Incremental cost-effectiveness ratio
<b>MD</b>	Mean difference
<b>QALY</b>	Quality-adjusted life year
<b>RCT</b>	Randomized controlled trial
<b>RR</b>	Risk ratio
<b>SBP</b>	Systolic blood pressure
<b>WCH</b>	White coat hypertension

# **Executive Summary**

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## **Objective**

The objective of this health technology assessment was to determine the clinical effectiveness and cost-effectiveness of 24-hour ambulatory blood pressure monitoring (ABPM) for hypertension.

## **Clinical Need: Condition and Target Population**

Hypertension occurs when either systolic blood pressure, the pressure in the artery when the heart contracts, or diastolic blood pressure, the pressure in the artery when the heart relaxes between beats, are consistently high. Blood pressure (BP) that is consistently more than 140/90 mmHg (systolic/diastolic) is considered high. A lower threshold, greater than 130/80 mmHg (systolic/diastolic), is set for individuals with diabetes or chronic kidney disease.

In 2006 and 2007, the age-standardized incidence rate of diagnosed hypertension in Canada was 25.8 per 1,000 (450,000 individuals were newly diagnosed). During the same time period, 22.7% of adult Canadians were living with diagnosed hypertension.

A smaller proportion of Canadians are unaware they have hypertension; therefore, the estimated number of Canadians affected by this disease may be higher. Diagnosis and management of hypertension are important, since elevated BP levels are related to the risk of cardiovascular disease, including stroke. In Canada in 2003, the costs to the health care system related to the diagnosis, treatment, and management of hypertension were over \$2.3 billion (Cdn).

## **Technology**

The 24-hour ABPM device consists of a standard inflatable cuff attached to a small computer weighing about 500 grams, which is worn over the shoulder or on a belt. The technology is noninvasive and fully automated. The device takes BP measurements every 15 to 30 minutes over a 24-to 28-hour time period, thus providing extended, continuous BP recordings even during a patient's normal daily activities. Information on the multiple BP measurements can be downloaded to a computer.

The main detection methods used by the device are auscultation and oscillometry. The device avoids some of the pitfalls of conventional office or clinic blood pressure monitoring (CBPM) using a cuff and mercury sphygmomanometer such as observer bias (the phenomenon of measurement error when the observer overemphasizes expected results) and white coat hypertension (the phenomenon of elevated BP when measured in the office or clinic but normal BP when measured outside of the medical setting).

## **Research Questions**

1. Is there a difference in patient outcome and treatment protocol using 24-hour ABPM versus CBPM for uncomplicated hypertension?
2. Is there a difference between the 2 technologies when white coat hypertension is taken into account?
3. What is the cost-effectiveness and budget impact of 24-hour ABPM versus CBPM for uncomplicated hypertension?

# Research Methods

## Literature Search

### *Search Strategy*

A literature search was performed on August 4, 2011 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 1997 to August 4, 2011. Abstracts were reviewed by a single reviewer. For those studies meeting the eligibility criteria, full-text articles were obtained.

Reference lists were also examined for any additional relevant studies not identified through the search. Articles with unknown eligibility were reviewed with a second clinical epidemiologist and then a group of epidemiologists until consensus was established. The quality of evidence was assessed as high, moderate, low, or very low according to GRADE methodology.

### *Inclusion Criteria*

- English language articles;
- published between January 1, 1997 and August 4, 2011;
- adults aged 18 years of age or older;
- journal articles reporting on the effectiveness, cost-effectiveness, or safety for the comparison of interest;
- clearly described study design and methods;
- health technology assessments, systematic reviews, meta-analyses, or randomized controlled trials.

### *Exclusion Criteria*

- non-English papers;
- animal or in vitro studies;
- case reports, case series, or case-case studies;
- studies comparing different antihypertensive therapies and evaluating their antihypertensive effects using 24-hour ABPM;
- studies on home or self-monitoring of BP, and studies on automated office BP measurement;
- studies in high-risk subgroups (e.g. diabetes, pregnancy, kidney disease).

## *Outcomes of Interest*

### Patient Outcomes

- mortality: all cardiovascular events (e.g., myocardial infarction [MI], stroke);
- non-fatal: all cardiovascular events (e.g., MI, stroke);
- combined fatal and non-fatal: all cardiovascular events (e.g., MI, stroke);
- all non-cardiovascular events;
- control of BP (e.g. systolic and/or diastolic target level).

### Drug-Related Outcomes

- percentage of patients who show a reduction in, or stop, drug treatment;
- percentage of patients who begin multi-drug treatment;
- drug therapy use (e.g. number, intensity of drug use);
- drug-related adverse events.

# Quality of Evidence

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

<b>High</b>	Further research is very unlikely to change confidence in the estimate of effect.
<b>Moderate</b>	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
<b>Low</b>	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
<b>Very Low</b>	Any estimate of effect is very uncertain.

## Summary of Findings

### Short-Term Follow-Up Studies (Length of Follow-Up of $\leq 1$ Year)

- Based on very low quality of evidence, there is no difference between technologies for non-fatal cardiovascular events.
- Based on moderate quality of evidence, ABPM resulted in improved BP control among patients with sustained hypertension compared to CBPM.
- Based on low quality of evidence, ABPM resulted in hypertensive patients being more likely to stop antihypertensive therapy and less likely to proceed to multi-drug therapy compared to CBPM.
- Based on low quality of evidence, there is a beneficial effect of ABPM on the intensity of antihypertensive drug use compared to CBPM.
- Based on moderate quality of evidence, there is no difference between technologies in the number of antihypertensive drugs used.
- Based on low to very low quality of evidence, there is no difference between technologies in the risk for a drug-related adverse event or noncardiovascular event.

### Long-Term Follow-Up Study (Mean Length of Follow-Up of 5 Years)

- Based on moderate quality of evidence, there is a beneficial effect of ABPM on total combined cardiovascular events compared to CBPM.
- Based on low quality of evidence, there is a lack of a beneficial effect of ABPM on nonfatal cardiovascular events compared to CBPM; however, the lack of a beneficial effect is based on a borderline result.
- Based on low quality of evidence, there is no beneficial effect of ABPM on fatal cardiovascular events compared to CBPM.
- Based on low quality of evidence, there is no difference between technologies for the number of patients who began multi-drug therapy.
- Based on low quality of evidence, there is a beneficial effect of CBPM on control of BP compared to ABPM. This result is in the opposite direction than expected.
- Based on moderate quality of evidence, there is no difference between technologies in the risk for a drug-related adverse event.

# Background

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## Objective of Analysis

The objective of this health technology assessment was to determine the clinical effectiveness and cost-effectiveness of 24-hour ambulatory blood pressure monitoring (ABPM) in the management of hypertension.

## Clinical Need and Target Population

### Description of Hypertension

Hypertension occurs when either systolic blood pressure (SBP), the pressure in the artery when the heart contracts, or diastolic blood pressure (DBP), the pressure in the artery when the heart relaxes between beats, are consistently high. Blood pressure (BP) that is consistently more than 140/90 mmHg (systolic/diastolic) is considered high. A lower threshold, more than 130/80 mmHg (systolic/diastolic), is set for individuals with diabetes or chronic kidney disease. (1)

Hypertension is a serious condition that can lead to coronary heart disease (CHD) and stroke. A meta-analysis of 61 prospective studies showed a strong relationship between average BP and vascular mortality; additional meta-analyses showed that antihypertensive drug therapy reduces the risk of cardiovascular events in hypertensive individuals. (2) The relationship between BP and risk of cardiovascular events is continuous, consistent, and independent of other risk factors. (3)

When hypertension occurs without an identified cause, it is referred to as uncomplicated, essential, primary, or idiopathic hypertension. If another condition causes hypertension, it is referred to as secondary hypertension. Since high BP has no symptoms, it can go undiagnosed and untreated. Its presence can cause damage to the heart, blood vessels, kidneys, and other parts of the body. Risk factors for hypertension include older age, ethnicity, being overweight or obese, lifestyle factors such as smoking, and family history.

To control and treat hypertension, BP medications, such as diuretics, beta blockers, and vasodilators, are used. They work in different ways to lower BP. (4) A majority of hypertensive patients will require 2 or more antihypertensive medications to effectively treat and control their elevated BP. (3)

The classification of BP is as follows: (2)

- Normal BP: < 120 mm Hg for SBP and < 80 mm Hg for DBP
- Pre-hypertension (“high-risk”): 120 to 139 mm Hg for SBP or 80 to 89 mm Hg for DBP
- Stage 1 hypertension: 140 to 159 mm Hg for SBP or 90 to 99 mm Hg for DBP
- Stage 2 hypertension: ≥ 160 mm Hg for SBP or ≥ 100 mm Hg for DBP

There is a natural variability of BP. This variability contributes to the complexities of its measurement, the diagnosis of hypertension, and the optimal management of hypertension with antihypertensive therapy.

The pattern of BP expression can be categorized as daytime and nighttime variability, referred to as the diurnal BP phenomenon. Typically, in-office measured daytime BP has been reported in previous studies in association with cardiovascular risk. However, increasing evidence is highlighting that nighttime BP may better reflect cardiovascular risk. Nighttime BP is the time period that coincides with an individual’s

sleep time. Within this time period, a decrease in blunted nocturnal BP, otherwise referred to as a nondipping status, is associated with an increased risk of cardiovascular events.

The ability to examine the circadian pattern of BP with 24-hour ABPM and optimize the effects of antihypertensive therapy over a 24-hour time period makes it a favoured choice in BP management. Whether cardiovascular risk is better evaluated using dipping status, such as determining which patients are normal dippers and which patients are nondippers, or whether classifying patients as displaying nocturnal normotension, defined as nighttime SBP less than or equal to 125 mm Hg or nighttime DBP less than or equal to 80 mm Hg, is not clear. (5) The suggested values for daytime, nighttime, and 24-hour average ambulatory BP (ABP) levels are shown below. The normal range for ABP was established by comparing the ABP level that corresponds to a conventional office or clinic blood pressure (CBP) levels of 140/90 mm Hg, and by relating ABP to the risk identified in prospective studies. (2)

The suggested values for daytime, nighttime, and 24-hour average ABP levels are as follows: (2)

- **Daytime:** optimal, < 130/80 mm Hg; normal, < 135/85 mm Hg; abnormal, > 140/90 mm Hg
- **Nighttime:** optimal, < 115/65 mm Hg; normal, < 120/70 mm Hg; abnormal, > 125/75 mm Hg
- **24-hour:** optimal, < 125/75 mm Hg; normal, < 130/80 mm Hg; abnormal, > 135/85 mm Hg

Hypertension is a silent disease that, over time, may cause accumulated damage to the body. Lifestyle modification is critical for the prevention of hypertension, especially for individuals who are in a prehypertensive state (and who do not require antihypertensive medication). These individuals are advised to modify their lifestyles, including losing weight, changing their diet, reducing alcohol intake, and engaging in regular aerobic physical activity.

The public health goal for patients with hypertension is treatment and management, in order to avoid the long-term effects of cardiovascular disease (CVD). Lifestyle modification is also relevant for patients with hypertension. Inadequate control of diagnosed BP may be due to: (3)

- the failure to prescribe lifestyle modifications,
- inadequate antihypertensive drug doses, and
- inappropriate drug combinations.

## Prevalence and Incidence of Hypertension

In 2006 and 2007, the age-standardized incidence rate of diagnosed hypertension in Canada was 25.8 per 1,000 people. During the same time period, 450,000 individuals were newly diagnosed. (6)

A smaller proportion of Canadians are unaware they have hypertension; therefore, the estimated number of Canadians affected by this disease may be higher. Diagnosis and management of hypertension is important, since elevated BP levels are associated with the risk of CVD. (7)

In Canada in 2003, the costs to the health care system related to the diagnosis, treatment, and management of hypertension were over \$2.3 billion (Cdn). (7)

## Ontario Context

The ABPM device is not insured in Ontario, Alberta, British Columbia, or the Yukon Territory. The service is covered as part of routine care in Nova Scotia, Manitoba, and New Brunswick. In Saskatchewan, the service is also covered with a limit of 1 billing per year per patient. The device is in use in Newfoundland and Labrador, but there is no associated fee code. In Ontario, patients who have been referred by their family physician to receive 24-hour ABPM pay approximately \$70 for using the technology.

The 24-hour ABPM device has been licensed by Health Canada since 1999 as a Class II device. Associated parts of the equipment include the adult cuff, recorder, and software, which are also licensed by Health Canada.

## Technology/Technique

### Twenty-Four-Hour Ambulatory Blood Pressure Monitoring Device

The 24-hour ABPM device consists of a standard inflatable cuff attached to a small computer weighing about 500 grams, which is worn over the shoulder or on a belt. The technology is noninvasive and fully automated. It takes BP measurements every 15 to 30 minutes over a 24-to 28-hour time period, thus providing extended, continuous BP recordings even during a patient's normal daily activities. Information on the multiple BP measurements can be downloaded to a computer.

The main detection methods used by the device are:

- auscultation, which detects Korotkoff sounds at the artery under a compression cuff using a microphone;
- cuff oscillometry, which detects cuff pressure oscillations; and
- volumetric oscillometry, which detects volume pulsations under a cuff.

The device avoids some of the pitfalls of conventional office or clinic blood pressure monitoring (CBPM) using a cuff and mercury sphygmomanometer, such as observer bias (the phenomenon of measurement error when the observer overemphasizes expected results) and white coat hypertension (WCH, the phenomenon of elevated BP when measured in the office or clinic but normal BP when measured outside of the medical setting). (8) The term WCH is typically reserved for untreated individuals, whereas the white coat effect refers to treated hypertensive patients who show a decrease in ABPM compared with CBPM. (9) Marked differences between CBPM and ABPM exist. (10) These differences have been confirmed by invasive blood pressure recordings. (11) Failure to limit patient-physician interaction and to minimize patient-related factors such as anxiety may contribute to these biases. (12)

Automatic BP monitoring as used in the ABPM does not induce an alarm reaction and a consequent BP rise, and thus does not overestimate daytime BP values. (13) The reason for concern with respect to WCH is that treatment for these individuals may be unwarranted. Furthermore, stopping drug therapy is not related to adverse outcomes in mild to moderate hypertension. (14) White coat hypertension is most common in the elderly population, and is estimated to occur in approximately 20% of individuals with hypertension. (8) A recent meta-analysis showed that there was no difference in the risk of cardiovascular events for untreated subjects with WCH compared to those with normotension (adjusted hazard ratio, 0.96; 95% confidence interval [CI], 0.65–1.42;  $P = 0.85$ ). (15)

Considering that over \$2.3 billion (Cdn) were spent on hypertension in Canada in 2003 (physician, medication, and laboratory costs), reducing or eliminating the population of white coat hypertensives who may inappropriately be treated would potentially result in cost savings on multiple levels of the health care system. A number of AMPB devices have been validated for use according to the British Hypertension Society (BHS) protocol and the United States Association for the Advancement of Medical Instrumentation (AAMI) protocol. These widely accepted protocols involve comparing the accuracy of ambulatory devices with CBPM (the latter being used as the reference standard), and assessing the level of agreement. (16) A recent systematic review examined the sensitivity and specificity for the comparison of ABPM versus CBPM; however, ABPM was used as the reference standard. The study showed poor sensitivity and specificity (74.6% for both), and highlighted that CBPM was insufficient as a single diagnostic test and that overdiagnosis was likely. (17)

The 24-hour ABPM device measures BP during waking hours and during sleep. It is helpful in monitoring BP during the transition period from sleep to wakefulness, during which time risk of cardiovascular events is elevated. However, CBPM is a static, daytime measurement. (18) Given that ABPM has been incorporated into the Canadian Hypertension Education Program<sup>1</sup>, it is considered by some to be the gold standard for BP measurement in Canada. (19)

## Clinical Indications and Indications for Repeat Use

Clinical indications for 24-hour ABPM include: (20)

- diagnosing patients with WCH (which is accentuated in patients with hypertension more than in patients who are normotensive);
- diagnosing patients with borderline hypertension (to prevent antihypertensive therapy from being unnecessarily prescribed);
- diagnosing elderly patients (who are increasingly susceptible to drug-related adverse effects, hypotension, and elevated BP on conventional measurement, leading to excessive antihypertensive therapy);
- diagnosing nocturnal hypertension (including identifying the absence of a dipping pattern);
- diagnosing patients with resistant hypertension (in whom the white coat effect maybe the culprit, as CBP above 150/90 mm Hg is sometimes detected despite the use of appropriate antihypertensive therapy);
- diagnosing WCH during pregnancy;
- diagnosing hypotension; and
- guiding antihypertensive drug therapy by overcoming the limitations of CBPM, for example
  - evaluating the efficacy of therapy in a nonmedical environment (thereby minimizing the possibility of the white coat effect),
  - identifying the excessive effects of antihypertensive drugs,
  - identifying symptoms with the use of therapy,
  - identifying the effect of drugs over a 24-hour period.

Potential indications for repeat use (i.e. more than once annually) of 24-hour ABPM include: (20)

- an excessive variability in BP;
- an inappropriate response to therapy;
- an adverse risk factor profile;
- the need for careful control of BP, such as in hypertensive patients with diabetes mellitus or renal disease.

It is typically unnecessary to repeat ABPM more frequently than annually. However, indications for annual remonitoring include: (20)

- untreated patients with WCH,
- treated patients with the white coat effect,
- elderly patients with hypotension,
- patients with nocturnal hypertension, and
- patients whose antihypertensive medications have been changed.

## Advantages of Twenty-Four-Hour Ambulatory Blood Pressure Monitoring

Overall, the advantages of 24-hour ABPM are as follows: (21)

- A more accurate representation of true BP is determined, because the device offers an increased number of BP measurements compared to CBPM.

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<sup>1</sup> The Canadian Hypertension Education Program is Canada's resource for recommendations and clinical guidelines regarding hypertension management.

- Since BP is determined outside a medical environment, individuals with WCH or masked hypertension can be identified.
- The efficacy of antihypertensive therapy can be better evaluated, because the behaviour of BP is examined over a 24-hour time period rather than at one point or a few points in time.
- Patients' individual patterns of nocturnal BP can be identified such as dippers, nondippers, extreme dippers, reverse dippers, and morning surge. High-risk individuals can be appropriately targeted with drugs.
- Other patterns of BP behaviour can be identified, such as isolated diastolic and systolic hypertension.
- There is increasing evidence that ABPM is a stronger predictor of cardiovascular morbidity and mortality than CBPM.

## **Safety**

There are no major safety concerns with using 24-hour ABPM. Discomfort associated with the use of the cuff is 1 reported minor complication. (8)

## **Alternative Technologies**

### **Self- or Home-Measured Blood Pressure**

Twenty-four-hour ABPM is not the same as self- or home-measured BP. Similar to 24-hour ABPM, self-measured BP monitoring devices provide BP recordings outside of the medical setting, such as in the patient's home, and therefore can also help to detect WCH. In contrast, however, patients using the self-measured BP monitoring device are sometimes trained to record their own BPs. Therefore, some of the devices are not fully automated. Patients may provide a written list of readings to their physicians. Home-based devices include mercury sphygmomanometers, aneroid manometers, semiautomatic devices, and fully automatic electronic devices. Repeat measurements can be taken with the self- or home-measured BP devices, but programmable and continuous BP readings, such as those taken with 24-ABPM devices, are not possible. (22)

### **Automated Office Blood Pressure Measurement**

Twenty-four-hour ABPM is not the same as automated office BP measurement. Automated office BP measurement records BP in the office with the patient resting quietly alone in the examining room. Readings are taken over 5 to 10 minutes. (19;23;24)

### **Standard Mercury Sphygmomanometers**

The method of measuring BP using mercury sphygmomanometers has been, to date, considered the gold standard for the clinical measurement of BP. It uses the auscultatory method, or Korotkoff technique, for measuring BP, while the brachial artery is occluded by a cuff placed around the upper arm and the cuff is inflated to above systolic pressure. Upon deflation, the pulsatile blood flow generates sounds that are detected by a stethoscope held over the artery and below the cuff, and which are translated into SBP and DBP readings that can be read from a mercury column. (2)

### **Other Sphygmomanometers**

Hybrid sphygmomanometers combine features of electronic and auscultatory devices. The mercury column is replaced by an electronic pressure gauge, as in oscillometric devices. Blood pressure is taken using a stethoscope and listening for Korotkoff sounds, as in auscultatory devices. The cuff pressure is identified from a simulated mercury column, digital readout, or simulated aneroid display. Aneroid sphygmomanometers involve a mechanical system and a cuff that register the pressure. (2)

# Evidence-Based Analysis

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## Research Questions

1. Is there a difference in patient outcome and treatment protocol using 24-hour ABPM versus CBPM for uncomplicated hypertension?
2. Is there a difference between the 2 technologies when WCH is taken into account?
3. What is the cost-effectiveness and budget impact of 24-hour ABPM versus CBPM for uncomplicated hypertension?

## Research Methods

### Literature Search

#### *Search Strategy*

A literature search was performed on August 4, 2011 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 1997 to August 4, 2011. Abstracts were reviewed by a single reviewer. For those studies meeting the eligibility criteria, full-text articles were obtained.

Reference lists were also examined for any additional relevant studies not identified through the search. Articles with unknown eligibility were reviewed with a second clinical epidemiologist and then a group of epidemiologists until consensus was established. The quality of evidence was assessed as high, moderate, low, or very low according to GRADE methodology.

### Inclusion Criteria

- English language articles;
- Published between January 1, 1997 and August 4, 2011;
- adults aged 18 years of age or older;
- journal articles reporting on the effectiveness, cost-effectiveness, or safety for the comparison of interest;
- clearly described study design and methods; and/or
- health technology assessments, systematic reviews, meta-analyses, or randomized controlled trials (RCTs).

### Exclusion Criteria

- non-English papers;
- animal or in vitro studies;
- case reports, case series, or case-case studies;
- studies comparing different antihypertensive therapies and evaluating their antihypertensive effects using 24-hour ABPM;
- studies on home or self-monitoring of BP, and studies on automated office BP measurement; and/or
- studies in high-risk subgroups (e.g. diabetes, pregnancy, kidney disease).

## **Outcomes of Interest**

### **Patient Outcomes**

- mortality: all cardiovascular events (e.g., myocardial infarction [MI], stroke);
- non-fatal: all cardiovascular events (e.g. MI, stroke);
- combined fatal and non-fatal: all cardiovascular events (e.g. MI, stroke);
- non-cardiovascular events; and/or
- control of BP (e.g. systolic and/or diastolic target level).

### **Drug-Related Outcomes**

- percentage of patients who show a reduction in, or stop drug treatment;
- percentage of patients who begin multi-drug treatment;
- drug therapy use (e.g. number, intensity of drug use); and/or
- drug-related adverse events.

## **Statistical Analysis**

A pooled analysis within subgroups was performed using Review Manager version 5. Otherwise, an analysis of individual studies was performed. Specific details of the analyses are described in the subsequent section, *Results of Evidence-Based Analysis*.

For dichotomous data, a risk ratio (RR) was calculated for RCTs. Statistical heterogeneity was assessed using the chi-square test. A *P* value less than or equal to 0.10 associated with a chi-square statistic was considered to indicate substantial heterogeneity and a random-effects model was used. In the absence of heterogeneity, a fixed-effects model was used. A *P* value less than 0.05 was considered statistically significant.

## **Quality of Evidence**

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (25) as presented below.

- Quality refers to the criteria such as the adequacy of allocation concealment, blinding and follow-up.
- Consistency refers to the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.
- Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

<b>High</b>	Further research is very unlikely to change confidence in the estimate of effect.
<b>Moderate</b>	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
<b>Low</b>	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
<b>Very Low</b>	Any estimate of effect is very uncertain.

# Results of Evidence-Based Analysis

The database search yielded 2,125 studies published between January 1, 1997 and August 4, 2011. Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. Three studies met the inclusion criteria (Table 1).

**Table 1: Body of Evidence Examined According to Study Design**

Study Design	Number of Eligible Studies
<b>RCT Studies</b>	
Systematic review of RCTs	-
Large RCT <sup>a</sup>	3
Small RCT	-
<b>Observational Studies</b>	
Systematic review of non-RCTs with contemporaneous controls	-
Non-RCT with contemporaneous controls	-
Systematic review of non-RCTs with historical controls	-
Non-RCT with historical controls	-
Database, registry, or cross-sectional study	-
Case series	-
Retrospective review, modelling	-
Studies presented at an international conference or other sources of grey literature	-
Expert opinion	-
<b>Total</b>	3

Abbreviation: RCT, randomized controlled trial.

<sup>a</sup>Large RCT ≥ 150 subjects.

## Health Technology Assessments

The 2011 health technology assessment conducted by the National Institute for Health and Clinical Excellence in the United Kingdom (26) was a partial update to 2 previous reports, published in 2004 and 2006. For the 2011 report, the search strategy was current as of November 2010. Among the research questions they examined was the question: Among adults treated for primary hypertension, what is the best method to measure blood pressure to determine response to treatment? The authors compared ambulatory versus office BP monitoring (as well as home-based BP monitoring, which is not discussed here).

The results showed that only 1 RCT was relevant for this evidence-based analysis (it was also identified in the search strategy for this evidence-based analysis). (27) The authors reported that ABPM (compared with CBPM) accounted for a greater reduction in 24-hour SBP after 1 year (mean difference [MD], -3.6; 95% CI, -7.0 to -0.3). In addition, the proportion of patients with controlled 24-hour BP after 1 year was significantly higher in the ABPM group compared with the CBPM group (RR, 1.41; 95% CI, 1.01–1.99). This was based on very low quality of evidence owing to limitations in allocation concealment, lack of blinding, and the lack of an intent-to-treat analysis. No differences between technologies were shown for

other BP control measures or the mean number of antihypertensive drugs used. Based on the research question, the authors recommended the following:

- CBPM should be used to monitor the response to antihypertensive treatment with lifestyle modification or drugs.
- ABPM should be considered as an adjunct to CBPM for those patients who display a white coat effect, in order to monitor the response to antihypertensive treatment with lifestyle modification or drugs.

The authors also examined the following research question: In adults with suspected primary hypertension, what is the best method to measure AMBP versus CMPB (versus home-based monitoring, which is not discussed here) to predict the development of cardiovascular events? The search strategy was current as of November 2010. The results identified 9 prognostic studies that compared ABPM to CBPM. In 8 of the studies, ABPM was deemed to be superior compared to CBPM, whereas 1 study found no difference between the technologies. Blood pressure measurements were statistically modeled as continuous variables (e.g., per 10 mm Hg increase). Overall, the increased accuracy afforded by ABPM strengthened the relationship between BP and cardiovascular risk (e.g., RR for ABPM > RR for CBPM).

In a 2002 health technology assessment (the search strategy was current as of March 2001) conducted by the Agency for Healthcare Research and Quality in the United States, (22) the researchers posed the following questions:

1. Is ABPM more or less strongly associated with BP-related target organ damage than CBPM?
2. Does ABPM predict subsequent clinical outcomes?
3. What is the ‘incremental gain’ in prediction of clinical outcomes from the use of ABPM beyond prediction from CBPM alone?
4. What is the effect of treatment guided by ABPM in comparison to treatment guided by CBPM (e.g., in terms of target organ damage, symptoms, use of antihypertensive therapy, and BP control)?
5. Do any of the above vary according to a patient’s age, gender, income level, race/ethnicity, and clinical subgroups such as patients with hypertension, or those with normotension, patients with diabetes, and those having had a renal transplant?

Regarding questions 2, 3, and 4, the results of the health technology assessment showed the following:

- A total of 10 prospective studies addressed the association between ABPM and clinical events. In each study, at least 1 dimension of ABPM predicted clinical events.
- A total of 9 prospective studies examined ABPM relative to CBPM and subsequent risk for clinical events. In 7 of 9 studies, ABPM was a better statistical predictor of clinical events than CBPM. In 2 of 9 studies, ABPM provided statistical ‘incremental gain’ beyond CBPM. The authors also concluded that the measurement of CBPM and types of comparative analyses were limited.
- A total of 2 trials examined the effect of treatment guided by ABPM versus CBPM. Since there were only 2 trials identified, the authors concluded insufficient evidence to determine the effects of treatment guided by ABPM.

Overall, the authors of the 2 health technology assessments concluded that there has been limited work on the topic. One of the health technology assessments recommended that ABPM be considered in conjunction with CBPM in patients experiencing the white coat effect. (26)

### **Relevant Additional Reviews (Non-Systematic)**

The 2001 Succinct and Timely Evaluated Evidence Review (STEER) conducted in the United Kingdom examined the clinical effectiveness of 24-hour ABPM compared to CBPM. (28) STEER is a short, pragmatic descriptive review. Included in the findings were 3 RCTs and 1 cohort study; however, 2 of the

included trials were based on the same study population at different time points of follow-up. The search strategy was current as of November 2001. Overall, the authors concluded that there was heterogeneity among studies and insufficient evidence to assess the clinical effectiveness in the long-term of ABPM compared to CBPM. The 1 study with long-term follow-up—included in this evidence-based analysis—and with information on cardiovascular events was limited by selection bias, lack of information on randomization details, and differential dropouts between the 2 arms of the trial. The authors concluded that there was weak evidence that ABPM may reduce the intensity of antihypertensive therapy in the short-term in patients with diastolic hypertension; however, this was taken from the same 2 RCTs at different time points of follow-up (1 month and 6 months).

A 2003 Canadian technology “pre-assessment” examined relevant publications on the topic of 24-hour ABPM, where pre-assessments are based on a limited non-systematic literature search. (29) Included in the findings were health technology assessments, systematic reviews, and practice guidelines. The search strategy was from 1998 onwards. The authors concluded that while there is a large body of literature on ABPM, there is a lack of quality of evidence, and additional clarification cannot be provided at this time on the role and value of ABPM.

## **Randomized Controlled Trials**

Three parallel RCTs were identified. (27;30;31) A summary of the studies and their characteristics are shown in Appendix 3, Tables A1–A4.

### ***Study Methods***

A multi-centre RCT conducted in Switzerland by Conen et al (27) compared 24-hour ABPM with CBPM in the management of antihypertensive therapy. The primary endpoint was the 1-year change in 24-hour systolic blood pressure measured by an ambulatory device (ASBP). The secondary endpoints were the 1-year change in 24-hour diastolic blood pressure as measured by an ambulatory device (ADBP), the 1-year change in conventionally measured systolic blood pressure (CSBP) and conventionally measured diastolic blood pressure (CDBP), and the proportion of patients with controlled 24-hour ABPM or CBPM at 1 year. Controlled BP was defined as CBP less than 140/90 mm Hg, or 24-hour ABP less than 130/80 mm Hg. Adverse events, defined as any cardiovascular event or any drug-related event, were also tabulated. The mean number of drugs used and the number of drugs used by drug class were also enumerated. Eligible individuals were those aged 18 years of age or older.

Individuals were screened for CSBP exceeding 140 mm Hg or CDBP exceeding 90 mm Hg, taken as the mean of 2 BP measurements on 2 different days. Those who displayed sustained hypertension ( $SBP \geq 130$  mm Hg) or DBP ( $\geq 80$  mm Hg) as determined by 24-hour ABPM were eligible for randomization.

Exclusion criteria included a history of

- severe cardiovascular or cerebrovascular disease;
- acute MI;
- stroke or revascularization procedure within 6 months; and
- severe concomitant disease (e.g. congestive heart failure, cancer).

Randomization was computer-generated and maintained by personnel not involved in the study. Physicians attending to patients were unaware of the assignment sequence. Randomization was 1:1 and stratified by whether hypertension was previously known to patients; therefore, both treated and untreated patients were randomized. Physicians were not blinded to the interventions.

Conventional office or clinic blood pressure monitoring was performed on patients in a sitting position for at least 5 minutes, using the left arm, an appropriate sized cuff, and a validated oscillometric device. Ambulatory blood pressure monitoring was performed every 20 minutes between 8 a.m. and 10 p.m. and

every 30 minutes between 10 p.m. and 8 a.m., during usual activity. The mean 24-hour ABPM was calculated using all values. Follow-up BP measurements were performed at 1 month, 6 months, and 1 year. Blood pressure measurements between follow-up visits were discouraged. Target BP values were less than 140/90 mm Hg for CBPM and less than 130/80 mm Hg for 24-hour ABPM. Treating physicians adjusted antihypertensive therapy according to target BP of the allocated intervention (not blinded). First-line therapy was telmisartan. Treatment was not adjusted in a blinded manner. Conventional office or clinic blood pressure monitoring and 24-hour ABPM were performed on all patients.

A multi-centre, RCT conducted in Germany by Schrader et al (30) compared 24-hour ABPM with CBPM in the management of antihypertensive therapy and CVD prognosis. Cardiovascular events were defined as MIs (fatal and non-fatal), stroke (fatal and non-fatal), and all other cardiovascular deaths. Information was gleaned from medical records or necropsy reports. Antihypertensive therapy dosage was compared using a drug-score method, where patients taking the daily recommended dosage of a given drug are assigned a score of 1, half the recommended dosage is assigned a score of 0.5, and double-dosage is assigned a score of 2 points. Eligible individuals were between 35 and 65 years of age.

Participants were eligible if they had CBP hypertension ( $> 140$  mm Hg SBP and/or  $> 90$  mm Hg DBP) determined from 3 measurements on 2 different days after 5 minutes sitting, using either the Riva-Rocci method or auscultatory method.

Among the exclusion criteria were:

- a contraindication for antihypertensive treatment;
- cardiac insufficiency;
- high-grade stenosis;
- women who were pregnant, lactating, or who had the potential to become pregnant;
- alcohol or drug abuse issues; and
- fatal disease.

After a washout period, patients were randomized to either the ABPM group or the CBPM group; therefore, patients were “untreated” at the time of randomization. Randomization details were not provided, although correspondence with the authors confirmed adequate randomization and allocation concealment. (Personal communication, clinical expert, November 19, 2011)

Patients randomized to the ABPM group were considered hypertensive and remained in the study if their average daytime (between 6 a.m. and 10 p.m.) ASBP was greater than 135 mm Hg and/or their average daytime ADBP was greater than 85 mm Hg, or if their average 24-hour ASBP was greater than 130 mm Hg and/or their average ADBP was greater than 80 mm Hg. Patients randomized to the ABPM group who did not meet these criteria were excluded on the basis that they were displaying WCH (22%, 189/859 patients).

Follow-up in both groups was performed at 2 to 4 weeks, 3, 6, 9, 12 months, and 2, 3, 4, and 5 years. Ambulatory blood pressure monitoring was performed once a year, or when a change of treatment seemed necessary according to CBP, or for clinical reasons. It was performed every 15 minutes between 6 a.m. and 10 p.m., and every 30 minutes between 10 p.m. and 6 a.m., using a validated device. Conventional office or clinic blood pressure monitoring was performed at each follow-up time period in both groups, as described above. Treating physicians adjusted antihypertensive therapy according to target BP of the allocated intervention (not blinded), as described above. Therapy was intensified according to BP target levels as described above (i.e., group therapy for patients in the CBPM group was intensified if CSBP was  $> 140$  mm Hg and/or CDBP  $> 90$  mm Hg). First-line therapy was ramipril. Treatment was not adjusted in a blinded manner.

A multi-centre RCT conducted in Belgium by Staessen et al (31) examined the management of antihypertensive treatment based on 24-hour ABPM compared with CBPM. Symptoms were ascertained using a self-administered questionnaire, and the intensity of drug treatment was scored. Eligible individuals were 18 years of age or older and had a mean CDBP between 95 and 114 mm Hg determined from the last of 3 consecutive measurements on 2 different days taken in the sitting position (additional inclusion criteria not mentioned here). Prior to determining eligibility, all antihypertensive drugs were discontinued and replaced by placebo. Exclusion criteria were contraindications for stopping treatment. Some examples of these criteria are:

- having overt heart failure,
- unstable angina pectoris,
- hypertensive retinopathy Stage 3 or 4,
- history of MI or cerebrovascular accident within 1 year.

In addition, the following exclusion criteria were listed:

- cancer,
- liver cirrhosis,
- elevated serum creatinine,
- mental disorder,
- addictions, and
- working night shifts.

The randomization protocol was computer-generated at the coordinating centre. For this multi-centre study (47 family practices and 9 clinics), stratification by centre was performed prior to randomization of eligible individuals. Patients were randomized to treatment based on either average daytime ABPM readings or CBPM readings. Ambulatory blood pressure monitoring was based on the average daytime (10 a.m.–8 p.m.) ABP; CBPM was performed on patients after sitting for 5 minutes. Blood pressure was taken as the average of 3 consecutive readings using DBP from a conventional sphygmomanometer. Ambulatory blood pressure monitoring was set-up to measure BP every 15 minutes (8 a.m.–10 p.m.) and every 30 minutes (10 p.m.–8 a.m.) using a validated device. Follow-up was at 1, 2, 4, and 6 months. At each scheduled follow-up visit, patients had ABPM and CBPM. Targeted BP levels were the same in both groups (DBP 80–89 mm Hg), and treatment was adjusted in a blinded fashion using 1 coordinating physician. Treatment could be increased if DBP was greater than 89 mm Hg, left unchanged if DBP was 80 to 89 mm Hg, or reduced in a stepwise fashion if DBP was less than 80 mm Hg. First-line therapy was lisinopril.

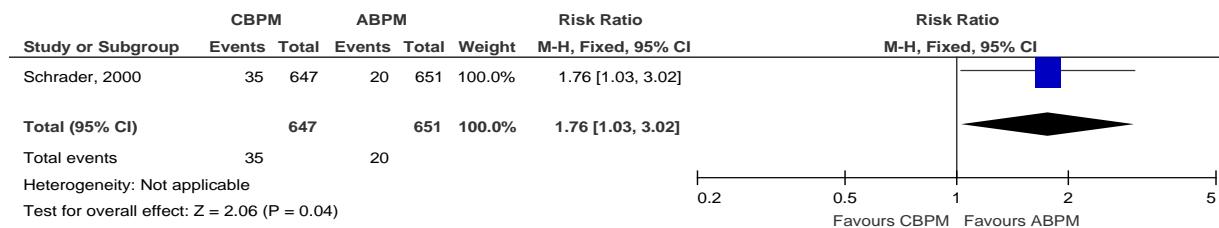
### **Answering Research Question 1: Is There a Difference in Patient Outcomes Between the Two Technologies?**

An analysis was performed to address the research question of whether there is a difference in patient outcome when using 24-hour ABPM versus CBPM for uncomplicated hypertension. Studies with data in a format suitable for analysis are shown below for the outcomes of total combined cardiovascular events, nonfatal cardiovascular events, fatal cardiovascular events, non-CVD events, patients who stopped antihypertensive therapy, patients who began sustained multi-drug therapy, control of BP, number of drugs used, drug intensity, and drug-related adverse events. Studies were grouped according to length of follow-up, with studies having a length of follow-up equal to or less than 1 year categorized together and studies having a length of follow-up of more than 1 year categorized together. The 1-year cutpoint was selected arbitrarily based upon the pool of included studies. The interpretation of the results differs based on the direction of change and the outcome measure. For consistency, a beneficial effect of ABPM appears on the right-hand side of the graph, while a beneficial effect of CBPM appears on the left-hand side of the graph. Results are presented as an RR for RCTs or as a mean difference. A formal meta-

analysis was not performed due to too few studies and the need for a stratified analysis based on length of follow-up. Where necessary, the exclusion of individuals with WCH at baseline was noted.

The outcomes were examined and are displayed in Figures 1–10 below:

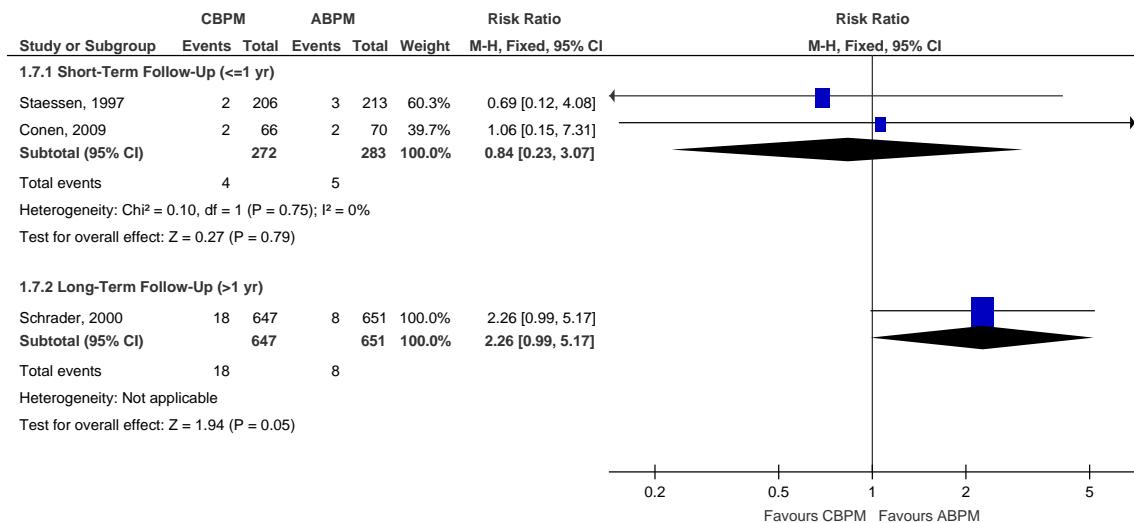
- Results showed an increased frequency of (unfavourable) combined cardiovascular events, non-fatal cardiovascular events, fatal cardiovascular events, and non-CVD events in the CBPM group compared to ABPM group (.risk ratios > 1), thereby demonstrating the beneficial effect of ABPM for these outcomes (Figures 1–4).
- An increased number of hypertensive patients who were able to stop antihypertensive drug treatment and an increased number of hypertensive patients who had control of BP are beneficial events in the ABPM group compared with the CBPM group (risk ratios > 1), indicating the beneficial effects of ABPM for these outcomes (Figures 5 and 7).
- For the remaining outcomes (i.e., an increased number of hypertensive patients who begin sustained multi-drug treatment, an increased number of drugs used, increased drug intensity, and an increased number of hypertensive patients who experienced a drug-related adverse event—all unfavourable events), results showed a beneficial effect of ABPM compared to CBPM (risk ratios > 1) (Figures 6, 8–10).



**Figure 1: Total Combined Cardiovascular Events, Mean of Five Years of Follow-Up, by Intervention Allocation<sup>a</sup>**

Abbreviations: ABPM, ambulatory blood pressure monitoring; CBPM, conventional blood pressure monitoring; CI, confidence interval; M-H, Mantel-Haenszel; WCH, white coat hypertension.

<sup>a</sup>Cardiovascular events defined as fatal and non-fatal myocardial infarction, stroke, and all other cardiovascular deaths. Patients with WCH were excluded from the ABPM group.



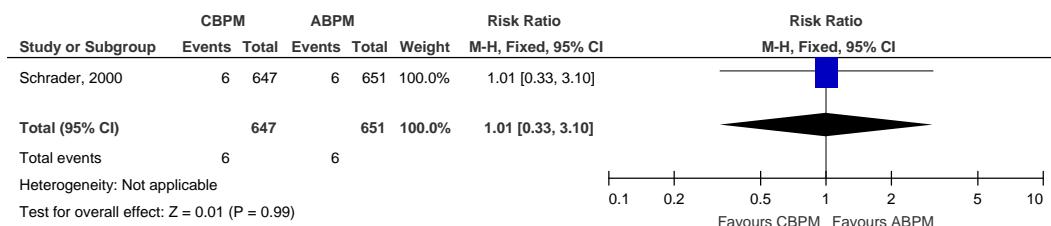
**Figure 2: Non-Fatal Cardiovascular Events, By Intervention Allocation<sup>a,b,c</sup>**

Abbreviations: ABPM, ambulatory blood pressure monitoring; CBP, conventionally measured blood pressure; CBPM, conventional blood pressure monitoring; CI, confidence interval; M-H, Mantel-Haenszel; WCH, white coat hypertension.

<sup>a</sup>Staessen et al, 1997 (31): Included non-fatal myocardial infarction (n = 3, ABPM = 2 vs. CBPM = 1) and heart failure (n = 2, ABPM = 1 vs. CBPM = 1). Patients with WCH were included in both CBPM and ABPM groups.

<sup>b</sup>Conen et al, 2009 (27): Included acute coronary syndrome (ABPM = 1), arterial revascularization (CBPM = 1), and stroke or transient ischemic attack (n = 2, ABPM = 1 vs. CBPM = 1). Sustained hypertensives were included in both CBP and ABPM groups.

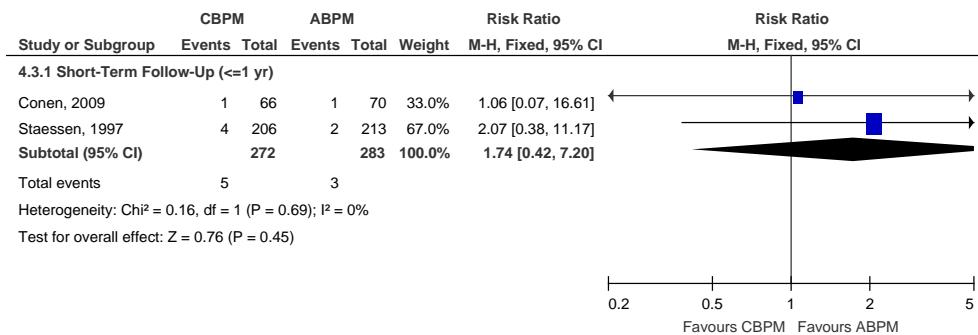
<sup>c</sup>Schrader et al, 2000 (30): Included myocardial infarction and stroke. Patients with WCH were excluded from the ABPM group.



**Figure 3: Fatal Cardiovascular Events, Mean of Five Years of Follow-Up, by Intervention Allocation<sup>a</sup>**

Abbreviations: ABPM, ambulatory blood pressure monitoring; CBPM, conventional blood pressure monitoring; CI, confidence interval; M-H, Mantel-Haenszel; WCH, white coat hypertension.

<sup>a</sup>Fatal cardiovascular events defined as fatal myocardial infarction and stroke. Patients with WCH were excluded from the ABPM group.

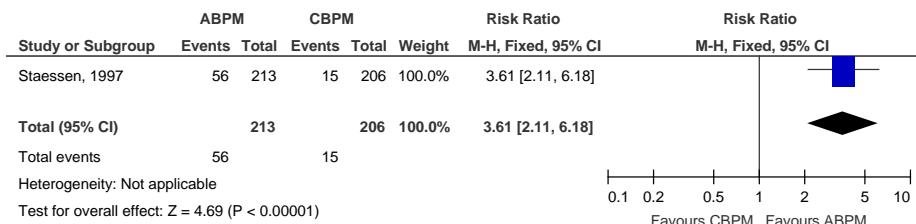


**Figure 4: Non-Cardiovascular Disease Events, by Intervention Allocation<sup>a,b</sup>**

Abbreviations: ABPM, ambulatory blood pressure monitoring; CBPM, conventional blood pressure monitoring; CI, confidence interval; M-H, Mantel-Haenszel; WCH, white coat hypertension.

<sup>a</sup>Conen et al, 2009 (27): Non-cardiac chest pain (n = 2, ABPM = 1 vs. CBPM = 1); sustained hypertensives in both the CBPM and ABPM groups.

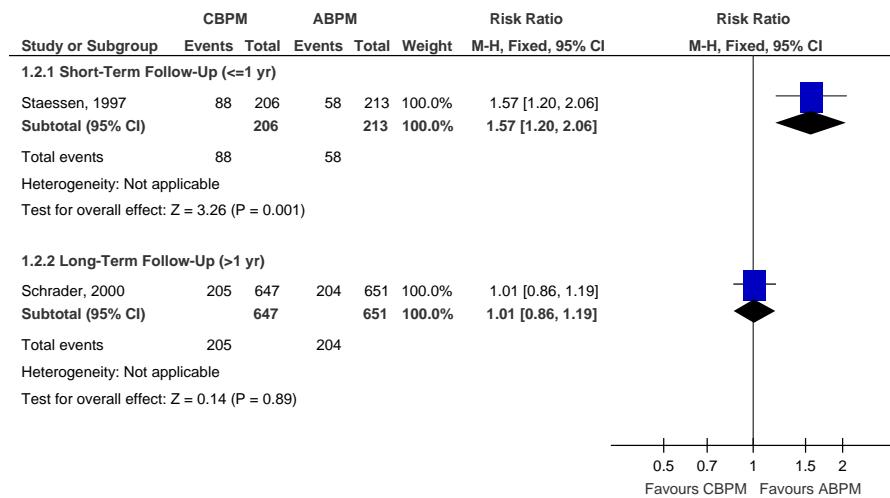
<sup>b</sup>Staessen et al, 1997 (31): Non-cardiovascular surgery (n = 6; ABPM = 2 vs. CBPM = 4). Patients with WCH were included in both the CBPM and ABPM groups.



**Figure 5: Number of Patients Who Stopped Antihypertensive Therapy (Six Months of Follow-Up), by Intervention Allocation<sup>a</sup>**

Abbreviations: ABPM, ambulatory blood pressure monitoring; CBPM, conventional blood pressure monitoring; CI, confidence interval; DBP, diastolic blood pressure; M-H, Mantel-Haenszel; WCH, white coat hypertension.

<sup>a</sup>Defined as the discontinuation of drug treatment at 1, 2, or 4 months until the end of the study (6 months) because DBP in either group was less than 80 mm Hg and remained at or below the specified target level of 80 to 89 mm Hg. Patients with WCH were included in both the CBPM and ABPM groups.

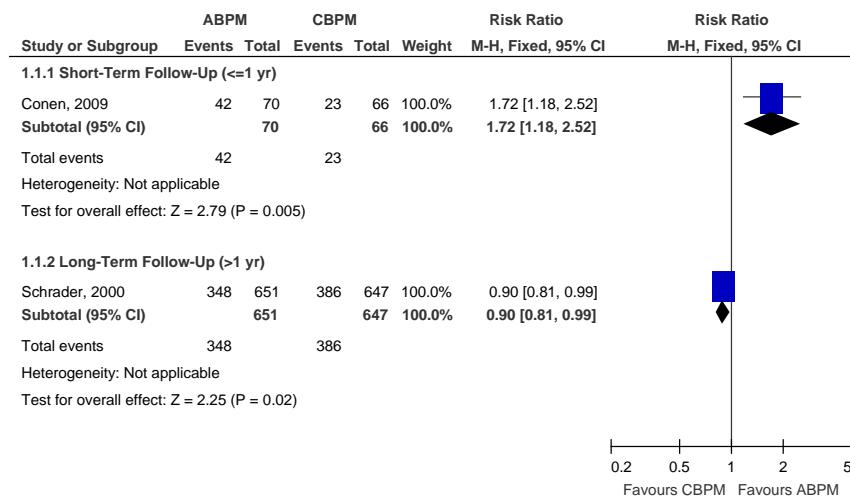


**Figure 6: Number of Patients Who Began Sustained Multi-Drug Therapy (Two or More Drugs), by Intervention Allocation<sup>a,b</sup>**

Abbreviations: ABPM, ambulatory blood pressure monitoring; CBPM, conventional blood pressure monitoring; CI, confidence interval; M-H, Mantel-Haenszel; WCH, white coat hypertension.

<sup>a</sup>Staessen et al, 1997 (31): Patients with WCH were included in both the CBPM and ABPM groups.

<sup>b</sup>Schrader et al, 2000 (30): Patients with WCH were excluded from the ABPM group.

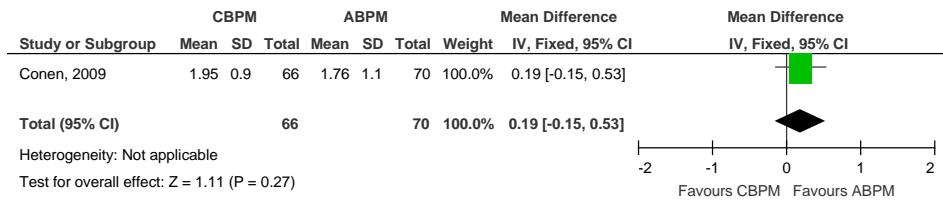


**Figure 7: Number of Patients With Controlled Blood Pressure, by Intervention Allocation<sup>a,b</sup>**

Abbreviations: ABPM, ambulatory blood pressure monitoring; ADBP, diastolic blood pressure measured by an ambulatory device; ASBP, systolic blood pressure measured by an ambulatory device; BP, blood pressure; CBPM, conventional blood pressure monitoring; CDBP, conventionally measured diastolic blood pressure; CI, confidence interval; CSBP, conventionally measured systolic blood pressure; M-H, Mantel-Haenszel; WCH, white coat hypertension.

<sup>a</sup>Conen et al, 2009 (27): Controlled BP was defined as CSBP less than 140 mm Hg and CDBP less than 90 mm Hg and for 24-hour ASBP less than 130 mm Hg and ADBP less than 80 mm Hg. (Sustained hypertensives were included in both the CBPM and ABPM groups.)

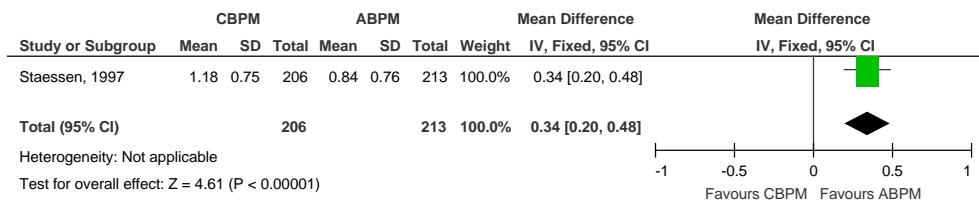
<sup>b</sup>Schrader et al, 2000 (30): Based on treatment management as above target level of CSBP greater than 140 mm Hg and/or CDBP greater than 90 mm Hg and for 24-hour ASBP greater than 130 mm Hg and/or ADBP greater than 80 mm Hg or average daytime ASBP greater than 135 mm Hg and/or ADBP greater than 85 mm Hg. Patients with WCH were excluded from the ABPM group.



**Figure 8: Mean Number of Drugs Used at One Year Follow-Up, by Intervention Allocation<sup>a</sup>**

Abbreviations: ABPM, ambulatory blood pressure monitoring; CBPM, conventional blood pressure monitoring; CI, confidence interval; IV, inverse variance; SD, standard deviation.

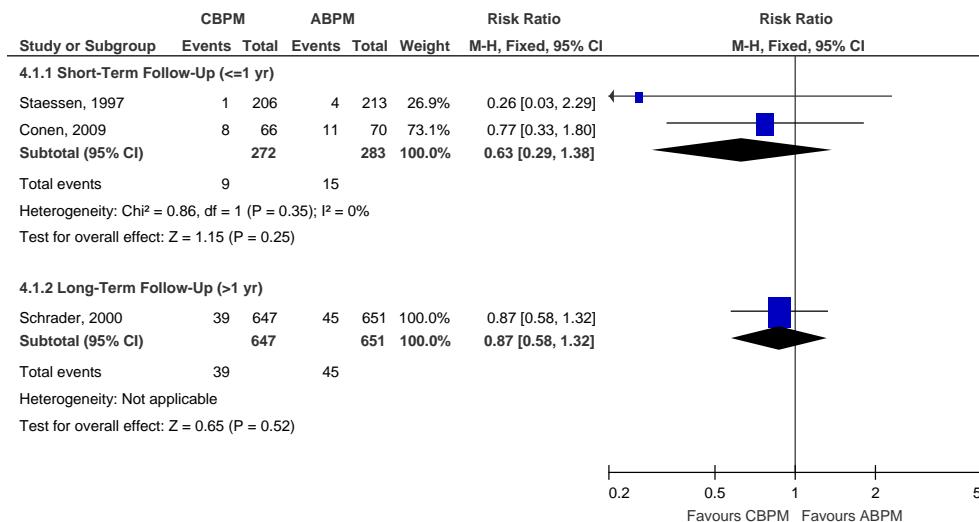
<sup>a</sup>Sustained hypertensives were included in both the CBPM and ABPM groups.



**Figure 9: Mean Drug Intensity at Six Months' Follow-Up, by Intervention Allocation<sup>a</sup>**

Abbreviations: ABPM, ambulatory blood pressure monitoring; CBPM, conventional blood pressure monitoring; CI, confidence interval; IV, inverse variance; SD, standard deviation; WCH, white coat hypertension.

<sup>a</sup>Patients with WCH were included in both the CBPM and ABPM groups.



**Figure 10: Drug-Related Adverse Events, by Intervention Allocation<sup>a,b,c</sup>**

Abbreviations: ABPM, ambulatory blood pressure monitoring; CBP, conventionally measured blood pressure; CBPM, conventional blood pressure monitoring; CI, confidence interval; M-H, Mantel-Haenszel; WCH, white coat hypertension.

<sup>a</sup>Conen et al, 2009 (27): Drug-related adverse events included dizziness (n = 13, ABPM = 8 vs. CBP = 5), erectile dysfunction (n = 4, ABPM = 1 vs. CBP = 3), and headache (ABPM = 2). Sustained hypertensives were included in both the CBPM and ABPM arms.

<sup>b</sup>Staessen et al, 1997 (31): Drug-related adverse events included depression (n = 3, ABPM = 2 vs. CBP = 1), rash (ABPM = 1), and peptic ulcerations (ABPM = 1). Patients with WCH were included in both the CBPM and ABPM groups.

<sup>c</sup>Schrader et al, 2000 (30): Drug-related adverse events included cough and allergic reaction. Patients with WCH were excluded from the ABPM group.

### ***Short-term***

The results of the analysis showed there was a *short-term* beneficial effect of managing hypertension by ABPM; patients were more likely to stop their antihypertensive therapy (RR, 3.61; 95% CI, 2.11–6.18), more likely to have control of BP (RR, 1.72; 95% CI, 1.18–2.52), and more likely to require less intensive drug therapy (MD, 0.34; 95% CI, 0.20–0.48), compared with patients being managed by CBPM.

Patients whose hypertension was managed by CBPM were more likely to progress to sustained multi-drug therapy compared with patients managed by ABPM (RR, 1.57; 95% CI, 1.20–2.06). No difference between technologies was found for the number of drugs used (MD, 0.19; 95% CI, –0.15 to 0.53), non-fatal cardiovascular events (RR, 0.84; 95% CI, 0.23–3.07), non-CVD events (RR, 1.74; 95% CI, 0.42–7.20), or drug-related adverse events (RR, 0.63; 95% CI, 0.29–1.38).

The results from this evidence-based analysis showed *short-term* beneficial effects of managing hypertension by ABPM compared with CBPM in the following aspects:

- being more likely to use fewer drugs,
- being more likely to stop using antihypertensive therapy,
- being more likely to have BP control, and
- being less likely to progress to sustained multi-drug therapy.

### ***Long-term***

In the *long-term*, the results showed beneficial effect on total combined cardiovascular events when hypertension was managed by ABPM compared with CBPM (RR, 1.76; 95% CI, 1.03–3.02). The results showed a beneficial effect of CBPM for control of BP compared to ABPM (RR, 0.90; 95% CI, 0.81–0.99). Although the upper confidence limit approaches 1.0, the *P* value is 0.02 due to an increased number of events and sample size. No difference was found between technologies for either fatal cardiovascular events (RR, 1.01; 95% CI, 0.33–3.10) or nonfatal cardiovascular events (RR, 2.26; 95% CI, 0.99–5.17); however, the CI is wide and approaches significance. No difference was found between technologies for either the number of hypertensive patients who begin sustained multi-drug therapy (RR, 1.01; 95% CI, 0.86–1.19) or the number of patients who experience drug-related adverse events (RR, 0.87; 95% CI, 0.58–1.32).

Compared with patients whose hypertension was managed by CBPM, patients whose hypertension was managed by ABPM were, in the *long term*, less likely to experience either a fatal or nonfatal cardiovascular event (Figure 1). There was also a trend showing a beneficial effect for nonfatal cardiovascular events (Figure 2). Overall, some of these results may be biased, as heterogeneous study populations were included. For some outcome measures, the results should be interpreted with caution.

## **Answering Research Question 2: Is There a Difference in Patient Outcome Between the Two Technologies When White Coat Hypertension is Taken Into Account?**

### ***Short-Term Studies (Length of Follow-Up of Less Than or Equal to One Year)***

The study populations differed for the 2 RCTs with short-term follow-up included in this evidence-based analysis. In the study by Conen et al, (27) hypertensive patients were randomized after all eligible patients were screened for WCH. Subsequently, only hypertensive patients who displayed sustained hypertension were randomized. No patients with WCH were included in the follow-up period. Ideally, to assess the effects of antihypertensive treatment on BP target levels, the study should include only those patients with hypertension confirmed by ABPM to minimize the inclusion of patients with WCH. (32) Although the result for control of BP in the short-term is based on 1 study, the result is not biased due to the inclusion of white coat hypertensives, and therefore ideally evaluates the effect of the different technologies. In addition, the use of an oscillometric device in Conen et al (27) for CBPM is less susceptible to error, (2;33) and is comparable to the ABPM device except for the timing and number of BP readings. Overall,

ABPM for the control of BP in the short-term is beneficial compared to CBPM. The GRADE quality of evidence for the outcome of control of BP in the short-term is shown in Appendix 2.

In the study by Staessen et al, (31), *short-term* beneficial effects were seen in ABPM patients regarding the following:

- less intense use of antihypertensive therapy,
- hypertensive patients being more likely to stop antihypertensive therapy, and
- hypertensive patients being less likely to proceed to sustained multi-drug therapy.

In this study, randomized patients were classified as having hypertension based on their DBP taken with conventional sphygmomanometry. Therefore, patients with WCH were included in both arms of the trial. The authors described that study subjects were selected to facilitate the extrapolation of results. However, a substantial proportion of individuals with WCH would have been treated erroneously in only 1 arm of the study. (Personal communication, clinical expert, October 4, 2011) (Note: once treated, the phenomenon of WCH is referred to as the white coat effect.) White coat hypertension patients who were randomized to the ABPM group would have had an attenuation of BP upon subsequent measurement with the ABPM device during follow-up. Also, in the CBPM group, the effects of treatment on target BP levels may not have been attributable to the drug itself, but may instead have been due to the attenuation of the white coat response with time. (34) Therefore, the inclusion of patients with WCH at baseline produced a heterogeneous study population consisting of individuals with hypertension and with WCH included in both arms of the trial.

Ambulatory blood pressure monitoring is shown to be beneficial in the short-term with regards to the use of antihypertensive therapy compared to CBPM; however, the inclusion of patients with WCH may have biased the results in favour of the ABPM technology. The GRADE quality of evidence for the outcomes of drug intensity, patients who stopped antihypertensive therapy, and patients who began sustained multi-drug therapy in the short-term is shown in Appendix 2.

The study by Conen et al (27) found no difference between the 2 technologies in the mean number of drugs used (only individuals with sustained hypertension were included in this study). In comparison, the study by Staessen et al (31) found that the ABPM group required less intense drug therapy compared to the CBPM group. This may have been due to the inclusion of individuals with WCH, which may have influenced the CBPM arm of the trial.

No difference between the 2 technologies was found for:

- non-fatal cardiovascular events (heterogeneous study populations, < 10 events per arm), and
- non-CVD events.

The GRADE quality of evidence for all outcomes with short-term follow-up is shown in Appendix 2.

In summary, the results from the short-term studies showed that:

- There is no difference between technologies for nonfatal cardiovascular events (very low quality of evidence).
- ABPM resulted in improved BP control among sustained hypertensives compared to CBPM (moderate quality of evidence).
- ABPM resulted in hypertensive patients being more likely to stop antihypertensive therapy and less likely to proceed to multi-drug therapy compared to CBPM (low quality of evidence).
- There is a beneficial effect of ABPM on the intensity of antihypertensive drug use compared to CBPM (low quality of evidence).
- There is no difference between technologies in the number of antihypertensive drugs used (moderate quality of evidence).

- There is no difference between technologies in the risk for a drug-related adverse event or non-cardiovascular event (low to very low quality of evidence).

### ***Long-Term Study (Mean Length of Follow-Up of Five Years)***

The long-term beneficial effects of ABPM were derived from 1 study that followed hypertensive patients for an average of 5 years. In this study by Schrader et al, (30) the study population consisted of individuals who were classified as hypertensive based on CBPM at the onset of the study; however, the hypertensive patients who were randomized to the ABPM group were further evaluated for WCH. Hypertensive patients displaying WCH were then excluded from the ABPM group. Therefore, individuals with sustained hypertension were remaining in the ABPM group during the follow-up period. Consequently, a substantial proportion of individuals with WCH would have remained and been treated erroneously in only 1 arm of the study. (Personal communication, clinical expert, October 4, 2011)

Patients with WCH are unaffected by antihypertensive treatment, with antihypertensive treatment lowering their CBP but not their ABPM measurement. (35) On the other hand, patients with sustained hypertension in the ambulatory group comprise a high-risk population. The heterogeneous population in the CBPM group coupled with 2 cutpoints to adjust treatment in the ABPM group may have caused differential treatment within and between groups. The inclusion of white coat hypertensives in the CBPM arm of the trial may have produced results that are more conservative than if those white coat hypertensives had been replaced with individuals with hypertension. Overall, the results suggest a beneficial effect of ABPM on total combined cardiovascular events. The borderline lack of a beneficial effect for nonfatal cardiovascular events may have been due to the small number of events (< 10 events) in the ambulatory group. The lack of a beneficial effect for fatal cardiovascular events may have been due to a small number of events in both arms. The GRADE quality of evidence for long-term follow-up and cardiovascular outcomes is shown in Appendix 2.

One study outcome showed CBPM to be the more favourable technology. A beneficial effect of CBPM was shown for control of BP in the long-term. In this study by Schrader et al, (30) the study population consisted of individuals with sustained hypertension in the ABPM group and a heterogeneous study population including individuals with WCH in the CBPM group. Control of BP was examined based on the intervention allocated, since treating patients with WCH on the basis of conventional sphygmomanometry lowers the clinic BP but not the daytime ABPM. (36) However, erroneously treating a substantial proportion of individuals with WCH in only 1 arm of the study may bias the results in favour of the CBPM group. (Personal communication, clinical expert, October 4, 2011) Overall, there was a beneficial effect of CBPM on control of BP in the long-term compared to ABPM. The GRADE quality of evidence for long-term follow-up and control of BP is shown in Appendix 2. The GRADE quality of evidence for all outcomes with long-term follow-up is shown in Appendix 2.

No difference was found between the technologies for drug-related adverse events in either the short- or long-term. The reported adverse effects are consistent with the known potential side effects of antihypertensive drugs. (Personal communication, clinical expert, October 12, 2011)

In summary, the results from the long-term follow-up study showed that:

- There is a beneficial effect of ABPM on total combined cardiovascular events compared to CBPM (moderate quality of evidence).
- There is a lack of a beneficial effect of ABPM on nonfatal cardiovascular events compared to CBPM; however, the lack of a beneficial effect is based on a borderline result (low quality of evidence).
- There is no beneficial effect of ABPM on fatal cardiovascular events compared to CBPM (low quality of evidence).

- There is no difference between technologies for the number of patients who began multi-drug therapy compared to CBPM (low quality of evidence).
- There is a beneficial effect of CBPM on control of BP compared to ABPM (low quality of evidence). This result is in the opposite direction than expected.
- There is no difference between technologies in the risk for a drug-related adverse event (moderate quality of evidence).

In conclusion, there is a beneficial effect of ABPM in that there is a favourable prognosis for CVD in the long-term, improved BP control in the short-term, no difference in the average number of antihypertensive drugs used in the short-term, and there is no indication of an increased frequency of adverse events in either the short- or long-term. The beneficial effect of ABPM with respect to stopping antihypertensive drug use needs to be interpreted with caution as these results were based on a heterogeneous study population. Consistent information across studies for patient and drug-related outcomes would have provided a clearer picture of the effect of WCH on outcomes for the comparison of interest. Automatic BP monitoring as used in the ABPM group does not induce an alarm reaction or a rise in BP and does not overestimate daytime BP values. (13) The concern for masked hypertension is not relevant for this evidence-based analysis since the screening criteria for all included studies was hypertension based on CBPM. Information on long-term follow-up is needed for use of antihypertensive drug therapy.

# Economic Analysis

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**DISCLAIMER:** Health Quality Ontario uses a standardized costing method for its economic analyses of interventions. The main cost categories and the associated methods from the province's perspective are as follows:

**Hospital:** Ontario Case Costing Initiative cost data are used for in-hospital stay, emergency visit and day procedure costs for the designated International Classification of Diseases (ICD) diagnosis codes and Canadian Classification of Health Interventions procedure codes. Adjustments may be required to reflect accuracy in estimated costs of the diagnoses and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis or procedure, the secretariat normally defaults to considering direct treatment costs only.

**Nonhospital:** These include physician services costs obtained from the Ontario Schedule of Benefits, laboratory fees from the Ontario Schedule of Laboratory Fees, drug costs from the Ontario Drug Benefit Formulary, and device costs from the perspective of local health care institutions whenever possible or its manufacturer.

**Discounting:** For cost-effectiveness analyses, a discount rate of 5% is applied as recommended by economic guidelines.

**Downstream costs:** All numbers reported are based on assumptions on population trends (i.e., incidence, prevalence, and mortality rates), time horizon, resource utilization, patient compliance, health care patterns, market trends (i.e., rates of intervention uptake or trends in current programs in place in the Province), and estimates on funding and prices. These may or may not be realized by the system or individual institutions and are often based on evidence from the medical literature, standard listing references, and educated hypotheses from expert panels. In cases where a deviation from this standard is used, an explanation is offered as to the reasons, the assumptions, and the revised approach. The economic analysis represents *an estimate only*, based on the assumptions and costing methods that have been explicitly stated above. These estimates will change if different assumptions and costing methods are applied to the analysis.

## Purpose

The Toronto Health Economics and Technology Assessment (THETA) Collaborative was commissioned by Health Quality Ontario (HQO) to predict the long-term costs and effects along with the cost-effectiveness of strategies for the management and treatment of hypertension. The results of the economic analyses of the following strategies are presented: 24-hour ABPM and CBPM of hypertension. Additionally, this report reviews published economic evaluations of 24-hour ABPM and presents estimates of the budget impact of implementing the intervention for the following populations: WCH patients and any patient suspected of having hypertension.

Health Quality Ontario conducts full evidence-based analyses of health technologies being considered for use in Ontario. These analyses are then presented to the Ontario Health Technology Advisory Committee (OHTAC), whose mandate is to provide evidence-based examination of proposed health technologies in the context of existing clinical practice and provide advice and recommendations to Ontario practitioners, the broader health care system, and the Ministry of Health and Long-Term Care.

## Background

Hypertension occurs when either SBP, the pressure in the artery when the heart contracts, or DBP, the pressure in the artery when the heart relaxes between beats, are consistently high. Blood pressure that is consistently more than 140/90 mmHg (systolic/diastolic) is considered high. A lower threshold, greater than 130/80 mmHg (systolic/diastolic), is set for individuals with diabetes or chronic kidney disease.

In 2006 and 2007, the age-standardized incidence rate of diagnosed hypertension in Canada was 25.8 per 1,000 (450,000 individuals were newly diagnosed). During the same time period, 22.7% of adult Canadians were living with diagnosed hypertension.

A smaller proportion of Canadians are unaware they have hypertension; therefore, the estimated number of Canadians affected by this disease may be higher. Diagnosis and management of hypertension are important, since elevated BP levels are related to the risk of CVD, including stroke. In Canada in 2003, the costs to the health care system related to the diagnosis, treatment, and management of hypertension were over \$2.3 billion (Cdn).

## Objective

The objective of this economic analysis was to perform a cost-effectiveness analysis (CEA) and report costs associated with providing 24-hour ABPM to patients suspected of having hypertension, and for ongoing monitoring of BP in Ontario.

## Economic Literature Review

A literature search was performed on August 4<sup>th</sup>, 2011 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, CINAHL, and Centre for Reviews and Dissemination/International Agency for Health Technology Assessment for studies published from 1948 to July week 4, 2011 for MEDLINE; and from 1980 to July week 31, 2011 for EMBASE. Included studies were those with full economic evaluations describing both costs and consequences of 24-hour ABPM for hypertension and BP monitoring; the same set of search keywords was used as for the clinical effectiveness systematic review in this report.

Several economic analyses have been performed related to home blood pressure monitoring (HBPM); however, 24-hour ABPM was not used as a comparator in these studies. (37-40) The literature search found 2 cost analyses comparing 24-hour ABPM directly to CBPM (standard care) for hypertension diagnosis and treatment: Krakoff et al 2006 (41;42) and Lovibond et al 2011 (41;42); the latter also compared 24-hour ABPM to HBPM.

Krakoff et al calculated the cost savings for using 24-hour ABPM as a secondary diagnostic test, after an initially raised BP reading for patients. (41) The costs of diagnosis and treatment were considered together, and cost savings ranged from approximately \$85,000 (US) to \$153,000 (US) per 1,000 patients when compared to CBPM. The range in savings was based on the assumption of the percentage of WCH patients confirmed to be hypertensive: \$85,000 (US) per 1,000 patients would be saved if 20% of WCH patients were confirmed to be hypertensive; \$153,000 (US) per 1,000 patients would be saved if 5% of WCH patients were hypertensive.

Lovibond et al presented a CEA based on a Markov economic model comparing 3 strategies for the accurate diagnosis and treatment of hypertension: CBPM, HBPM, and (24-hour) ABPM. (42) The United Kingdom population of interest was aged 40 years or older with a screening blood pressure measurement greater than 140/90 mm Hg, with an average risk of CVD equivalent to that of the general population. Results of the study suggested ambulatory monitoring (i.e., HBPM or 24-hour ABPM) for hypertension after an initially raised CBPM reading would reduce the number of misdiagnoses and save costs. The incremental cost-effectiveness ratio (ICER) ranged from about £3,000 (GBP) to £26,000 (GBP) per quality-adjusted life year (QALY) for 24-hour ABPM compared to CBPM, based on the initial age of the patient. It was further shown that 24-hour ABPM dominated CBPM and HBPM by providing a greater increase in QALYs, but for lower costs for the average patient.

# **Primary Economic Evaluation**

The published economic evaluations identified in the literature review addressed the intervention of interest (i.e., 24-hour ABPM). However, none of these published studies took a Canadian perspective. Due to these limitations, a primary economic evaluation of 24-hour ABPM was conducted.

## **Interventions Evaluated**

As stated above, the intervention of interest is 24-hour ABPM. The primary evaluation will compare the 2 strategies of providing 24-hour ABPM or CBPM or “usual care” for hypertension. Twenty-four-hour ABPM was defined as the use of an ABPM measuring device for the diagnosis of hypertension, with a maximum of 3 diagnostic physician visits per year. Conventional blood pressure monitoring was defined as in-office measurement of BP for suspected hypertensive patients, with a maximum of 5 physician visits per year for the diagnosis of hypertension. Both strategies include subsequent, long-term consequences of developing the following CVDs: a) CHD (includes coronary death, MI, coronary insufficiency, angina); and b) cerebrovascular disease (referred to here as “stroke”, but includes ischemic stroke, hemorrhagic stroke, and transient ischemic events).

## **Target Population**

The target population of this economic analysis is patients suspected of having hypertension (i.e., management of hypertensive patients), which includes WCH patients, and aged 45 years or older with an average risk of CVD similar to the general population in Ontario.

## **Perspective**

The primary analytic perspective of the CEA is that of the Ontario Ministry of Health and Long-Term Care.

# **Economic Analysis Method**

The current economic analysis is a cost-effectiveness analysis of 24-hour ABPM versus CBPM using health-related quality of life (HRQOL) to calculate the ICER in Canadian dollars (Cdn) per QALY. More specifically, as the current CEA analyzes QALYs gained or lost by patients as the main measure of effect, the CEA is developed as a cost utility analysis.

## **Discounting and Time Horizon**

Costs and outcomes (QALYs) were discounted at a 5% annual rate as recommended by economic guidelines. (43) The economic model is based on an annual cycle and aggregates patient costs and outcomes over their lifetime.

## **Variability and Uncertainty**

Variability and uncertainty in the model were assessed using a probabilistic sensitivity analysis. Model parameter uncertainty was assessed by assigning distributions around the point estimate and results were presented in the form of probability of cost-effectiveness by ceiling ratio, i.e., willingness to pay values.

## **Generalizability**

The findings of this economic analysis cannot be generalized to all patients with hypertension. They may, however be used to guide decision making about the specific patient populations addressed in the trials investigated at HQO. Note that 2 scenarios are presented in the analysis which examine the option of

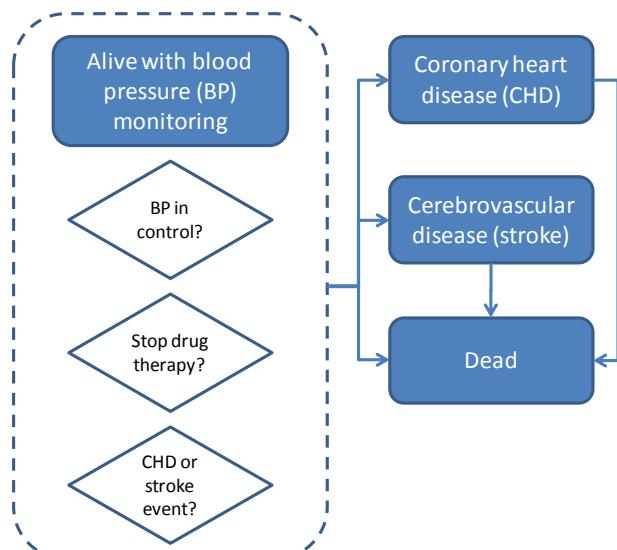
providing 24-hour ABPM to patients only with BP measurements that are raised or not in control, or providing 24-hour ABPM to all patients suspected of hypertension annually, but limited to 1 test per year per patient.

## Model Structure

The model used in the CEA is Markov simulation, a decision analytic. Figure 11 shows a schematic representation of the model with 4 health states:

- alive with BP monitoring;
- CHD;
- cerebrovascular disease (stroke); and
- dead.

The arrows indicate possible transitions between the 4 health states and the 3 decision-tree diamonds represent events which transition patients from health state 1 to the remaining 3 health states. The parameters informing the transition probabilities are taken from the current HQO clinical effectiveness review and are summarized in Table 2. Transitions from health state 1 to “dead” were informed by Ontario-specific life tables pooled from 2005 to 2007 as derived by Canadian Human Mortality Database and published by Statistics Canada. (44)



**Figure 11: Schematic Diagram of the Decision-Analytic Markov Model Evaluating Twenty-Four-Hour ABPM**

## Model Input Parameters

A number of different model input parameters were used to populate the model. These include variables used to model the natural history of the disease and variables used to modify the natural history model to account for the treatment effects and costs of 24-hour ABPM and CBPM.

### Natural History Model Input Parameters

The main outcomes considered in this CEA were taken from the current HQO clinical effectiveness review and consist of the following as summarized in Table 2: control of BP, drug-related outcomes (i.e., patients who stopped anti-hypertensive drug therapy, change in drug intensity/dosage), and CVD-related

outcomes (i.e., patients having any fatal or non-fatal CVD event including MI or stroke). In order to simplify the analysis, MI and stroke events were chosen as representative of CHD and cerebrovascular events, respectively (i.e., only MI and stroke risk and health states were modelled). The 3 main RCTs identified in the review were used to estimate the relative risk of CHD- or cerebrovascular disease-related events for 24-hour ABPM. (27;30;31) However, the relative risks in the RCTs were estimated specifically for the MI or stroke population; it is an assumption in the current CEA that the relative risk parameters for MI or stroke are representative of those for CHD and cerebrovascular disease, in general.

The 10-year risk of CVD, CHD, or stroke listed in Table 2 were taken from de Oliveira et al and derived from an Ontario-based study examining the effect of the Heart and Stroke Foundation of Ontario's (HSFO's) Hypertension Management Initiative (HMI) on the management of hypertension in primary care physician offices. (45) The 10-year risk was calculated specifically from the Framingham risk score according to the framework of d'Agostino et al (46) and used risk-factor values from the Ontario population assigned to "standard care" (CBPM) in the study by de Oliveira et al. (45) The 10-year risk of CVD shown in Table 2 is the average risk for the population of interest, whereas the actual 10-year risk values used in the economic model were age-specific (5-year age groups), but with average (population) values used for the other risk factors (i.e., BP of 134.4 mmHg, total cholesterol of 4.26 mmol/L, high-density lipoprotein cholesterol of 1.42 mmol/L, and the proportion of diabetics and smokers being 21.6% and 9.1%, respectively).

**Table 2: Epidemiologic Parameters Used in the Cost-Effectiveness Analysis**

Description	Average	CI Lower	CI Upper	Reference
<i>10-Year Cardiovascular Disease Risk (CBPM)</i>				
Mean 10-year risk of CVD	0.107	0.102	0.112	de Oliveira et al (2011) (45)
Mean 10-year risk of CHD	0.072	0.069	0.075	de Oliveira et al (2011) (45)
Mean 10-year risk of stroke	0.020	0.020	0.021	de Oliveira et al (2011) (45)
<i>Relative Risk Estimates (24-Hour ABPM vs. CBPM)</i>				
Having any CVD event (i.e., combined MI or stroke, and all other CVD deaths)	0.570	0.330	0.970	Schrader et al (2000) (30)
Death from CVD event (MI or stroke)	0.990	0.320	3.070	Schrader et al (2000) (30)
Having non-fatal CVD event (MI or stroke)	0.440	0.190	1.010	Schrader et al (2000) (30)
Control of BP (i.e., reached target levels by allocation intervention)	1.720	1.180	2.520	Conen et al (2009) (27)
Stopped antihypertensive drug therapy	3.610	2.110	6.180	Staessen et al (1997) (31)
<i>Mean Difference Estimates (24-Hour ABPM vs. CBPM)</i>				
Drug intensity score	-0.340	-0.480	-0.200	Staessen et al (1997) (31)
Change in mean drug Intensity score from baseline (24-hour ABPM)	-0.310	-0.480	-0.200	Calculated
<i>Disease-Specific Mortality (per 100,000)</i>				
Hypertensive heart disease (I11)	2.1			Statistics Canada (2008) (47)
Ischemic heart diseases (I20-I25)	110.0			Statistics Canada (2008) (47)
Cerebrovascular diseases (I60-I69)	40.1			Statistics Canada (2008) (47)
<i>Proportion of CHD, Stroke Events</i>				
Proportion of CHD among all CVD events	60.86%			d'Agostino et al (2008) (46)
Proportion of stroke among all CVD events	23.85%			d'Agostino et al (2008) (46)

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CBPM; conventional blood pressure monitoring; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; MI, myocardial infarction.

Note: The Statistics Canada disease-specific mortality rates are based on codes from the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada (ICD-10-CA).

## Clinical Model Input Parameters

Table 3 summarizes the HRQOL utilities used for the current CEA, based on estimates derived from the CEA performed by NICE (26) and Lovibond et al (42), with references to Kind et al (48), Meslop et al (49), Tengs et al (50), and Goodacre et al (51). An average utility was used for health states 2 (i.e., CHD) and 3 (i.e., stroke), and was calculated as the mean of MI and other CHD utility values, and the mean of stroke and population norm utility values, respectively. The utility associated with health state 1 (i.e., alive with BP monitoring) was assigned to be the same as the general population norm. Also note that the utility values listed in Table 3 represent patient population preferences in the United Kingdom and United States, which are unlikely to be significantly different from the preferences of the general population in Ontario.

**Table 3: Health-Related Quality of Life and Utilities Used in the Cost-Effectiveness Analysis**

Utilities	Value	References
<i>Coronary Heart Disease (CHD)</i>		
Myocardial infarction	0.760	NICE (2011); Goodacre et al (2004) (26;51)
Unstable angina	0.770	NICE (2011); Goodacre et al (2004) (26;51)
Stable angina	0.808	NICE (2011); Meslop et al (2003) (26;49)
<i>Average utility (averaged over the above CHD health states)</i>	0.779	<i>Calculated</i>
<i>Cerebrovascular Disease ("Stroke")</i>		
Stroke	0.629	Tengs et al (2003) (50)
Transient ischemic attack (TIA) (same as population norm)	See below	NICE (2011); Kind (1998) (26;48)
<i>Average utility (averaged over stroke and population norms)</i>	See below	<i>Calculated</i>
<i>General Population Utilities (Population Norm)</i>		
Age 45–54	0.869	NICE (2011) (26)
Age 55–64	0.826	NICE (2011) (26)
Age 65–74	0.784	NICE (2011) (26)
Age 75–84	0.741	NICE (2011) (26)
Age 85–94	0.699	NICE (2011) (26)
Age 95+	0.656	NICE (2011) (26)

The cost of the 2 strategies compared for the CEA (i.e., 24-hour ABPM vs. CBPM) include physician, hospital, ambulatory monitoring device, and drug costs that are consistent with the Ministry perspective taken in the economic analysis. The costs are summarized in the tables below.

Table 4 shows the annual physician costs anticipated for 24-hour ABPM and CBPM through consultations with clinical experts. Approximately 5 visits to the physician office over 6 months are often necessary for the initial, accurate diagnosis of hypertension for suspected patients using standard CBPM. The effect of using 24-Hour ABPM for the diagnosis of hypertension would reduce the number of in-office physician visits required in the first year by about 2 visits (i.e., about 3 visits would be required for 24-hour ABPM). As shown in Table 4, the difference in cost was calculated to be approximately \$51.80 (Cdn) less than CBPM on average per patient for the first year of diagnosis. The physician assessment fee codes were taken from the Ontario Schedule of Benefits for Physician Services and the fee code for the interpretation of the 24-hour ABPM test was taken from the Saskatchewan Payment Schedule for Insured Services Provided by Physicians. (52;53)

**Table 4: First-Year Costs of Physician Assessments for Hypertension for CBPM and Twenty-Four-Hour ABPM**

Description	Fee code	Amount (Cdn)
<b>CBPM</b>		
5 visits over 6 months (initial + follow-up)	A005 Consultation (1 initial consultation) A007 Intermediate assessment (4 follow-up visits)	\$77.20 \$138.80
	<i>Total cost per patient</i>	<i>\$216.00</i>
<b>24-Hour ABPM</b>		
3 visits over 6 months (initial + ABPM + follow-up)	A005 Consultation (1 initial consultation) A007 Intermediate assessment (2 follow-up visits) 145D professional component only—1 per patient per year (ABPM interpretation)	\$77.20 \$69.40 \$24.90
	<i>Total cost per patient</i>	<i>\$171.50</i>

Abbreviations: ABPM, ambulatory blood pressure monitoring; CBPM; conventional blood pressure monitoring.

Through consultations with device manufacturers, the associated costs of providing 24-hour ABPM to patients for diagnosing and monitoring hypertension were determined and are summarized in Table 5. The device costs include the actual cost of the device, analysis software, reusable cuffs and covers, and an annual maintenance contract to service the devices as necessary. Table 5 shows device costs for 50 devices; the distributed cost is approximately \$2,557 (Cdn) per individual device. Clinical experts suggested that two 24-hour ABPM devices could be used to diagnose or monitor patients by providing between 1.5 to 3.5 tests per week over 50 weeks per year, depending on whether the clinic would service a “low” or “high” number (volume) of patients, respectively. As a result, the average cost per test is estimated to range from about \$68 to \$29 (Cdn) (i.e., approximately \$5,114 (Cdn) for 2 devices distributed over 75 to 175 tests per year).

**Table 5: Annual Device Costs per Patient for Twenty-Four-Hour ABPM**

Cost per Device	Amount (Cdn) (50 Devices)	Total Cost per Device (Cdn)
ABPM devices (includes reusable cuffs, covers, software)	\$121,270.00	\$2,425.40
Maintenance (yearly contract)	\$6,570.00	\$131.40
<i>Total cost per device</i>	<i>\$127,840.00</i>	<i>\$2,556.80</i>
Cost per Patient per Year	Number of Tests (or Patients) per Year	Device Cost per Test (or Patient)
Low test volume (2 devices, 1.5 tests per week x 50 weeks)	75	\$68.18
Medium test volume (2 devices, 2.5 tests per week x 50 weeks)	125	\$40.91
High test volume (2 devices, 3.5 tests per week x 50 weeks)	175	\$29.22

Abbreviation: ABPM, ambulatory blood pressure monitoring.

The costs associated with ongoing monitoring of BP and treatment of hypertension for CBPM and 24-hour ABPM are shown in Table 6. Physician, hospital, and drug costs were obtained from the study by de Oliveira et al (45) and based on 30-patient-day costs calculated according to the “phase of care” method. Briefly, in this approach, the total costs per patient are divided into distinct phases over time as characterized by different patterns of resource use, which produce time-dependent cost estimates. In the case of hypertension, “stable” and “pre-death” cost phases were used corresponding to a period of relatively constant costs before death and another period of high costs just prior to death, respectively. In the current Markov model, the average costs associated with the “stable” period are accrued annually,

with the costs of “pre-death” added to the annual costs in the year of death of the patient. The “initial” period for physician costs represent the costs of diagnosis of hypertension in the first year and are added only once for each patient; the “BP reassessment” cost phase is applicable for physicians reassessing patients when BP readings are raised or out of control (necessitating a possible change in drug intensity or regimen); the “stable” phase costs include other costs of patient care associated with hypertension and are accrued annually. A common stable phase cost of \$223 (Cdn) was included in the analysis for other patient care costs not specific to BP monitoring, with a corresponding common pre-death cost of \$3,352 (Cdn) for care not specific to BP monitoring. The costs associated with 24-hour ABPM listed in Table 6 were taken from costs observed for the HSFO’s HMI program in Ontario. Whereas this is a limitation in cost estimation, the costs of hypertension management (i.e., monitoring and treatment) using 24-hour ABPM are considered to be comparable to those of the HMI program. The cost of the CBPM device was omitted, as regular CBPM equipment is already paid for by the clinic and is not part of the Ministry analytic perspective.

**Table 6: Annual Physician, Hospital, Device, and Drug Costs Associated With CBPM and Twenty-Four-Hour ABPM**

Type of Cost	Cost Phase	CBPM (Cdn)	24-Hour ABPM (Cdn)
<i>Hypertension (BP Monitoring)</i>			
Physician costs	Initial BP assessment	\$230.60	\$178.80
	BP reassessment	\$69.40	\$34.70
	Stable (regular care)	\$3.38	\$3.00
Device costs	Stable	N/A	\$40.91
Drug costs	Stable	\$23.11	\$20.49
<i>Coronary Heart Disease (CHD)</i>			
Physician costs	Pre-death	\$177.74	\$158.01
	Stable	\$60.14	\$53.46
Hospital costs	Pre-death	\$956.63	\$850.44
	Stable	\$83.48	\$74.21
Drug costs	Pre-death	\$77.58	\$68.97
	Stable	\$34.22	\$30.42
<i>Cerebrovascular Disease (Stroke)</i>			
Physician costs	Pre-death	\$238.87	\$210.45
	Stable	\$21.07	\$18.57
Hospital costs	Pre-death	\$1,429.22	\$1,259.14
	Stable	\$29.25	\$25.77
Drug costs	Pre-death	\$99.49	\$87.65
	Stable	\$11.99	\$10.57

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CBPM, conventional blood pressure monitoring.

In order to approximate the associated increase or decrease in drug cost with changing drug intensity score, a cost “multiplier” was calculated and used in the simulation model to represent the average annual effect of a decrease in intensity score for 24-hour ABPM. Specifically, the average drug costs for CBPM and 24-hour ABPM were taken from the HMI study by de Oliveira et al (45) (i.e., \$23.11(Cdn) and \$20.49 (Cdn), respectively) and divided by the corresponding mean baseline intensity score as reported by Staessen et al (31). This multiplier was used to calculate new drug costs associated with changes in intensity score for a given treatment year.

The CEA results below are presented for 2 modelling assumptions related to the frequency of follow-up or continuing use of 24-hour ABPM devices for monitoring BP. The first scenario accrues the device costs (i.e., physician interpretation and test costs) only for patients observed to have a raised BP reading,

or who may require changes in drug intensity or regimen; the second scenario accrues 24-hour ABPM device costs annually for patients (i.e., maximum of 1 physician interpretation per year).

## Cost-effectiveness Analysis Results

The cost-effectiveness of providing 24-hour ABPM for the management of hypertension in Ontario is shown below in Table 7. It can be seen that 24-hour ABPM is very similar to CBPM when it is provided to patients only when a raised BP reading is observed or BP is not in control (i.e., drug dosage or regimen review required). Whereas the average lifetime costs of 24-hour ABPM are nearly identical to CBPM (i.e., cost difference of -\$4 Cdn), the intervention provides greater effect (i.e., +0.135 QALYs) compared to CBPM and is a cost-effective strategy. In the case of providing 24-hour ABPM for the management of all (suspected) hypertensive patients annually, the results suggest it is still cost-effective, with an ICER of \$4,160 (Cdn) per QALY (i.e., the ICER is well below the standard \$50,000 per QALY threshold).

**Table 7: Annual Physician, Hospital, Device, and Drug Costs Associated With CBPM and Twenty-Four-Hour ABPM**

Strategy	Mean Cost (Cdn)	Incremental Cost (Cdn)	Mean Effect	Increment Effect	ICER (Cost (Cdn) per QALY)
<b>24-Hour ABPM Device Costs Incurred Only When BP Raised or not in Control</b>					
CBPM	\$47,216		12.905 QALYs		
24-hour ABPM	\$47,220	\$4	13.040 QALYs	0.135 QALYs	\$30 / QALY
<b>24-Hour ABPM Device Costs Incurred Annually for BP Monitoring</b>					
CBPM	\$47,533		12.905 QALYs		
24-hour ABPM	\$48,095	\$561	13.040 QALYs	0.135 QALYs	\$4,160 / QALY

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CBPM, conventional blood pressure monitoring; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

A probabilistic sensitivity analysis was performed that allowed all clinical and cost parameters to vary according to specific probability distributions. Clinical and epidemiologic parameters found in Table 2 were varied according to their 95% CIs, with proportions modelled as being normally distributed and relative risk estimates modelled with log-normal distributions. The costs of providing 24-hour ABPM (i.e., costs listed under “Hypertension (BP Monitoring)” in Table 6 for the “24-Hour ABPM” scenario) were modified in the sensitivity analysis by increasing (decreasing) the listed cost by 50%; costs related to “Coronary Heart Disease (CHD)” or “Cerebrovascular Disease (Stroke)” were unmodified. In both scenarios considered above, the strategy of providing 24-hour ABPM to patients was cost-effective in approximately 97% of the randomly sampled parameter combinations at the standard \$50,000 per QALY threshold willingness-to-pay. More specifically, providing a 24-hour ABPM test annually to all patients, or providing the test only for the investigation of raised BP readings, resulted in marginally increased costs (or cost savings) for patients followed over a lifetime in Ontario in 97% of cases.

## Budget Impact Analysis – Ontario Perspective

A budget impact analysis of providing 24-hour ABPM to hypertension patients was calculated over the next 5 years (i.e., fiscal years FY2011–FY2016) to estimate the economic burden in Ontario. All costs are reported in current 2011 Canadian dollars. The projected Ontario population from 2011 to 2015 as developed by the Ontario Ministry of Finance was used in the current budget impact analysis for Ontario. (54) The projected population is presented in Table 8 together with the estimated hypertensive (high BP) cases expected to benefit from using 24-hour ABPM. The prevalence of high BP in Ontario was estimated as being 23.7% for the population aged 45 to 64 years, and 49.7% for the population aged 65 years or

older. (55) The incidence of diagnosed hypertension in Canada was used to estimate the number of cases in Ontario—approximately 2.21% of the population aged 20 years or older. (6)

**Table 8: Ontario Hypertensive Population Expected to Benefit From Twenty-Four-Hour ABPM**

Age Group	2011	2012	2013	2014	2015
<i>Ontario Population (Projected)</i>					
45–64	3,764,830	3,803,310	3,842,030	3,884,230	3,926,140
65 +	1,891,890	1,971,110	2,047,060	2,119,850	2,193,600
<i>Hypertensive (High BP)—Prevalence</i>					
45–64	892,265	901,384	910,561	920,563	930,495
65 +	940,269	979,642	1,017,389	1,053,565	1,090,219
<i>Hypertensive (High BP)—Incidence</i>					
45–64	83,203	84,053	84,909	85,841	86,768
65 +	41,811	43,562	45,240	46,849	48,479

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure.

The costs are presented below for 2 scenarios:

- provision of 24-hour ABPM for monitoring all (suspected) hypertensive patients annually, and
- provision of 24-hour ABPM for the monitoring of only patients with raised CBP readings annually.

The costs were taken from the current CEA and represent mean scenario cost differences between 24-hour ABPM and CBPM. Table 9 shows the budget impact of using 24-hour ABPM for the 2 age groups mentioned above (i.e., patients aged 45–64 years, and 65+ years). The costs for the prevalent hypertensive population are distributed across the first 3 years (i.e., 2011, 2012, 2013), with the incident population being the only new cases starting in the fourth year (i.e., 2014).

The first scenario, in which patients would receive 24-hour ABPM monitoring only for raised BP readings, was shown to save costs in the CEA. As a result, it is anticipated that approximately \$19 million (Cdn) could be saved annually (i.e., average annual savings) in Ontario using ABPM. The largest cost savings would be about \$34 million (Cdn) and \$8 million (Cdn) in physician and drug spending, respectively. However, for the second scenario, providing 24-hour ABPM to the hypertensive population annually, the increased cost is anticipated to be approximately \$37 million (Cdn) per year in Ontario. The increased cost is made up mostly of increased device (24-hour ABPM test) expenditures, which include the cost and maintenance of the device and a professional fee for the test's interpretation.

In order to estimate the budget impact of providing 24-hour ABPM to only WCH patients, the numbers shown in Table 10 are multiplied by the prevalence of WCH among hypertensive patients. According to Staessen et al, (31) approximately 20% to 35% (average 27.5%) of the hypertensive population can be considered to have WCH.

## Limitations

Twenty-four-hour ABPM was found to be cost-effective and potentially cost saving from the perspective of the Ontario Ministry of Health and Long-Term Care. However, several limitations exist in the current economic analysis:

- All cardiovascular health states were not represented in the Markov model, which may increase costs for certain diseases influenced by ongoing patient BP monitoring.

- Estimates of clinical effectiveness were mixed interchangeably, using 5-year and 6-month RCT data (i.e., used both short-term and long-term effects for model parameters affecting cost distributions).
- The cost of the 24-hour ABPM device (i.e., the cost of the device and maintenance only) was calculated as an Ontario Schedule of Benefits “technical fee” and assumes the device will be paid for within 1 year of its first use.
- The health state utilities may not be representative of Ontario and instead reflect specific preferences of hypertensive patients in the United Kingdom.
- CVD risk may not be representative of risks associated with hypertension in Ontario (i.e., applicability of the Framingham risk study and regression equations to Ontario).

**Table 9: Ontario Budget Impact (in Millions of Canadian Dollars) of Providing Twenty-Four-Hour ABPM Compared to CBPM**

Type of Cost	Age Group	2011	2012	2013	2014	2015	Annualized Average
<b>24-Hour ABPM Used Only When BP is Raised or Not Under Control</b>							
<b>Physician</b>	45–64	-\$7.9	-\$15.4	-\$22.5	-\$23.2	-\$23.9	-\$18.6
	65+	-\$7.0	-\$13.6	-\$19.6	-\$19.1	-\$18.6	-\$15.6
	All	-\$14.9	-\$28.9	-\$42.2	-\$42.3	-\$42.4	-\$34.2
<b>Hospital</b>	45–64	-\$0.1	-\$0.3	-\$0.6	-\$0.9	-\$1.2	-\$0.6
	65+	-\$0.3	-\$0.8	-\$1.5	-\$2.0	-\$2.5	-\$1.4
	All	-\$0.4	-\$1.1	-\$2.1	-\$2.9	-\$3.7	-\$2.0
<b>Drug</b>	45–64	-\$0.8	-\$1.5	-\$2.2	-\$2.3	-\$2.8	-\$1.9
	65+	-\$2.7	-\$5.2	-\$7.4	-\$7.1	-\$6.8	-\$5.8
	All	-\$3.4	-\$6.7	-\$9.6	-\$9.4	-\$9.6	-\$7.8
<b>Device</b>	45–64	\$5.8	\$11.3	\$16.5	\$16.9	\$17.2	\$13.6
	65+	\$5.1	\$9.8	\$14.0	\$13.4	\$12.8	\$11.0
	All	\$10.9	\$21.1	\$30.6	\$30.3	\$30.0	\$24.6
<b>Total</b>	45–64	-\$9.9	-\$19.4	-\$28.5	-\$28.7	-\$29.2	-\$23.2
	65+	-\$4.9	-\$9.7	-\$14.5	-\$14.9	-\$15.1	-\$11.8
	All	-\$7.8	-\$15.6	-\$23.4	-\$24.4	-\$25.8	-\$19.4
<b>24-Hour ABPM Used Annually</b>							
<b>Physician</b>	45–64	-\$3.7	-\$7.3	-\$10.7	-\$11.1	-\$11.4	-\$8.8
	65+	-\$3.4	-\$6.7	-\$9.8	-\$9.6	-\$9.5	-\$7.8
	All	-\$7.2	-\$14.0	-\$20.5	-\$20.7	-\$20.9	-\$16.7
<b>Hospital</b>	45–64	-\$0.1	-\$0.4	-\$0.7	-\$1.0	-\$1.3	-\$0.7
	65+	-\$0.3	-\$0.8	-\$1.5	-\$2.0	-\$2.5	-\$1.4
	All	-\$0.4	-\$1.1	-\$2.1	-\$3.0	-\$3.8	-\$2.1
<b>Drug</b>	45–64	-\$0.8	-\$1.5	-\$2.2	-\$2.3	-\$2.8	-\$1.9
	65+	-\$2.7	-\$5.2	-\$7.4	-\$7.1	-\$6.8	-\$5.8
	All	-\$3.4	-\$6.7	-\$9.6	-\$9.4	-\$9.6	-\$7.8
<b>Device</b>	45–64	\$14.7	\$28.7	\$41.8	\$42.8	\$43.8	\$34.4
	65+	\$13.3	\$25.5	\$36.7	\$35.1	\$33.6	\$28.9
	All	\$28.0	\$54.2	\$78.5	\$77.9	\$77.4	\$63.2
<b>Total</b>	45–64	\$6.7	\$12.8	\$18.5	\$18.8	\$18.8	\$15.1
	65+	\$6.9	\$12.9	\$18.0	\$16.3	\$14.8	\$13.8
	All	\$17.0	\$32.4	\$46.3	\$44.8	\$43.1	\$36.7

Abbreviations: ABPM, ambulatory blood pressure monitoring; CBPM, conventional blood pressure monitoring; BP, blood pressure.

# Conclusions

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Limitations of CBPM have led to the need for alternative ways to better manage hypertension. This evidence-based analysis examined whether there is a difference in patient outcome and treatment protocol when using ABPM compared to CBPM for uncomplicated hypertension. Data was abstracted and analyzed in a pooled analysis using Review Manager based on length of study follow-up. A Markov model determined the ICER and a budget impact analysis examined the effect on the Ontario health care system. The quality of evidence was assessed using the GRADE Working Group criteria. A systematic literature search of MEDLINE, EMBASE, CINAHL, Wiley Cochrane, and Centre for Reviews and Dissemination (1997–2011) identified 2,125 citations, where 3 RCTs were included. A 2-fold increased risk for CBPM was shown for total combined cardiovascular events (RR, 1.79; 95% CI, 1.03–3.02) over 5 years. Patients using ABPM were more likely to have control of blood pressure (RR, 1.72; 95% CI, 1.18–2.52) and to discontinue drug therapy (RR, 3.61; 95% CI, 2.11–6.18) in short-term studies. Ambulatory blood pressure monitoring would save the health system \$19 million (Cdn) over 5 years, with a borderline dominant effect (ICER: \$30 per QALY). The quality of evidence was heterogeneous.

# **Existing Guidelines for Twenty-Four-Hour Ambulatory Blood Pressure Monitoring**

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## **2010 Canadian Guidelines**

The 2010 Canadian Hypertension Education Program recommendations include the following: (33)

- The use of ABPM in the diagnosis of hypertension. However, this is based on grade C level of evidence. At follow-up, a 24-hour ASBP  $\geq$  130 mm Hg and ADBP  $\geq$  80 mm Hg, or daytime ASBP  $\geq$  135 mm Hg and ADBP  $\geq$  85 mm Hg is sufficient for a diagnosis of hypertension.
- ABPM should also be considered when an office-induced increase in BP is suspected in treated patients with BP that is not below target values despite receiving appropriate chronic antihypertensive therapy (grade C level of evidence).
- ABPM should also be considered when an office-induced increase in BP is suspected in treated patients with symptoms suggestive of hypotension (grade C level of evidence).
- ABPM should also be considered when an office-induced increase in BP is suspected in treated patients with variable CBPM readings (grade D level of evidence).
- Only validated devices with established protocols should be used (grade D level of evidence).
- Therapy should be adjusted based upon 24-hour ABPM of ASBP  $\geq$  130 mm Hg or ADBP  $\geq$  80 mm Hg, or daytime ASBP of  $\geq$  135 mm Hg or daytime ADBP  $\geq$  85 mm Hg (grade D level of evidence).
- Nocturnal ABPM should be taken into account in clinical decision-making regarding prescribing or withholding antihypertensive therapy (grade C level of evidence)

## **2011 United Kingdom National Institute for Health and Clinical Excellence**

The 2011 United Kingdom National Institute for Health and Clinical Excellence recommends the following: (26)

- For diagnosis of hypertension, if CBP is  $\geq$  140/90 mm Hg, ABPM can be offered to confirm the diagnosis of hypertension.
- In doing so, at least 2 measurements per hour should be taken during usual waking hours.
- Additionally, use the average value of at least 14 measurements taken during usual waking hours.
- For suspected WCH, ABPM can be considered as an adjunct to CBPM.
- Use an ambulatory device that is validated and with an appropriate cuff size.
- For monitoring of BP during antihypertensive therapy, target values include  $< 135/85$  mm Hg for those  $< 80$  years old and  $< 145/85$  for those  $\geq 80$  years old.

## **2011 Australian Consensus Position Statement**

The Ambulatory Blood Pressure Monitoring Working Group recommends the following: (56)

- CBPM remains useful for screening and management of suspected and true hypertension, however ABPM provides considerable added value for an accurate diagnosis of hypertension and the provision of optimal care for hypertension. Also, there are specific situations in which ABPM is useful, including the diagnosis and monitoring of WCH. [paraphrased]

# Glossary

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<b>Age-standardized incidence rate</b>	The number of individuals newly diagnosed among those at risk during a given time period that has accounted for the age structure of the population.
<b>Aneroid sphygmomanometers</b>	Non-automatic BP measuring device that uses a needle to determine BP readings.
<b>Auscultatory method</b>	The process of measuring BP by listening to sounds (otherwise referred to as the Korotkoff technique).
<b>Beta blocker</b>	Antihypertensive medication that helps the heart beat slower and with less force, causing a reduction in BP.
<b>Combination therapy</b>	Antihypertensive therapy that begins with a baseline drug, and adds additional drugs as needed. Includes a variety of drug classes and doses.
<b>Coronary heart disease</b>	A condition in which fat and cholesterol deposits build up in the coronary arteries resulting in potential adverse health outcomes. Also referred to as coronary artery disease.
<b>Dippers</b>	Persons in whom BP lowers by 10–20% during sleep.
<b>Diuretics</b>	Antihypertensive medication that helps to lower BP by reducing the amount of fluid in the body.
<b>Extreme dippers</b>	Persons in whom the difference between daytime BP and nighttime BP is more than 20%.
<b>First-line treatment</b>	The preferred treatment initially given to a patient.
<b>Hypertension</b>	SBP of $\geq 140$ mm Hg <b>or</b> DBP of $\geq 90$ mm Hg.
<b>Isolated diastolic hypertension</b>	DBP of $\geq 90$ mm Hg <b>and</b> SBP of $< 140$ mm Hg.
<b>Isolated systolic hypertension</b>	SBP of $\geq 140$ mm Hg <b>and</b> DBP of $< 90$ mm Hg.
<b>Masked hypertension</b>	Normal BP in the office and elevated BP outside of the medical setting.
<b>Mercury sphygmomanometer</b>	Non-automatic BP measuring device that uses a column of mercury to determine BP readings.
<b>Morning surge</b>	An excessive increase in morning BP upon waking.
<b>Nondipper</b>	A person who has a diminished nocturnal dip in BP.
<b>Normal hypertension</b>	SBP of $< 120$ mm Hg <b>and</b> DBP of $< 80$ mm Hg.
<b>Oscillometry method</b>	The process of measuring BP indirectly using an algorithm and determining the maximal pressure in the cuff during gradual deflation.
<b>Prehypertension</b>	SBP of 120–139 mm Hg <b>and</b> DBP of 80–89 mm Hg.

<b>Resistant hypertension</b>	Elevated BP as measured by both CBPM and ABPM.
<b>Reverse dipper</b>	A person whose BP elevates to above daytime levels during the night.
<b>Stage 1 hypertension</b>	SBP of 140–159 mm Hg <b>and</b> DBP of 90–99 mm Hg.
<b>Stage 2 hypertension</b>	SBP of $\geq$ 160 mm Hg <b>or</b> DBP of $\geq$ 100 mm Hg.
<b>Stepwise therapy</b>	Therapy that progresses through clearly determined steps with respect to drug class and dose.
<b>Sustained hypertension</b>	Hypertension displayed by both CBPM and ABPM.
<b>Vasodilator</b>	Antihypertensive medication that relaxes the muscles in blood vessel walls, therefore causing a reduction in BP.
<b>Washout period</b>	The time point during which all medication are ceased.
<b>White coat effect</b>	The difference between the CBPM and daytime ABPM, where CBPM is greater than daytime ABPM. The white coat effect is responsible for white coat hypertension.
<b>White coat hypertension</b>	BP that is persistently elevated in the presence of a health care worker, yet is not elevated when measured elsewhere (e.g., outside of the medical setting), in patients not taking antihypertensive medications. (Persistently elevated average CBPM $>$ 140/90 mm Hg and average daytime ABPM of $<$ 135/85 mm Hg.) This phenomenon occurs in approximately 15–20% of patients with Stage 1 hypertension.

# Acknowledgements

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# Appendices

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## Appendix 1: Literature Search Strategies

Search date: August 4, 2011

Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, CINAHL, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1948 to July Week 4 2011>, Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations <August 03, 2011>, Embase <1980 to 2011 Week 30>

Search Strategy:

- 
- 1 exp Blood Pressure Monitoring, Ambulatory/ use mesz (5674)
  - 2 exp ambulatory monitoring/ use emez (7196)
  - 3 exp blood pressure/ use emez (298523)
  - 4 exp blood pressure measurement/ use emez (45882)
  - 5 exp blood pressure monitoring/ use emez (17350)
  - 6 or/3-5 (324707)
  - 7 2 and 6 (3028)
  - 8 1 or 7 (8702)
  - 9 ((ambulatory or nocturnal or diurnal or portable or automated or continuous or "24" or 24-h or 24h or twenty-four) adj2 blood pressure).ti,ab. (18411)
  - 10 (abpm or abp).ti,ab. (8787)
  - 11 or/8-10 (26595)
  - 12 limit 11 to english language (22604)
  - 13 limit 12 to yr="1997 -Current" (15592)
  - 14 limit 13 to human (12796)
  - 15 limit 13 to humans (12796)
  - 16 14 or 15 (12796)
  - 17 limit 16 to (meta analysis or randomized controlled trial) (2043)
  - 18 exp Technology Assessment, Biomedical/ or exp Evidence-based Medicine/ use mesz (62280)
  - 19 exp Biomedical Technology Assessment/ or exp Evidence Based Medicine/ use emez (491662)
  - 20 (health technology adj2 assess\$).ti,ab. (2744)
  - 21 exp Random Allocation/ or exp Double-Blind Method/ or exp Control Groups/ or exp Placebos/ use mesz (194386)
  - 22 Randomized Controlled Trial/ or exp Randomization/ or exp RANDOM SAMPLE/ or Double Blind Procedure/ or exp Triple Blind Procedure/ or exp Control Group/ or exp PLACEBO/ use emez (869342)
  - 23 (random\* or RCT).ti,ab. (1202786)
  - 24 (placebo\* or sham\*).ti,ab. (401601)
  - 25 (control\* adj2 clinical trial\*).ti,ab. (33789)
  - 26 meta analysis/ use emez (54756)
  - 27 (meta analy\* or metaanaly\* or pooled analysis or (systematic\* adj2 review\*) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab. (235979)
  - 28 or/17-27 (2074229)
  - 29 16 and 28 (3075)
  - 30 remove duplicates from 29 (1935)

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CINAHL

#	Query	Results
S8	S4 and S7	329
S7	S5 or S6	147997
S6	random* or sham*or rct* or health technology N2 assess* or meta analy* or metaanaly* or pooled analysis or (systematic* N2 review*) or published studies or medline or embase or data synthesis or data extraction or cochrane or control* N2 clinical trial*	140059
S5	(MH "Random Assignment") or (MH "Random Sample+") or (MH "Meta Analysis") or (MH "Systematic Review") or (MH "Double-Blind Studies") or (MH "Single-Blind Studies") or (MH "Triple-Blind Studies") or (MH "Placebos") or (MH "Control (Research)")	79737
S4	(S1 or S2 or S3) Limiters - Published Date from: 19970101-20111231; English Language	1495
S3	abpm or abp	293
S2	ambulatory N2 blood pressure or nocturnal N2 blood pressure or diurnal N2 blood pressure or portable N2 blood pressure or automated N2 blood pressure or continuous blood N2 pressure or "24" N2 blood pressure or 24-h N2 blood pressure or 24h N2 blood pressure or twenty-four N2 blood pressure	1526
S1	(MH "Blood Pressure Monitoring, Ambulatory")	1021

## Appendix 2: GRADE Summary Tables

Table A1: GRADE Summary Table for Patient and Drug-Related Outcomes

Quality Assessment							No. of Patients		Effect		Quality
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other	ABPM or CBPM		Relative Risk (95% CI)	Absolute	
<b>BP Control—Short-Term Follow-Up (<math>\leq 1</math> Year) (Follow-Up 1 Year)</b>							<b>ABPM</b>	<b>CBPM</b>			
1 randomized trials	serious <sup>a</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none		42/70 (60%)	23/66 (34.8%)	RR 1.72 (1.18 to 2.52)	251 more per 1000 (from 63 more to 530 more)	⊕⊕⊕O MODERATE
								34.8%			
<b>BP Control—Long-Term Follow-Up (<math>&gt; 1</math> Year) (Follow-Up Mean 5 Years)</b>							<b>ABPM</b>	<b>CBPM</b>			
1 randomised trials	serious <sup>a</sup>	no serious inconsistency	serious <sup>c</sup>	no serious imprecision	none		348/651 (53.5%)	386/647 (59.7%)	RR 0.90 (0.81 to 0.99)	60 fewer per 1000 (from 6 fewer to 113 fewer)	⊕⊕OO LOW
								59.7%			
<b>Multi-Drug Therapy—Short-Term Follow-Up (<math>\leq 1</math> Year) (Follow-Up 6 Months)</b>							<b>CBPM</b>	<b>ABPM</b>			
1 randomized trials	very serious <sup>b,d</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none		88/206 (42.7%)	58/213 (27.2%)	RR 1.57 (1.20 to 2.06)	155 more per 1000 (from 54 more to 289 more)	⊕⊕OO LOW
								27.2%			
<b>Multi-Drug Therapy—Long-Term Follow-Up (<math>&gt; 1</math> Year) (Mean Follow-Up 5 Years)</b>							<b>CBPM</b>	<b>ABPM</b>			
1 randomized trials	very serious <sup>a</sup>	no serious inconsistency	serious <sup>c</sup>	no serious imprecision	none		205/647 (31.7%)	204/651 (31.3%)	RR 1.01 (0.86 to 1.19)	3 more per 1000 (from 44 fewer to 60 more)	⊕⊕OO LOW
								31.3%			
<b>Total Combined Cardiovascular Outcomes—Long-Term (Mean Follow-Up 5 Years)</b>							<b>CBPM</b>	<b>ABPM</b>			
1 randomized trials	serious <sup>a</sup>	no serious inconsistency	serious <sup>c</sup> (but more conservative results +1)	no serious imprecision	none		35/647 (5.4%)	20/651 (3.1%)	RR 1.76 (1.03 to 3.02)	23 more per 1000 (from 1 more to 62 more)	⊕⊕⊕O MODERATE
								3.1%			

Quality Assessment							No. of Patients		Effect		Quality
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other	ABPM or CBPM	Relative Risk (95% CI)	Absolute		
<b>MI/Stroke Nonfatal—Short-Term Follow-Up (<math>\leq 1</math> Year)</b>							CBPM	ABPM			⊕OOO VERY LOW
2	randomized trials	very serious <sup>a,b</sup>	no serious inconsistency	no serious indirectness	serious <sup>e</sup>	none	4/272 (1.5%)	5/283 (1.8%)	RR 0.84 (0.23 to 3.07)	3 fewer per 1000 (from 14 fewer to 37 more)	
								2.1%		3 fewer per 1000 (from 16 fewer to 43 more)	
<b>MI/Stroke Non-Fatal—Long-Term Follow-Up (<math>&gt; 1</math> Year) (Mean Follow-Up 5 Years)</b>							CBPM	ABPM			⊕⊕OO LOW
1	randomized trials	very serious <sup>a</sup>	no serious inconsistency	serious <sup>c</sup> (but more conservative results +1)	serious <sup>e</sup>	none	18/647 (2.8%)	8/651 (1.2%)	RR 2.26 (0.99 to 5.17)	15 more per 1000 (from 0 fewer to 51 more)	
								1.2%		15 more per 1000 (from 0 fewer to 50 more)	
<b>Fatal Cardiovascular Outcomes—Long-Term (Mean Follow-Up 5 Years)</b>							CBPM	ABPM			⊕⊕OO LOW
1	randomized trials	very serious <sup>a</sup>	no serious inconsistency	serious <sup>c</sup> (but more conservative results +1)	serious <sup>e</sup>	none	6/647 (0.9%)	6/651 (0.9%)	RR 1.01 (0.33 to 3.10)	0 more per 1000 (from 6 fewer to 19 more)	
								0.9%		0 more per 1000 (from 6 fewer to 19 more)	
<b>Stopped Therapy—Short-Term Follow-Up (<math>\leq 1</math> Year) (Follow-Up 6 Months)</b>							ABPM	CBP			⊕⊕OO LOW
1	randomized trials	very serious <sup>b,d</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	56/213 (26.3%)	15/206 (7.3%)	RR 3.61 (2.11 to 6.18)	190 more per 1000 (from 81 more to 377 more)	
								7.3%		191 more per 1000 (from 81 more to 378 more)	
<b>Drug Intensity—Short-Term Follow-Up (<math>\leq 1</math> Year) (Follow-Up 6 Months)</b>							CBPM	ABPM			⊕⊕OO LOW
1	randomized trials	very serious <sup>b,d</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	206	213	-	MD 0.34 higher (0.2 to 0.48 higher)	
<b>Number of Drugs—Short-Term Follow-Up (<math>\leq 1</math> Year) (Follow-Up 1 Year)</b>							CBPM	ABPM			⊕⊕⊕O MODERATE
1	randomized trials	serious <sup>a</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	66	70	-	MD 0.19 higher (0.15 lower to 0.53 higher)	
<b>Drug-Related Adverse Events—Short-Term Follow-Up (<math>\leq 1</math> Year)</b>							CBP	ABPM			⊕⊕OO LOW
2	randomized trials	serious <sup>a,b</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/272 (3.3%)	15/283 (5.3%)	RR 0.63 (0.29 to 1.38)	20 fewer per 1000 (from 38 fewer to 20 more)	
								8.8%		33 fewer per 1000 (from 62 fewer to 33 more)	

Quality Assessment							No. of Patients		Effect		Quality
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other	ABPM or CBPM	Relative Risk (95% CI)	Absolute		
<b>Drug-Related Adverse Events—Long-Term (&gt; 1 Year) (Mean Follow-Up 5 Years)</b>							CBPM	ABPM			
1	randomized trials	serious <sup>a</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	39/647 (6%)	45/651 (6.9%)	RR 0.87 (0.58 to 1.32)	9 fewer per 1000 (from 29 fewer to 22 more)	⊕⊕⊕O MODERATE
<b>Non-CVD events—Short-Term Follow-Up (≤ 1 Year)</b>							CBPM	ABPM			
2	randomized trials	serious <sup>a,b</sup>	no serious inconsistency	no serious indirectness	serious <sup>e</sup>	none	5/272 (1.8%)	3/283 (1.1%)	RR 1.74 (0.42 to 7.20)	8 more per 1000 (from 6 fewer to 66 more)	⊕000 VERY LOW
										9 more per 1000 (from 7 fewer to 74 more)	

Abbreviations: ABPM, 24-hour ambulatory blood pressure monitoring; BP, blood pressure; CBPM, conventional blood pressure monitoring; CI, confidence interval; CVD, cardiovascular disease; MD, mean difference; MI, myocardial infarction; No., number; RR, risk ratio.

<sup>a</sup>Not blinded.

<sup>b</sup>Limited information on allocation concealment.

<sup>c</sup>White coat hypertension was excluded from the ABPM group only.

<sup>d</sup>White coat hypertension was included at randomization.

<sup>e</sup>Small number of events.

## Appendix 3: Summary Tables

**Table A2: Summary of Study Characteristics (N = 3 Studies)**

Author, Year	Study Location	Type or Subtype of Hypertension by Arm (ABPM / CBPM)	Study Design	Length of Follow-Up	Number of Patients per Arm (ABPM / CBPM)	Losses to Follow-Up (ABPM / CBPM)
Conen et al, 2009 (27)	2 medical centres, Switzerland	Sustained/sustained	Parallel RCT	Up to 1 year	86/79	16/13
Schrader et al, 2000 (30)	50 general practitioners, Germany	Sustained/WCH	Parallel RCT	Up to 6 years <sup>a</sup>	651/647	239/208
Staessen et al, 1997 (31)	47 family practices, 9 clinics, Belgium	WCH/WCH	Parallel RCT	Up to 8.6 months <sup>b</sup>	213/206	14/16

Abbreviations: ABPM, 24-hour ambulatory blood pressure monitoring; CBPM, conventional blood pressure monitoring; RCT, randomized controlled trial; WCH, white coat hypertension.

<sup>a</sup>Mean length of follow-up: 5 years, range: 4–6 years.

<sup>b</sup>Median length of follow-up: 6 months, range: 2.8–8.6 months.

**Table A3: Detailed Summary of Study Design Characteristics (N = 3 Studies)**

Author, Year	Comparator	Study Population	Intervention	Results	Additional Comments
Conen et al, 2009 (27)	ABPM vs. CBPM	Aged ≥18 years; Screening CSBP ≥140 mm Hg or CDBP ≥ 90 mm Hg (mean of 2 BP <sub>s</sub> /2 days) <i>plus</i> sustained hypertension by 24-hour ABPM ≥ 130 mm Hg or DBP ≥ 80 mm Hg (WCH excluded prior to randomization, FU: 1 year	Validated device (Mobil-O-Graph or Spacelabs 90207—both oscillometric devices), BP measured every 20 min (8 a.m.–10 p.m.) or 30 min (10 p.m.–8 a.m.) on left arm Antihypertensive management based on average 24-hour ABPM	No sign baseline differences, mean age 56 years.  Baseline BP, no sign differences in baseline CSBP and 24-hr ASBP between groups ( $P > 0.20$ )  Change in BP, 1-year BP change from baseline, increased reduction in 24-hr ASBP for ABPM (n = 136) (-3.6, 95% CI: -7.0 to -0.3, $P = 0.03$ ) <sup>†adj</sup> ; no sign difference in change for 24-hr ADBP, CSBP, CDBP; ITT (n = 165) for 24-hr ASBP only, increased reduction for ABP (-2.8, 95% CI: -5.9 to 0.2; $P = 0.06$ ); BP control, higher % for ABP by 24-hr ABPM (AMB: 60 vs. CBP: 42%, $P = 0.04$ ), no diff between groups by CBP (AMB: 41 vs. CBP: 35%, $P = 0.4$ ) [as per BP target levels]  BP therapy, mean no. drugs used lower for ABP (1.8 vs. 2, $P = 0.05$ )  CVD, non-CVD or drug-related adverse events, ABP (14/70, 20%) vs. CBP (11/66, 16.7%), $P$ value not given, calculated based on reported results	Both CBPM and ABPM were performed on all patients, not blinded treatment adjustment; those with prevalent diabetes were included; analysis on those with 6 months of FU data (last value carried forward and a reduced sample size); only subgroup ITT analysis; subgroup analysis on patients with hypertension at baseline; additional info on drug class; overall DO-AMB: 28/86 (32.6%) vs. DO-CBP: 18/79 (22.8%); DO excluding patients with at least 6 months of FU data, DO-AMB: 16/86 (18.6%) vs. DO-CBP: 13/79 (16.5%)  Only study to comment on lifestyle changes according to current guidelines given to patients

Author, Year	Comparator	Study Population	Intervention	Results	Additional Comments
Schrader et al, 2000 (30)	ABPM vs. CBPM	<p>Aged 35–65 years.</p> <p>CSBP &gt; 140 mm Hg and/or DBP &gt; 90 mm Hg (3 BPs/2 days), <u>WCH excluded</u> after randomization in the ABP group only, for those without average daytime (6 a.m.–10 p.m.) ASBP &gt; 135 mm Hg and/or DBP &gt;85 mm Hg, or average 24-hour ASBP &gt; 130 mm Hg and/or DBP &gt;80 mm Hg, mean FU: 5 years</p>	<p>Validated device (Spacelabs 90207 oscillometric device), BP measured every 15 min (6 a.m.–10 p.m.) or 30 min (10 p.m.–6 a.m.)</p> <p>Antihypertensive management based on average daytime ABP (6 a.m.–10 p.m.), or average 24-hour AMB</p>	<p>No sign baseline differences, mean age 54 years (SD: 9.4).</p> <p>Baseline BP, 1.7 mm Hg lower CSBP in ABP vs. CBP; 24-hour ABP lower in ABP vs. CBP.</p> <p>CVD outcomes, total combined fatal/non-fatal MI + stroke + all other CVD deaths, AMB: 20/651 (3.1%) vs. CBP: 35/647 (5.4%), <math>P = 0.04</math>; fatal MI + stroke, AMB: 6/651 (0.9%) vs. CBP: 6/647 (0.9%).</p> <p>BP, BP control as allocated, ABP (24-hour or daytime): 53.4% vs. CBP: 59.7%, <math>P</math> value not given.</p> <p>BP therapy, % 1 drug, AMB: 68.7 vs. CBP: 68.3, % 2 drugs, 23.8 vs. 25.1, % &gt; 2 drugs, 7.5 vs. 6.6, <math>P</math> values not given.</p> <p>Drug-related adverse events, ABP (45/651, 6.9%) vs. CBP (39/647, 6%), <math>P</math> value not given.</p>	<p>CBP was measured in both groups at each visit; ABP was measured annually; not blinded treatment adjustment; CVD outcomes; ITT for all; additional information for nonvascular endpoints; additional information for dosage and number of dose-titration steps for first-line drug, and drug scoring method with data not shown; DO-ABPM: 239/651 (36.7%) vs. DO-CBPM: 208/647 (32.1%); 22% with WCH excluded initially</p> <p>Drug scoring method: 1 point = daily recommended dose of each drug; 0.5 point = half of the recommended dose; 2 point = double-dosage</p>

Author, Year	Comparator	Study Population	Intervention	Results	Additional Comments
Staessen et al, 1997 (31)	ABPM vs. CBPM	Aged ≥18 years, CDBP of 95–114 mm Hg (last of 3 BPs/both of 2 visits), median of FU: 6 months	Validated device (Spacelabs 90207 — oscillometric), BP measured every 15 min (8 a.m.–10 p.m.) or every 30 min otherwise	No sign baseline difference except for age, sex; mean age 53 years (calculated from 2 arms).  Baseline BP, no sign difference in CSBP, CDBP, daytime ASBP, daytime ADBP ( $P > 0.05$ ).	Inclusion criteria based on DBP; treatment adjusted based on blinded physician; ITT for all; additional info on symptoms, LVM, and compliance of therapy (tablet counts); additional adjusted results, DO-ABPM: 14/213 (6.6%), DO-CBP: 16/206 (7.8%)  Drug scoring method: 0.5 point = daily dose of 10 mg lisinopril, 50 mg atenolol, 12.5 mg hydrochlorothiazide; 1 point = daily dose of 20 mg lisinopril, 100 mg atenolol, 5 mg amlodipine; 0 point = untreated patients.

Abbreviations: ABPM, ambulatory blood pressure monitoring; ADBP, ambulatory diastolic blood pressure; ABP, ambulatory blood pressure; ASBP, ambulatory systolic blood pressure; BP, blood pressure; CBP, conventional blood pressure; CSBP, conventionally measured systolic blood pressure; CDBP, conventionally measured diastolic blood pressure; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; DO, dropouts; FU, follow-up; hr, hours; ITT, intent-to-treat analysis; LVM, left ventricular mass; MI, myocardial infarction; min, minutes; no., number; SBP, systolic blood pressure; SD, standard deviation; WCH, white coat hypertension.

†Adjusted for baseline blood pressure and baseline hypertension status.

‡Adjusted for baseline blood pressure, sex, and age.

**Table A4: Summary of Treatment Protocol and Blood Pressure Measurement (N = 3 Studies)**

Author, Year	Treatment Initiation <sup>a</sup>	Drug Provision and Doses <sup>b</sup>	Treatment Target/Threshold	BP Measurement	Data Handling of Ambulatory BPs
Conen et al, 2009 (27)	Untreated patients received first-line treatment	Stepwise therapy: Telmisartan, 80 mg (first-line) Hydrochlorothiazide, 12.5 mg Nifedipine, 20 mg	CBP < 140/90 mm Hg (< 140 mm Hg AND < 90 mm Hg)  24-hr ABPM < 130/80 mm Hg (< 130 mm Hg AND < 80 mm Hg)	CBP and ABP were measured at each scheduled visit for all patients.	Unedited
	Treated patients, optimization of established regimen, and then same steps as untreated patients				
Schrader et al, 2000 (30)	Untreated patients received first-line treatment.	Combination therapy: Ramipril, 1.25 mg (titrated) (first-line) Felodipine, 5mg or Nifedipine, 10 mg Hydrochlorothiazide, 12.5 mg Metoprolol, 100 mg	CBP > 140/90 mm Hg (> 140 mm Hg AND/OR > 90 mm Hg )  24-hr ABP > 130/80 mm Hg (> 130 mm Hg AND/OR > 80 mm Hg ), or daytime ABP > 135/85 mm Hg (> 135 mm Hg AND/OR > 85 mm Hg )	CBP was measured at each scheduled visit for all patients.  ABPM was performed annually	Unknown
	Treated patients, washout period, and then received first-line treatment				
Staessen et al, 1997 (31)	Untreated patients received first-line treatment	Stepwise therapy: Lisinopril, 10 mg <sup>c</sup> [first-line] Lisinopril, 20 mg <sup>c</sup> Hydrochlorothiazide, 12.5 mg Amlodipine, 5 mg	DBP for both groups (average daytime DBP for ABPM)	CBP and ABP were measured at each scheduled visit for all patients	Unknown
	Treated patients, therapy was gradually discontinued and replaced by placebo, and then same steps as untreated patients		DBP > 89 mm Hg ↑ therapy, DBP 80–89 mm Hg therapy unchanged, DBP <80 mm Hg ↓ therapy		

Abbreviations: ABP, ambulatory blood pressure; ABPM, ambulatory blood pressure monitoring; CBP, conventional blood pressure; CBPM, conventional blood pressure monitoring; DBP, diastolic blood pressure; mm Hg, millimetres of mercury.

<sup>a</sup>In Conen et al (2009) (27), untreated and treated patients were randomized; in Schrader et al (2000) (30), untreated patients were randomized; in Staessen et al (1997) (31), untreated patients were randomized.

<sup>b</sup>Types of antihypertensive medications include angiotensin II receptor blockers (telmisartan), diuretics (hydrochlorothiazide), calcium antagonists (nifedipine, felodipine and amlodipine), angiotensin converting enzyme inhibitors (ramipril and lisinopril), and beta blockers (metoprolol).

<sup>c</sup>Atenolol at 50 mg and 100 mg for patients with contraindications to angiotensin converting enzyme inhibitors.

**Table A5: Study Design—Strengths and Limitations**

Author, Year	Study Design—Strengths and Limitations <sup>a</sup>									
	Hypertension Study Population	Adequate Sample Size <sup>b</sup>	Exclusions Detailed	Randomization Achieved	Blinding	Adequately Measured Compliance	All-Cause Mortality	Survival Analysis	Intent to Treat Analysis	Minimal Attrition <sup>c</sup>
Conen et al, 2009 <sup>d</sup> (27)		✓ <sup>e</sup>	✓	✓	✓					✓
Schrader et al, 2000 <sup>d</sup> (30)		✓ <sup>f</sup>		✓	✓				✓	
Staessen et al, 1997 <sup>d</sup> (31)	✓		✓	✓	✓		✓ <sup>g</sup>		✓	✓

<sup>a</sup>Allocation concealment was unclear for Staessen et al (1997); ✓ indicates the presence of study design strengths or limitations.

<sup>b</sup>Lack of sample size based on reported sample size calculation for the primary association of interest.

<sup>c</sup>Minimal attrition based on examination of total and per-arm losses to follow-up/drop-outs, with < 20% attrition deemed to be adequate as minimal attrition.

<sup>d</sup>Primary analysis on those with at least 6 months of data (last value carried forward) and a reduced sample size; intent-to-treat analysis as a subgroup analysis.

<sup>e</sup>Patients with sustained hypertension.

<sup>f</sup>Patients with sustained hypertension in the ambulatory group only.

<sup>g</sup>Kaplan-Meier curves.

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