Interfacing the Circadian Variation of Blood Pressure and Cardiovascular Events
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Release Date: July 15, 2003
Expiration Date: June 30, 2006

Target Audience:
Physicians, pharmacists, nurse practitioners, physician assistants, and certified case managers.

Program Goal:
To appreciate the impact of circadian variation on blood pressure and cardiovascular events.

Program Overview:
This course will review current evidence relevant to hypertension and circadian variation of blood pressure. Conventional, 24-hour, daytime and nighttime BP are all compared and contrasted. Evidence will include data relevant to difficulties with treatment management, consequences of poor 24-hour BP control, and pharmacologic data supporting optimal management strategies.

Statement of Need:
Recent studies have shown that ambulatory blood pressure monitoring is more predictive of cardiovascular events than conventional blood pressure measures. Both assessment and treatment practices will be influenced by averaged blood pressure measures using 24-hour blood pressure monitoring.

Intended Outcome:
Intended outcome is to support practicing clinicians with knowledge relative to the importance of optimal 24-hour hypertension control.

Educational Objectives:
Upon completion of this activity, participants should be able to:

1. Discuss the predictability of conventional, 24-hour, daytime and nighttime BP in identifying cardiovascular risk.
2. Review the physiologic variables contributing to early am BP surge.
3. Identify rationale supporting use of ambulatory BP monitoring.
4. Explain how antihypertensive pharmacodynamics impact BP control and relative risk of cardiovascular complications.

Principal Faculty:
William B. White, MD
Dr. White serves as a Professor of Medicine and Chief of the Section of Hypertension and Clinical Pharmacology at the University of Connecticut, School of Medicine, in Farmington, Connecticut. Dr. White is U.S. board certified in both internal medicine and clinical pharmacology. He is also a certified clinical hypertension specialist by the American Society of Hypertension. Dr. White is a Fellow of the American College of Physicians, the Council for High Blood Pressure Research of the American Heart Association and the International Society for Hypertension in Blacks and a charter member of the American Society of Hypertension. He is the Editor-in-chief for the journal Blood Pressure Monitoring.
Disclosure:
Dr. White has received grant support from Pfizer, Inc., AstraZeneca, Forest Pharmaceuticals, Merck & Co., Inc., and Boehringer Ingelheim.

Commercial Support:
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Software Requirements:

**PC**
- Windows 98 SE or above
- Internet Explorer 5.5 or above
- Netscape 7.02 or above
- Flash Player Plugin
- *Sound Card & Speakers
- 800 x 600 Minimum Monitor Resolution (1024 x 768 Recommended)
- Adobe Acrobat Reader (Printable Version Only)

**MAC**
- Mac OS 10.2
- Netscape 7.02 only
- Flash Player Plugin
- *Sound Card & Speakers
- 800 x 600 Minimum Monitor Resolution (1024 x 768 Recommended)
- Adobe Acrobat Reader (Printable Version Only)
- Internet Explorer Not Supported

*SLIDES AND AUDIO ONLY

**Estimated time to complete this educational activity:**
This activity is expected to take one hour to complete.

**Continuing Education Credit:**
**Requirements for Credit:** In order to receive credit, participants must review the entire activity, complete and submit an evaluation, and score at least 70% on the self-assessment test. A statement of credit will be issued only upon receipt of a successfully completed post-test (70% or better) and activity evaluation form.

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**Fee:**
This program is provided free of charge.

**Editorial Review Board:**
M. Kathleen Ebener, PhD, RN and Jon S. Holman, BS, PharmD
Welcome to our program: Interfacing the Circadian Variation of Blood Pressure and Cardiovascular Events. This program has been sponsored through an educational grant from Boehringer Ingelheim.
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This program has been sponsored through an educational grant from Boehringer Ingelheim. The following program is a taped presentation by Dr. William B. White. Dr. White serves as a Professor of Medicine and Chief of the Section of Hypertension and Clinical Pharmacology at the University of Connecticut, School of Medicine, in Farmington, Connecticut. Dr. White is U.S. board certified in both internal medicine and clinical pharmacology. He is also a certified clinical hypertension specialist by the American Society of Hypertension. Dr. White is a Fellow of the American College of Physicians, the Council for High Blood Pressure Research of the American Heart Association and the International Society for Hypertension in Blacks and a charter member of the American Society of Hypertension. He is the Editor-in-chief for the Journal Blood Pressure Monitoring.

During the presentation, you will be asked a few brief questions. Your response will remain confidential and will be used to generate information about current clinician knowledge and practice patterns. When these questions appear, click on your answer to continue. Dr. White will address each of these questions in the discussion that follows.
Hi, this is Dr. William White of the University of Connecticut School of Medicine in Farmington, Connecticut.

Today, we have an interactive educational program entitled “Interfacing the Circadian Variation of Blood Pressure and Cardiovascular Events”.

The interface between circadian variation of blood pressure and cardiovascular events is an area of great interest in recent times, particularly for clinicians who manage clinical hypertension. I propose to talk a little bit about the epidemiology of hypertension, the clinical meaning of 24-hour blood pressure, and then relate this information to some of the latest data regarding treatment of this particular problem.
Question:

Current evidence indicates that hypertension is strongly linked to cardiovascular disease. In your adult population, which measures do you routinely utilize to diagnose hypertension?

a) Two or more BP measures collected on separate office visits
b) Patient recorded journal with several BP measures over time, random times
c) Patient recorded journal with several BP measures over time, including early am and evening times
d) 24-hour blood pressure monitoring

For this first question, would you please indicate which measures are routinely utilized to diagnose adult hypertension within your practice.

Current evidence indicates that hypertension is strongly linked to cardiovascular disease. In your adult population, which measures do you routinely utilize to diagnose hypertension?

Two or more BP measures collected on separate office visits
Patient recorded journal with several BP measures over time, random times
Patient recorded journal with several BP measures including early morning and evening times.
24-hour blood pressure monitoring
Looking at this slide, one can see that hypertension and cardiovascular disease are inextricably linked.

Twenty-four hour blood pressure has been well-correlated with target organ damages, left ventricular mass and left ventricular hypertrophy, impairment in left ventricular function (especially diastolic function), microalbuminuria in both diabetic hypertensives and non-diabetic hypertensives, different forms of brain damage including ischemic diseases of the brain (i.e. lacunar infarctions or periventricular hyperintensity on magnetic resonance imaging), and a variety of retinopathies seen primarily in patients with visual field defects.
One study that was done over ten years ago by myself and my colleagues here in the Cardiology Unit at University of Connecticut was an assessment of previously untreated patients in which we correlated left ventricular mass index with different kinds of blood pressure measurements. This is relevant information because left ventricular mass index (LVMI) is an indicator of target organ damage in hypertension.

Data from 15 patients with moderate to severe hypertension were analyzed (White et al, 1993). Systolic measures were used because of earlier data suggesting that the correlation of 24-h ambulatory BP monitoring (ABPM) and left ventricular mass index (LVMI) is generally better for systolic compared with diastolic blood pressure (Ravgoli et al, 1990).

This slide illustrates how the different sets of systolic blood pressure measurement correlate with changes and/or levels of left ventricular size. Note that the conventional or “casual” BP measurement typically taken in a doctor’s office was a very poor or weak correlate with left ventricular mass, whereas the average 24-hour pressure or elevation in daytime or nighttime average blood pressures were much better at predicting left ventricular hypertrophy.
We progressed over the next several years from target organ disease evaluations to actual morbidity and mortality research using ambulatory blood pressure measures and comparing these to clinical measurements. This table lists some of the original trials plus several more recent studies looking at the predictability of risk of cardiovascular events using ambulatory blood pressure versus a casual or conventional "clinic BP" measurement.

The index study was conducted by Dr. Dorothea Perloff, who studied the risk of having an MI, stroke or other cardiovascular death based on the ambulatory versus casual blood pressure measurements. She was the first person to demonstrate that your cardiovascular event risk was lower if your ambulatory pressure was lower than your casual blood pressure. She basically was the first person to diagnose white coat hypertension, although she didn’t call it that.

Many years later we had two big trials from the Syst-Eur study, using untreated patients with isolated systolic hypertension. Each of these studies demonstrated that ambulatory pressure was far better at predicting cardiovascular events, particularly stroke, in the isolated systolic hypertensive over the age of 60 years. And just in the June 12, 2003 edition of *The New England Journal of Medicine*, Clement and colleagues are publishing the Office Versus Ambulatory Study, or the OVA trial. This study followed almost 2,000 patients for many years, and found that in the treated hypertensive patient, elevated ambulatory blood pressure was better than the casual blood pressure in predicting cardiovascular events.
**Question:**

Which blood pressure measures do you currently recognize as significant predictors of future cardiovascular events?

- a) Casual or conventional random pressures
- b) Nighttime pressures
- c) Daytime pressures
- d) Averaged 24-hour pressures
- e) Early morning pressures
- f) All of the above

At this point, we would like to pose another question to the audience. Which blood pressure measures do you currently recognize as significant predictors of future cardiovascular events?

- a) Casual or conventional random pressures
- b) Nighttime pressures
- c) Daytime pressures
- d) Averaged 24-hour pressures
- e) Early morning pressures
- f) All of the above

It is important to recognize that all of these blood pressure measures are clinically meaningful. However, the clinician who recognizes the diagnostic implications of each measure will be more successful in designing an appropriate treatment strategy for the adult hypertensive patient.
This data comes from Paolo Verdeccia and colleagues in Italy, and diagrams the concept of blood pressure and risk. Verdeccia’s data base, from North Central Italy, showed that the normotensive group (Group A) had a very small risk of having a cardiovascular event (around 5%, approximately 1% per year) at the end of approximately four to five years of follow up. For those having a day time ambulatory pressure of less than 130/80 (Group B), the risk was almost indistinguishable from that of the normotensive group. The individuals in Group B are essentially normotensive despite having an elevated clinical blood pressure; these are the white coat hypertensives.

Looking at the two orange and orange-red bars (Groups C and D), note that patients in these groups had increasing levels of 24-hour blood pressure, along with substantially increased risk over time. Note that very conservative levels of daytime ambulatory pressure were used in this study to define who was at risk and who was not at risk. Since we cannot use the same values for the daytime ambulatory pressure as we can for causal measurements, 130/80 seems to be the new threshold for defining this problem in clinical practice.

A note about white coat hypertensives (WCH): the rate of major CV morbid events did not differ significantly between the normotensive Group A and Group B with WCH defined using restrictive criteria (a mean daytime ABP lower than 130 mmHg systolic and 80 mmHg diastolic). However, the rate of events significantly increased in Group C (a group defined with more liberal criteria), which in turn did not differ significantly from Group D (the group with ambulatory hypertension). The data suggest that WCH should be restrictively defined by very low limits of ABP (average ABP < 130 mmHg systolic and 80 mmHg diastolic) in order to avoid extending the definition of WCH to subjects at increased risk of CV morbidity events.
This systolic hypertension in Europe study (Syst-Eur) was conducted in about 4,000 patients with isolated systolic hypertension in the elderly. Study participants were given placebo or Nifedipine (calcium antagonist) with add-on therapy as a diuretic or ACE inhibitor. This slide shows the findings in the placebo group only as a way to demonstrate differences between prediction of cardiovascular end points based on casual/conventional measurements or the ambulatory blood pressure measurements.

The yellow line going between 160 systolic to 219 systolic (lower right-hand portion of the figure) demonstrates a positive but very weak relationship between cardiovascular events over the four years of follow up. Contrast the yellow line with the green and orange lines (reflecting different components of ambulatory monitoring). For example, the orange curve represents the overall 24-hour average in that same population, and some of these patients had very normal-looking blood pressures. In fact, those are the white coat hypertensives. But more importantly, this is a much steeper curve, similar to the green night time blood pressure curve or the blue daytime blood pressure curve. Patients with very low systolic pressures (< 130 systolic) had very low event rates(< 2% over a 2-4 year follow up period) whereas those patients who had a 170-190 systolic BP had nearly a quadrupling of their event rate over that same period of time. This is one example of how the 24-hour pressure was much better than the casual or conventional blood pressure at predicting cardiovascular events.
Night-to-day Ratio and 24-h Systolic BP as Predictors of Cardiovascular Endpoints – Syst-Eur

This 3-D diagram presents another way at looking at the data. Systolic BP over 24 hours (right-hand side) is contrasted with the night-to-day ratio (left-hand side) and the mortality and morbidity rates for a 2-year incidence of cardiovascular events.

Night-to-day ratio refers to the likelihood that a person has a decline in blood pressure during sleep. For example, if the ratio was 0.8, that meant that they had a 20% reduction in blood pressure during sleep compared to when they were awake. These individuals would be called “dippers” in the so-called 24-hour profile. Contrast a night-to-day ratio of 0.8 with a value of 1.2, meaning that BP during sleep and at night is actually 20% higher than the day time value. The higher value is a highly abnormal finding in an hypertensive individual, and this diagram shows that these individuals live with substantial risk.

Scrubtinizing this 3-D diagram further, note that if your systolic BP over 24 hours is < 134 and you are a “dipper”, your risk of having a cardiovascular event is next to zero. However, if you have a systolic BP > 165 during the 24-hour period and you are a “non-dipper”, then your risk goes up to between 5 and 10%, a highly unacceptable rate over the course of the two to three-year follow-up period.

This study provided a great deal of natural history information, but will never be repeated because it was a placebo-controlled trial in which patients with systolic hypertension were never treated. However, the findings help us appreciate the kind of threshold needed to minimize cardiovascular events (defining ambulatory hypertension versus ambulatory normotension).
Focusing again on the individual patient (and away from epidemiology), we see a 24-hour pressure profile in a typical hypertensive patient, including the period of time where we have a morning blood pressure surge. Note the systolic and the diastolic pressure curve, illustrating a typical morning surge.

At the very left-hand portion of this graph, the patient runs a BP about 170/110 at six o’clock or 18:00 military time. Getting closer to midnight, when the patient is falling asleep, the reduction in BP is substantial (falling to about 135/80, a 30% reduction which would be at the high end of average BP reduction during sleep). So this patient has a “dipper” profile. Then note that upon awakening there is a very steep and rapid rise in BP for several hours. This morning BP surge averages about 5/3 mm Hg each hour for about 4-6 hours post-awakening. Then for the rest of the day, the BP stays up until the patient goes back to sleep again. This 24-hour cycle is repeated over and over, and is a highly reproducible phenomenon in patients who get up in the morning, go to work, come home, rest and then go to sleep.
A great deal of research has focused on circadian variation in cardiovascular disease, and this particular graph demonstrates the relationship between circadian variation in blood pressure with the sympathetic nervous system. David Mulcahey from Ireland conducted this study a number of years ago.

Note that at the same time there is this morning surge in blood pressure and heart rate, there is also a fairly steep increase in both plasma adrenaline and noradrenaline levels. These things go up almost in concert with each other – increased BP in response to noradrenaline and increased heart rate in response to adrenaline. This phenomenon also enhances the risk of having cardiovascular events.
Chronobiological studies over the last 50 years have clearly demonstrated that cardiovascular complications do not have a static distribution over the course of the day. Between six o’clock in the morning and noon, sudden death, acute MI, angina pectoris, myocardial ischemia, stroke and variant angina pectoris all seem to be increased. At the same time of these events occurring, we also know that there is enhanced platelet aggregation in association with activation of the sympathetic nervous system.

So this is an area of great interest.
This seminal study from Jim Mueller and his colleagues at New England Deaconess Hospital, Boston reviewed the circadian related incidents of cardiovascular events (specifically mild cardiac infarction) at several hospitals within the Boston area. They used the CPK/MB fraction levels to assess when the MI was probably occurring as well as the history of chest pain (Muller et al, 1985).

As you can see, between about five o’clock in the morning up to about noontime, there was a substantial increase in the number of infarctions that occur on an hourly basis. There was a three-fold increase in the frequency of onset of myocardial infarction at peak (09:00 h) compared with trough (21:00 h) periods.

This work has been extended by this group, and they now have about 75,000 heart attacks in their data base. This pattern has remained consistent, and is absolutely well defined.
This particular study examines the incidence of another major cardiovascular event – ischemic stroke. Professor Marler (National Institute of Stroke at NIH), reviewed ischemic stroke events according to time of day.

This study reflects data from almost 1,200 stroke victims who actually knew exactly when they experienced onset of symptoms based on either weakness, difficulty in speaking, facial droop, or things of that nature. Note that during the middle of the night, the stroke rate was at its lowest. In the early morning period, it jumped up dramatically around eight o’clock in the morning and persisted until about noon and then it stayed about the same level. In fact, this circadian pattern demonstrated approximately a three-fold increased risk of having a stroke in the early morning period compared to the middle of the night (Marler et al, 1989).
A fairly recent study has been published by Professor Kario and colleagues in Japan, along with collaboration from Dr. Thomas Pickering at Mt. Sinai School of Medicine in New York. This interesting study correlates the morning BP surge to a prediction of future stroke. This is a prospective study, unlike the cross sectional studies shown in the two previous slides.

Over 500 Japanese patients with systolic hypertension in the elderly were evaluated. Kario and colleagues defined a morning surge as the difference between the pre-awake BP and the morning BP. Among the top 20% of these patients, or top quintile, this value was about 35 mm Hg systolic.
When looking at the systolic BP characteristics of Kario’s morning “surge group”, one can differentiate about 34 mm Hg variation versus only 9 mm Hg in the “non-surge group”. Most of the other group characteristics were fairly similar. The 24-hour blood pressure was a little bit higher in the “surge group”, but basically what distinguished these two groups was having that steep increase in BP during the early morning period.
Silent Cerebrovascular Disease and Stroke Prognosis

<table>
<thead>
<tr>
<th>Measures</th>
<th>Surge Group (n = 53)</th>
<th>Non-Surge Group (n = 466)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silent ischemic infarcts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence %</td>
<td>70 †</td>
<td>48</td>
</tr>
<tr>
<td>Average Number</td>
<td>2.3±2.6</td>
<td>1.3±2.6</td>
</tr>
<tr>
<td>Multiple ischemic infarcts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence %</td>
<td>57*</td>
<td>33</td>
</tr>
<tr>
<td><strong>Prospective data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic Strokes (%)</td>
<td>19.0 †</td>
<td>7.3</td>
</tr>
</tbody>
</table>

* P < 0.001, † P < 0.01


When examining this same group of Japanese patients for risk of having a silent ischemic brain infarct (detected using MRI), “surge group” patients had a significantly higher risk both from a prevalence standpoint and from the number of strokes per patient.

Data revealed that 19% of patients in the “surge group” eventually had a stroke over the next few years, compared to just 7% in patients within the “non-surge group”. These were thrombotic strokes, not hemorrhagic strokes, suggesting that a several-hour period of accelerated, uncontrolled hypertension during the early morning period predisposes small vessel disease in the brain which then causes endothelial dysfunction, increased platelet aggregation, and subsequent development of ischemic or thrombotic strokes – this is the first study that has ever shown this.
Silent Cerebrovascular Disease and Stroke Prognosis in Groups Matched for Age and 24-Hour Ambulatory BP

<table>
<thead>
<tr>
<th>Measures</th>
<th>Morning Surge (n = 46)</th>
<th>Non-Surge (n = 145)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>76±6.9</td>
<td>76±6.9</td>
</tr>
<tr>
<td>Male %</td>
<td>39</td>
<td>37</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.4±3.4</td>
<td>24.0±3.6</td>
</tr>
<tr>
<td>24-Hour SBP, mm Hg</td>
<td>142±15</td>
<td>142±15</td>
</tr>
<tr>
<td><strong>Silent Cerebrovascular Infarcts</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence, %</td>
<td>70‡</td>
<td>49</td>
</tr>
<tr>
<td>Average Number</td>
<td>2.0±2.1†</td>
<td>1.5±2.0</td>
</tr>
</tbody>
</table>

* P < 0.001, † P < 0.01, ‡ P < 0.05

One methodological concern in the Kario et al study relates to subtle differences in 24-hour BP measures (refer to slide 16 to note the slightly lower BP measures describing the “non-surge group”). So a sub-analysis was actually performed - matching age and 24-hour BPs in both the “surge group” and the “non-surge group”. This sub-analysis revealed the same information that was noted in the larger analysis; the prevalence of silent cerebrovascular infarctions substantially increased among those individuals in the “surge group”.

This study by Kario et al has revealed some important new information. The incidence of silent cerebrovascular disease, and the prognosis of stroke, is not only related to 24-hour BP levels but also related to the pattern of blood pressure over a 24-hour period.
Some interesting information for those of you who travel a lot. You might be interested to know the effects of jet leg on subsequent timing of cardiovascular events.

This was a very interesting forensic study published more than 13 years ago. Among Hawaiian residents living on the island of Kauai, both MI and sudden death rates peaked during the early morning periods shown in the green bar. This is consistent with previous studies correlating rhythmic BP variations with cardiovascular events. However, island visitors who typically came from the continental U.S. and were several hours ahead from the standpoint of time zones, had their MI’s shifted to a timeframe between noon to six o’clock because their circadian variation biologically had not yet changed. So this study demonstrates that the pattern of cardiovascular events such as MI and sudden death stays linked to the individual’s circadian rhythm – and that probably within a few days the individual will adjust.

So the bottom line is: if you are a traveler, make sure you take your aspirin, your antihypertensive medications and take it easy on that first day, especially in the afternoon hours.
Question:

Which physiologic mechanisms do you primarily recognize as major contributors to the early morning blood pressure surge phenomenon?

a) Hypothalamus-pituitary axis
b) Renin-angiotensin system
c) Platelet aggregation
d) Vasoconstriction

At this point, we would like to pose another question to the audience.

Which physiologic mechanisms do you primarily recognize as major contributors to the early morning blood pressure surge phenomenon?

a) Hypothalamus-pituitary axis
b) Renin-angiotensin system
c) Platelet aggregation
d) Vasoconstriction

Many of you will readily choose the renin-angiotensin system because of its known vasoconstricting effects whenever blood flow through the kidneys is reduced. The hypothalamus produces ADH, and both platelet aggregation and vasoconstriction are linked to neuroendocrine changes; but these are not considered primary contributors to the early morning blood pressure surge.
Getting back to the biology and the physiology of circadian variation on cardiovascular measures, this slide examines the patterns of BP, heart rate, several hemodynamic measures, and renal function.

As individuals fall asleep, most people experience a drop in BP. Salt and water delivery to the kidney drops substantially because obviously we are not eating or drinking, and our blood pressure goes down. As this is all happening, our plasma renin activity, angiotensin and plasma aldosterone levels begin to rise throughout the night - peaking in the early morning period (this is yet another mechanism for increasing BP, increasing sheer stress on blood vessels, and increasing cardiac workload in the early morning period). So the clinician will naturally want to know what can done to address this phenomenon.
Angiotensin II Receptor Blockers

- **COZAAR™ (losartan)** - Merck 1995
- **DIOVAN™ (valsartan)** - Novartis 1997
- **AVAPRO™ (irbesartan)** - Bristol-Myers Squibb 1997
- **ATACAND™ (candesartan)** - AstraZeneca 1998
- **MICARDIS™ (telmisartan)** - Boehringer Ingelheim 1998
- **TEVETEN™ (eprosartan)** - Biovail 1999
- **BENICAR (olmesartan)** - Sankyo and Forest 2002

Well, we have a lot of angiotensin II receptor blockers now available on the market. I’ll just describe them briefly according to their indication and their pharmacological half-life.

- Cozaar or Losartan, which came out first, is now used in doses of 50 and 100 mg daily. It has a fairly short half-life of about six hours. So in some patients, it is required to give it twice a day if you carefully monitor these individuals.

- Diovan or Valsartan came out next, and is used in doses of 80 all the way up to 320 mg once or twice daily. Diovan also has an indication for CHF in patients who cannot tolerate ACE inhibitors and in that instance, it should be used twice daily. Diovan, also has a half-life also of about six to nine hours.

- Avapro, or Irbesartan is an intermediate-acting angiotensin receptor blocker with a half-life of about 12 hours. Usual dosing consists of 75, 150 and 300 mg once daily.

- Atacand, or Candesartan, has a fairly short half-life and is used in doses of 8, 16 or 32 mg per day. Atacand has fairly strong affinity for the angiotensin receptor-binding site, and therefore is usually quite effective as a once-daily drug.

- Micardis, or Telmisartan, has a very long half-life of over 24 hours and is used in doses of 40 and 80 mg once daily. This once daily dosing is appropriate for virtually every indication because of this long half-life.

- Teveten, or Eprosartan, has a short half life of about five to seven hours and has a fairly intermediate to weak binding of the angiotensin receptor. Using doses of 400, 600 or 800 mg a day, it will often control blood pressure better using BID dosing although it can be given once daily in mild hypertensives.

- Benicar, or Olmasartan, is the most recent entry into the angiotensin receptor market at doses of 10 and 20 mg a day. It actually has a half-life of about 13 hours, is usually given once daily, and is fairly effective over 24 hours.
Comparative Efficacy:
24-h Mean Systolic BP Reductions

Looking at some clinical trial data relating these longer and shorter-acting drugs with 24-hour blood pressure control, we have an analysis done by Davis Smith and his colleagues from Orange County California. Telmisartan at 40 and 80 mg was contrasted to placebo to Losartan and to Valsartan. Certainly with the 80 mg dose of Telmisartan, one can notice a much larger numerical reduction in systolic pressure than what is seen with either Losartan or Valsartan. Even the 40 mg dose of Telmisartan was significantly better than Losartan 50.
Looking at a recent study just completed in the United States and Canada, the Micado-2 Trial, there was a forced titration design comparing Telmisartan 40 mg and then up to 80 mg versus Valsartan 80 mg and then up to 160 mg once a day. Ambulatory blood pressure monitoring was done at baseline and then after six to eight weeks of additional double blind treatment. The primary end-point of the study was reduction in blood pressure from baseline.
Systolic BP Change of Telmisartan or Valsartan (after 6-8 weeks)

Note that Valsartan was beginning to have less efficacy for the last eight hours of the dosing period in the red curve, in contrast to Telmisartan which kept the blood pressure fairly stabilized throughout the entire 24-hour period. Study findings show a reduction in systolic BP of about 13 mm Hg at the end of the dosing period (Telmisartan group) in contrast to about 9 or 10 mm Hg (Valsartan group). This was a significant finding for both systolic and diastolic blood pressure although I am only showing the systolic pressure today.

This study reminds me that if you were actually seeing a patient at 9, 10, 11 or 12 o'clock in the office after they have taken their morning antihypertensive dose, we wouldn’t really distinguish these drugs very well from each other. However, at the last hours of the dosing period when we are not seeing patients because they are either sleeping or first getting up and having that early morning surge, there is a clinically significant difference in BP based on the activity or the half life of these agents.
Another study out of Canada was done with two drugs of the same half-life, Telmisartan and Amlodipine, contrasting their effects using ambulatory monitoring. This study, directed by Eve Lacourssiere from Quebec, randomized patients to either placebo, Telmisartan, or Amlodipine. At the end of 12-weeks of double blind treatment, I think you can see that both Amlodipine and Telmisartan were highly effective at reducing 24-hour blood pressure for the entire duration. However, note that Telmisartan was numerically greater at reducing blood pressure at doses between 40 and 120 mg, average of 80, versus Amlodipine 5 to 10 mg, average 8 mg per day. Also note that during the middle of the night and during the first four hours upon awakening, Telmisartan was significantly more effective than Amlodipine at lowering blood pressure.

This gets back to that concept that if you have a substrate to work on such as angiotensin excess or activation of the renin-angiotensin system, the drug which has an effect on angiotensin receptor blockade may in fact be better than a nonspecific vasodilator at lowering blood pressure. So this looks like a winner as far as a long-acting agent, but it also looks like a possibility for combination since we know that we have to use drugs in combination these days. I have noticed favorable results in clinical practice when combining Telmisartan plus Amlodipine.
Now I’d like to shift gears for just a minute and talk a little bit about using 24-hour blood pressure in clinical practice. This slide by Dr. Grin and myself, published in *The Annals of Internal Medicine* more than ten years ago, reviewed the impact of ambulatory blood pressure on therapeutic decision making for practicing physicians in central and northern Connecticut.

Practicing physicians ordered 24-hour blood pressure monitoring in their patients because they were having some kind of trouble getting their blood pressure under control. Of 237 patients that were referred to us, about one-third to one-half had changes in their therapy after the data were reported to the referring physicians. Sometimes physicians initiated new drug therapy or discontinued therapy, but most of them increased or changed medication in order to get better blood pressure control. This is not the reason that most people think to use ambulatory recorders. Most clinicians think ABPM is used to rule out white coat hypertension, but there is a whole other rationale for using it based on getting patients under better control. Particularly with the new JNC-VII guidelines suggesting that we should be getting our diabetics, patients with target organ disease, and patients with renal disease down to 130/80 or less.
So I have developed a schema, which was recently published in *The New England Journal of Medicine*, on the use of ambulatory blood pressure monitoring in hypertension management. Walking through this schema, if patients come into your office with a BP >140/90 and they have no identified risk of cardiovascular disease other than their hypertension or if they have BP > 130/80 and they are high risk, that is, they have overt target organ disease such as a history of an MI or stroke or diabetes which greatly increases their risk, then I’m an advocate of first doing self-monitoring or home monitoring of the blood pressure. Now by doing that, I mean that the patient must take their blood pressure several times over the course of a week. Then the measures are averaged, and if that average value is > 135/85, I think they should be initiated onto antihypertensive therapy.

Let’s say, however, that the self-monitored blood pressure is actually < 135/85. In those patients, I would want to rule out white coat hypertension. I would perform ambulatory blood pressure monitoring. If the ambulatory blood pressure was < 130/80, (based on the OVA Trial and the data from Syst-Eur as well as data from Paolo Verdecchia in Italy), I think it is appropriate at this point in time to follow these patients with non-drug therapy for up to 6-12 months and repeat ambulatory monitoring within a couple of years to make sure that they are staying below 130/80. What I am recommending is a novel decision, yet it is based on the last decade of data.

In contrast, if the patient’s 24-hour BP is > 130/80, then I would initiate anti-hypertensive therapy based on the study and the evidence that we have to date. At some point in time over the next several months, once dosing and therapeutic regimen has been stabilized, do a 24-hour blood pressure monitoring trial and then make decisions based on the recorded values. If the 24-hour blood pressure is < 130/80, maintain the present therapy and consider re-monitoring them in a few years. If the 24-hour blood pressure is still basically higher than 130/80, modification of antihypertensive therapy seems to be appropriate to improve control. Once you get them there, you follow up with ambulatory recordings in a couple of years. I think that this is a reasonable strategy, based on the latest data published in the last several years.
Medicare DECISION

- “At this point in time*, ABPM will be covered for those patients with suspected WCH.”
- Suspected WCH will be defined as office BP > 140/90 mmHg on at least 3 separate office visits (2 separate measurements per visit)
- In addition, at least 2 BP measurements outside of the office that are < 140/90 mmHg.
- There should be no evidence of end-organ damage

* October 2001 (activated April 2002)

Now I’m not alone in making this kind of striking paradigm shift from hypertension management using these monitors. In fact, in 2002, Medicare made a decision that ambulatory monitoring will be covered for patients with suspected white count hypertension and that means that their office blood pressure is elevated on several visits and that some form of their office reading is in fact lower.

I am however going one step further in my basic recommendation; I am saying that it is probably reasonable to perform ambulatory blood pressure monitoring in the treated hypertensive patient, not just the untreated, newly diagnosed hypertensive patient. Medicare’s decision was based on data primarily from Verdeccia, Syst-Eur and other studies focusing on the untreated patient who had been followed for several years. Of course, they did not have results of the OVA Trial at the time they made this decision.
So in conclusion, it is clear to me that 24-hour blood pressure measurement gives an enhanced prediction of cardiovascular risk.

Patients with white coat hypertension, when defined as < 130/80, are clearly at low risk for cardiovascular events over a many year follow-up period, and are not very different from a normotensive group of patients.

24-hour blood pressure measurement also clearly gives the best correlation with the effects of drug treatment on target organ damage.

And very recently, we have learned that the morning surge of blood pressure independently predicts ischemic stroke.
Conclusions

24-hour blood pressure measurement is the best method for evaluating important features of drug treatment such as

- Duration of action
- Effects on the circadian rhythm of BP
- Effects of varying the timing of dosing

In addition, when we are evaluating hypertensive therapy, over two decades of research has shown us that 24-hour blood pressure is the best method for evaluating duration and action of drugs, the effects of the circadian rhythm of blood pressure, and also whether or not it is a reasonable thing to vary the timing of drug dose — either giving it at night, giving it in the morning, or giving it twice daily.

These kinds of data are currently available in the literature where they weren’t 10 or 20 years ago. When physicians ask “can I just go ahead and give all the beta blocker at night?” or “can I just go ahead and give all the ACE inhibitor at night?” I recommend to actually evaluate whether or not that drug has been studied by giving it at different times of day and if it’s not, give it in the morning. If they have the availability of 24-hour blood pressure monitoring in their practice community, I recommend doing the study. Find out what the profile looks like, and then vary the medication according to the way the pattern of the blood pressure looks for that individual patient.
Thank you for your participation in this presentation.

This concludes our program. Thank you for participating in: Interfacing the Circadian Variation of Blood Pressure and Cardiovascular Events.

Please proceed now to the post-test.