Review Paper

Ambulatory Blood Pressure Monitoring as an Investigative Tool for Characterizing Resistant Hypertension and Its Rational Treatment

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Ambulatory blood pressure (BP) monitoring has matured into a useful methodology that obtains automated measurements of brachial artery BP during a 24-hour period. Cardiovascular outcomes in the treated patient with hypertension are often better predicted by ambulatory BP than by office pressures. Consensus guidelines have advocated lower goals of treated office BP in the majority of patients with hypertension; guidelines for the goal of ambulatory BP are needed as well. Recently, prospective cohort studies have shown that individuals whose clinic pressure is relatively normal but whose 24-hour BP is elevated are more likely to have a cardiovascular event than individuals with both normal clinic BP and ambulatory BP. Along with the knowledge gained from analyses of higher-risk hypertension patients, recommendations can now be made for how to use ambulatory BP monitoring in clinical practice. For example, ambulatory BP monitoring may be useful in verifying 24-hour control in high-risk patients whose office BP appears to be normal at rest or during the peak effect time of their antihypertensive agents. Evidence is mounting from studies that support the use of ambulatory BP monitoring in patients with resistant hypertension at the time of diagnosis and following clinically guided therapy. (J Clin Hypertens. 2007;9(1 suppl 1):25–30) ©2007 Le Jacq

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Ambulatory blood pressure monitoring (ABPM) is a method that obtains automated measurements of brachial artery pressure during a 24-hour period while a patient is engaging in their usual activities of daily living.[1,2] In a patient with hypertension, ABPM yields greater blood pressure (BP) values in all of a patient's activities, including sleep, and is more representative of the BP burden than what might be obtained in a visit in the doctor's office setting.[1,3] Gaining acceptance of this technique for clinical practice had been difficult, and many experts in cardiovascular (CV) medicine have been uncomfortable relegating office BP to secondary importance compared with any other means of BP measurement. Office BP has certain important and clinically relevant shortcomings, however. Standardized methodology is not routinely used in the doctor's office, and repeat measurements over several minutes in the examination room are the exception rather than the rule.[1] Thus, a white coat effect (increase in pressure only in the medical care environment) has been reported in 20%–35% of patients with hypertension.[3,4]

USING ABPM TO EVALUATE THE PATIENT WITH HYPERTENSION

Outcome research with ABPM is relatively new compared with studies that have used office values.

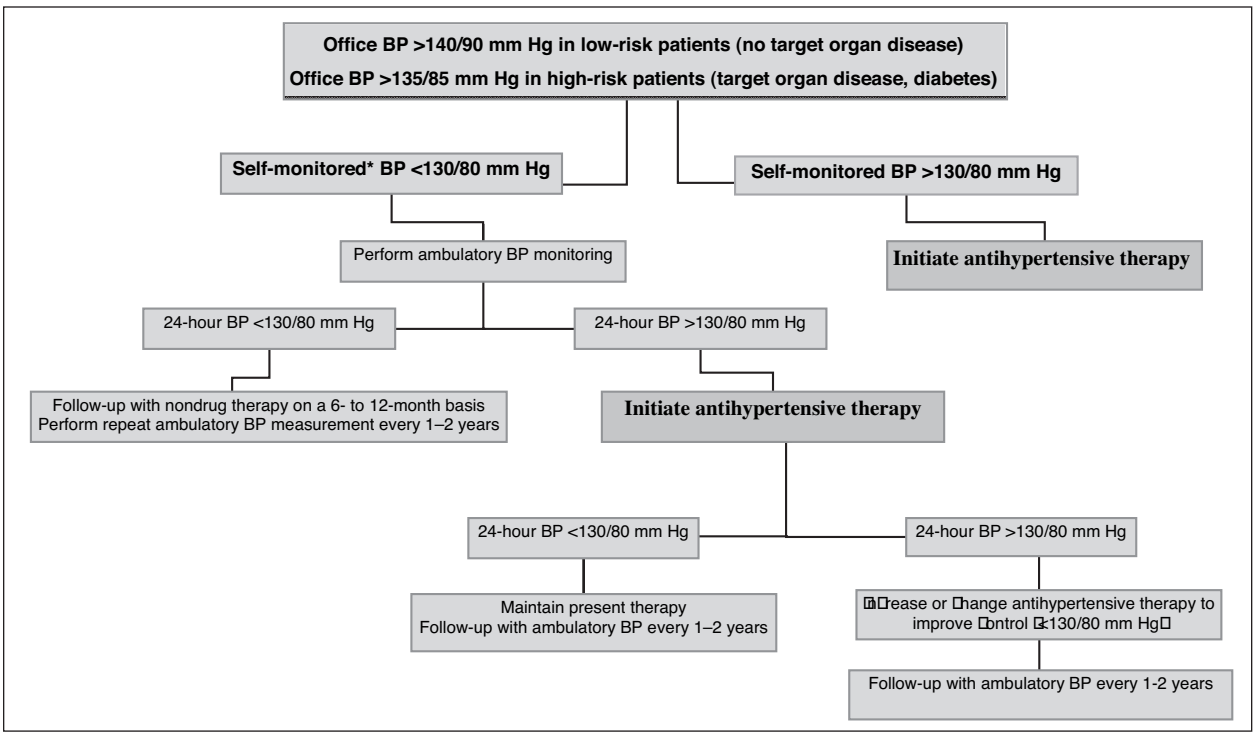

*Figure 1. Schema for the use of ambulatory blood pressure (BP) monitoring in the management of patients with hypertension. *Self-monitoring of BP should include at least 1 week of recording by the patient in duplicate each day at home and in the work environment. Adapted from White.*[1]

Since 1994, several studies have demonstrated that patients with newly diagnosed and those with untreated white coat hypertension have a more benign outcome compared with patients who are considered hypertensive with office and home BPs, but may have more events than normotensives in office and home BPs. Patients who have a white coat effect do not appear to benefit greatly from antihypertensive drug therapy.[4] More recently, studies using ABPM have also shown that patients with masked hypertension (higher out-of-office BP than in-office BP) have poorer outcomes than would be expected based on their office readings.[5] Clement and associates[6] demonstrated that CV outcomes in the treated patient with hypertension are better predicted by ambulatory BP than by office (or clinic) BP. The value of these findings is that all patients were on drug therapy and their treatment was representative of community practice. Most notable was the finding that patients whose 24-hour BP exceeded 135/85 mm Hg while on treatment had approximately twice as many CV events as patients with 24-hour mean BPs <135/85 mm Hg regardless of the level of office BP.[6]

With the knowledge we have gained from analyses of higher-risk hypertensive patients, recommendations can now be made for how to use ABPM in clinical practice (Figure 1). Self-monitoring (home and worksite together) of BP determines whether a large disparity exists between the office and out-of-office pressure before consideration of ambulatory monitoring. It is likely that many patients whose self-monitored BPs are considered normal may have elevated ambulatory BP that requires antihypertensive therapy. For those whose ambulatory BPs are truly normotensive (<130/80 mm Hg), despite an elevated clinic pressure, and who lack evidence of other CV risk factors or target organ disease, avoidance of unnecessary drug therapy may be a benefit of the monitoring procedure.

USEFULNESS OF ABPM IN EVALUATING RESISTANT HYPERTENSIVE PATIENTS

The utility of ABPM for the assessment of patients with resistant hypertension was derived from early clinical trials that screened patients for a white coat effect before randomization.[7] Nearly 1 in 4 patients who have a clinic BP of >140/90 mm Hg typically have a daytime BP of <135/85 mm Hg and will therefore have a modest response to an antihypertensive agent. When the clinic BP is raised to higher values for purposes of inclusion into a study, the screen failure rate using ABPM is lower, typically 20%. Using this approach to screen patients for antihypertensive therapy trials has become quite common in phase 2 and 3 drug development studies.

Table I. Characteristics of Patients With True vs White Coat Resistant Hypertension*

Characteristic	True (n=313)	White Coat (n=184)	*P*
Male sex, %	34	23	.01
Age, y	59	62	.04
Physical inactivity, %	76	67	.05
No. of antihypertensive drugs	3.7	3.6	.85
Office BP, mm Hg	183/102	172/97	<.001
24-Hour BP, mm Hg	151/87	121/71	<.001
Daytime BP, mm Hg	153/89	123/73	<.001
Nighttime BP, mm Hg	142/79	113/65	<.001
24-Hour protein, g/24 h	0.39	0.22	<.001
24-Hour albumin, mg/24 h	64	33	<.001
Echocardiographically derived			
Septal wall thickness, mm	12.1	11.0	<.001
Posterior wall thickness, mm	11.7	10.6	<.001
Left ventricular mass index, g/m^2	153	133	<.001

*True resistant hypertension: office blood pressure (BP) >140/90 mm Hg and daytime ambulatory BP >135/85 mm Hg; white coat resistant hypertension: office BP >140/90 mm Hg and daytime ambulatory BP <135/85 mm Hg. Adapted from Muxfeldt et al.[8]

Muxfeldt and colleagues[8] characterized true resistant hypertension vs white coat resistant hypertension using office and ambulatory BP measurements in 497 patients. The investigators classified true resistant hypertension as patients taking 3 antihypertensive drugs who had elevated office BP (>140/90 mm Hg) and ambulatory BP (daytime BP >135/85 mm Hg); white coat resistant hypertension was classified in patients with elevated office and controlled daytime BP (<135/85 mm Hg). Of the original cohort, 63% had true resistant hypertension; they were more likely to be men and slightly younger than the white coat resistant hypertensives, but both groups were taking an average of 3.6 antihypertensive drugs (100% were on diuretics based on the definition of resistant hypertension). As expected, there were marked discrepancies in the ambulatory BP values for the true vs white coat resistant hypertensives (Table I), and far more metabolic abnormalities and target organ involvement occurred in the true resistant hypertensive compared with the white coat resistant hypertensive.

A similar use of ABPM in resistant hypertension comes from a recent assessment by Pierdomenico and associates[9] of various hypertensive subgroups. This study investigated a group of treated patients who were followed in a hypertension specialty practice in Italy, some of whom were well-controlled based on the clinic measurements and others who were uncontrolled. When examining these groups using 24-hour ABPM, it was noteworthy that 37% of the patients in both groups were uncontrolled and hence misclassified by the results of the office BP values. Approximately 1 in 4 patients in the controlled office BP group had masked hypertension,

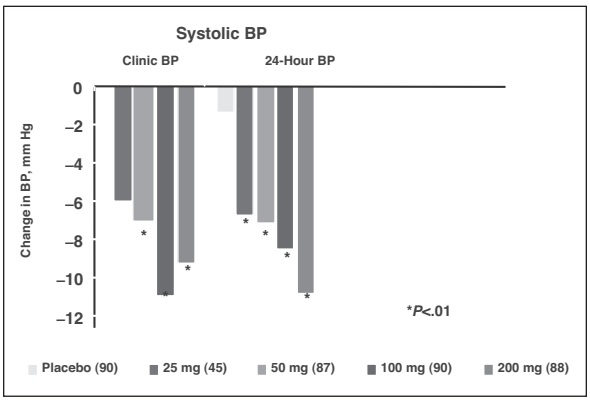

Figure 2. Changes from baseline in clinic and 24-hour ambulatory blood pressure (BP) after 12 weeks of therapy with eplerenone (25–200 mg/d) and placebo. Adapted from White et al.[15]

and these patients had significantly more CV events during a follow-up observational period. Not surprisingly, patients with true resistant hypertension also had much higher CV event rates compared with patients who had false resistant hypertension (4.1 events per 100 patient-years vs 1.2 events per 100 patient-years, respectively).[9] Thus, both of these recent studies demonstrate the importance of obtaining ambulatory BP recordings in patients with resistant hypertension for risk stratification and eventual management strategies.

ABPM FOR EVALUATING ANTIHYPERTENSIVE RESPONSES IN PATIENTS WITH RESISTANT HYPERTENSION

As discussed above, white coat hypertension and the white coat effect give the impression of resistance to antihypertensive therapy and an overestimation

Table II. Impact of Dosing Time of Antihypertensive Therapies on Ambulatory BP

Parameter	All Morning Drugs	One Drug at Bedtime	*P*
No. of patients	260	318	
Duration of sleep, h	9	9	.55
24-Hour BP, mm Hg	138/80	134/79	.003/.011
Daytime BP, mm Hg	139/83	137/82	.049/.205
Nighttime BP, mm Hg	134/75	128/72	<.001/<.001
Day/night ratio for SBP, %	4.1	6.3	<.001
Day/night ratio for DBP, %	9.2	11.9	<.001

Day/night ratio indicates the percentage decline in blood pressure (BP) during nighttime BP relative to daytime BP (index of dipping). Adapted from Hermida et al.[11]

Table III. Office and Ambulatory BP Values Before and After Treatment for Primary Hyperaldosteronism

Parameter	Pretreatment	Posttreatment	*P*
Office BP, mm Hg	165/100	144/90	.006/.05
Awake BP, mm Hg	156/93	130/78	.003/.001
Sleep BP, mm Hg	140/77	115/67	.003/.015
Awake-sleep difference			
Systolic BP, mm Hg	17	16	ns
Diastolic BP, mm Hg	16	12	ns
Dippers/nondippers	8/4	9/3	ns

BP indicates blood pressure; ns, not significant. From Mansoor and White.[14]

of the patient's true BP. The inclusion of white coat hypertensive patients in an antihypertensive drug trial that uses only office BP criteria for study entry will have a potentially confounding effect on efficacy, as these patients are often not hypertensive outside of the medical care environment.[7] In addition, patients may develop drug-induced side effects without much change in BP, especially if titration of the dose is based on office pressures.

In a small study by Weber and colleagues,[10] a sustained fall in BP was found across a group of study patients taking a long-acting form of diltiazem. In a subset of only 6 patients who had hypertensive office BP readings but whose ambulatory BPs were indicative of normotension (ie, a white coat hypertensive group), no significant ambulatory BP changes from placebo baseline (0/1 mm Hg) were observed. In contrast, diltiazem therapy decreased 24-hour BP by 18/13 mm Hg in the subgroup of 9 patients who were hypertensive according to both office and ambulatory BP. Thus, treating white coat hypertension in this study was of little benefit to patients when BP reduction was observed in the medical care environment.

In contrast to the scenario of the white coat effect leading to a form of pseudoresistant hypertension, ABPM also lends itself toward diagnosis of more clinically worrisome syndromes of resistant hypertension. Muxfeldt and colleagues[8] have determined that a large proportion of patients with true resistant hypertension (ie, confirmed by ABPM) have a nondipper BP pattern. The absence of 24-hour therapeutic coverage in patients with once-daily dosing of drugs has been recognized as one cause of resistant hypertension and high nocturnal BP.[11] In a recent study in which patients received all of their medications in the morning vs 1 drug at bedtime, Hermida and colleagues[11] showed improvement in the nocturnal BP that led to an overall reduction in 24-hour BP values (Table II). The proportion of patients characterized as nondippers remained high since early morning BP was also affected by nighttime dosing of medications. The authors concluded that taking into account the individual circadian BP rhythm allows for targeted treatment that can result in reduction of true resistance, especially nocturnal hypertension, or nondipper status.

CIRCADIAN BP VARIATION IN HYPERTENSIVE PATIENTS WITH MINERALOCORTICOID EXCESS

The 24-hour profile of BP is a result of complex interactions of neurohormonal circadian changes and superimposed effects of mental and physical activity, including posture.[7] The extent of BP reduction during sleep is affected by age, sleep quality, and underlying comorbidities such as autonomic dysfunction, volume excess syndromes, and diabetes mellitus.[12,13] Study results of patients

Table IV. Effects of Eplerenone Added to a 4-Drug Regimen in a Patient With Resistant Hypertension and Coronary Disease

	Clinic BP, mm Hg	24-Hour BP, mm Hg	Drug Regimen (Excluding Eplerenone)
Baseline	162/102	150/92	Amlodipine, 10 mg once daily Atenolol, 50 mg twice daily Furosemide, 20 mg once daily Lisinopril, 20 mg once daily
Eplerenone (50 mg daily) 2 weeks	118/74	—	Amlodipine, 10 mg once daily Atenolol, 50 mg twice daily Furosemide, 20 mg once daily Lisinopril, 20 mg once daily
Eplerenone (50 mg daily) 6 weeks	106/66	—	Amlodipine, 10 mg once daily Atenolol, 50 mg twice daily
Eplerenone (50 mg daily) 12 weeks	112/72	114/68	Amlodipine, 5 mg once daily Atenolol, 50 mg once daily
Eplerenone (50 mg daily) 36 weeks	118/70	—	Amlodipine, 5 mg once daily Atenolol, 50 mg once daily

with primary hyperaldosteronism have been mixed and have shown that both nondipper and dipper profiles may exist.[14] In a study by Mansoor and White[14] involving patients with primary hyperaldosteronism, most patients had true resistant hypertension based on ABPM. Following treatment for the hyperaldosteronism with adrenalectomy or medical therapy, ambulatory BPs were reduced dramatically in some cases, but the awake-sleep BP difference remained unchanged (Table III).

The findings from the above-referenced study encouraged work with the selective aldosterone receptor antagonist, eplerenone, which had been shown in an original dose-ranging study to reduce ambulatory BP in a significant dose-related fashion (Figure 2).[15] Subsequently, studies with eplerenone in low renin patients[16] and isolated systolic hypertension in the elderly[17] demonstrated that this agent had superior efficacy to the angiotensin receptor blocker losartan and similar efficacy to the calcium antagonist amlodipine in these difficult-to-treat and often resistant hypertensive patients.

Twenty-four–hour monitoring of the BP was performed in the study evaluating the effects of eplerenone compared with amlodipine in 269 patients with isolated systolic hypertension (baseline clinic BP, 166/86 mm Hg in each treatment group; baseline 24-hour BP, 154/84 mm Hg and 150/84 mm Hg in the eplerenone and amlodipine groups, respectively). As shown in Figure 3, 24-hour control of the systolic BP was similar in both

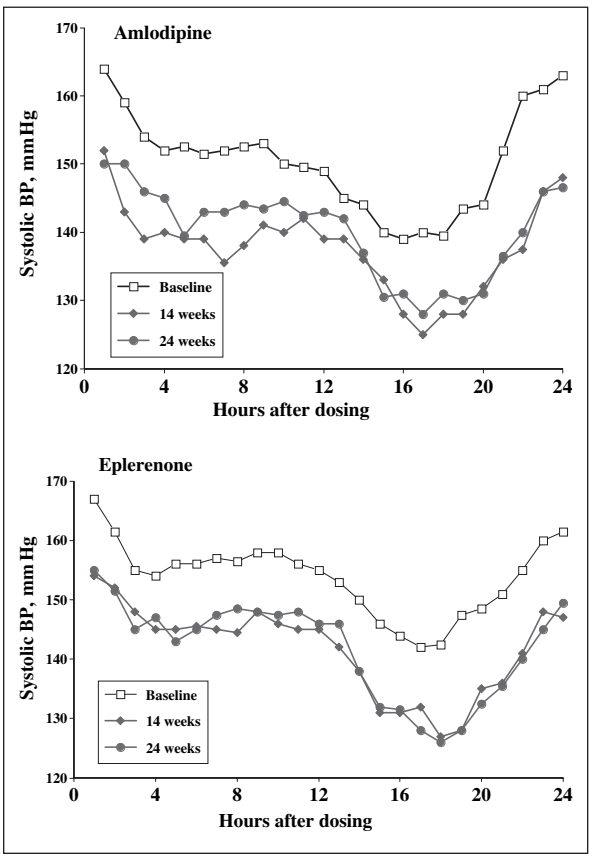

Figure 3. Effects of amlodipine (top) and eplerenone (bottom) on 24-hour blood pressure (BP) at baseline and following 14 and 24 weeks of double-blind therapy in patients with systolic hypertension. Adapted from White et al.[17]

treatment groups and showed sustained effects throughout the dosing interval.

The results of these data with eplerenone in various difficult-to-manage patient populations led us to initiate a formal evaluation of the drug in patients with more classically defined resistant hypertension. As shown in Table IV, in one of the first patients to complete the trial, the degree of BP reduction in certain individual patients can be quite dramatic. In addition, a substantial reduction in prior drug therapy may possibly be expected. This ongoing study will allow us to assess the benefits of selective aldosterone blockade in truly resistant hypertension stratified for aldosterone and renin status.

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Please Select the One Best Answer for Each Question and Place Your Selection on the Answer Grid.

RESISTANT HYPERTENSION: CURRENT DIAGNOSIS, TREATMENT, AND MANAGEMENT STRATEGIES

EPSTEIN (PAGES 2–6)

1. The prevalence of hyperaldosteronism is particularly high in cases of resistant hypertension.
   A___ True
   B___ False
2. Blood pressure (BP) and the number of patients with hypertension increase with sleep apnea severity as indicated by the respiratory disturbance index.
   A___ True
   B___ False
3. In addition to promoting sodium retention and hypervolemia, aldosterone produces hypertension by several extrarenal mechanisms including its direct vasoconstrictor effects and by altering vascular compliance.
   A___ True
   B___ False

PARK AND CAMPESE (PAGES 7–12)

1. A 48-year-old patient presented with newly diagnosed hypertension with BP levels of 164/112 mm Hg. His medical history, family history, review of systems, and physical examination were otherwise noncontributory. Other than a serum potassium level of 3.7 mEq/L, laboratory chemistry results were normal. He was treated with chlorthalidone 12.5 mg/d and lisinopril 20 mg/d, with minimal changes in BP. Amlodipine 10 mg/d was added, and his BP was 146/96 mm Hg. Blood chemistry results showed serum potassium of 2.8 mEq/L. Chlorthalidone was stopped and, after taking potassium supplements for 2 weeks, serum K+ increased to 3.5 mEq/L. At that point, plasma renin activity was 0.2 and plasma aldosterone was 6 pg/mL. What is the most likely cause of resistant hypertension in this patient?
   A___ Renovascular disease
   B___ Pheochromocytoma
   C___ Primary aldosteronism
   D___ Liddle syndrome
2. A 49-year-old African American man was referred to you with a diagnosis of resistant hypertension. He had a strong family history of hypertension. He was prescribed metoprolol 100 mg/d, lisinopril 40 mg/d, losartan 100 mg/d, clonidine 0.2 mg 3 times daily, and valsartan 160 mg/d. His BP was 150/100 mm Hg. His urinalysis and blood chemistry results were normal. What is the most likely cause of resistant hypertension in this patient?
   A___ Secondary form of hypertension
   B___ Inappropriate regimen
   C___ Drug abuse
   D___ Poor compliance with medications
3. What would be your next drug of choice for this patient?
   A___ Amlodipine 10 mg/d
   B___ Furosemide 40 mg PO daily
   C___ Chlorthalidone 25 mg/d
   D___ Amiloride 10 mg/d

DUPREZ (PAGES 13–18)

1. Aldosterone may cause endothelial dysfunction, vascular remodeling, and vascular injury.
   A___ True
   B___ False
2. Aldosterone increases arterial stiffness and consequently arterial BP.
   A___ True
   B___ False
3. Mineralocorticoid receptors are present in the heart, vasculature, and brain.
   A___ True
   B___ False

CALHOUN (PAGES 19–24)

1. Lifestyle modifications are generally of little value in treating resistant hypertension and therefore should not be recommended.
   A___ True
   B___ False
2. The prevalence of primary aldosteronism in patients with resistant hypertension is approximately:
   A___ 10%
   B___ 20%
   C___ 30%
   D___ 40%
3. Aldosterone antagonists have been shown to provide significant additional BP benefit when added to existing multidrug regimens, including a diuretic and angiotensin-converting enzyme inhibitor.
   A___ True
   B___ False

WHITE (PAGES 25–30)

1. The likelihood of a patient with a normotensive office BP reading (<140/90 mm Hg) having an elevated ambulatory BP reading while on therapy is approximately:
   A___ 6%
   B___ 25%
   C___ 48%
   D___ 80%
2. Compared with patients with resistant hypertension due to the white coat effect, true resistant hypertension is associated with:
   A___ A higher number of antihypertensive drugs
   B___ A lower office BP
   C___ Large left ventricular mass index
   D___ Lower nocturnal BP
3. Studies with the selective aldosterone blocker eplerenone in patients with low-renin hypertension have shown an effect:
   A___ Similar to placebo
   B___ Superior to a thiazide diuretic
   C___ Inferior to a calcium antagonist
   D___ Superior to an angiotensin receptor blocker

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CME Answer Grid

Answer the questions from the previous pages by selecting the best choice of A, B, C, or D.

Questions: Epstein	1.__	2.__	3.__
Questions: Park and Campese	1.__	2.__	3.__
Questions: Duprez	1.__	2.__	3.__
Questions: Calhoun	1.__	2.__	3.__
Questions: White	1.__	2.__	3.__

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Please evaluate the effectiveness of this CME activity on the scale of 1 (lowest) to 5 (highest).

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2. The articles were presented in a clear and effective manner.	1.__	2.__	3.__	4.__	5.__
3. The articles were current and clinically relevant.	1.__	2.__	3.__	4.__	5.__
4. Achievement of educational objectives	1.__	2.__	3.__	4.__	5.__
5. This CME activity provided a balanced, scientifically rigorous presentation of the topic, without commercial bias.	1.__	2.__	3.__	4.__	5.__

Please comment on the impact (if any) that this CME activity might have on your management of patients. _____

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