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When to Order a Sleep Study and How to Read the Report—Part II

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Editor's Note—*This is the final in a 2-part series on when to order a sleep study and how to read the report. The sleep study report contains essential information for diagnosing common sleep-related physiological disorders. The report format is not standardized, so a variety of formats are used by different facilities. However, generally the same information should be found in any sleep study report. Typically the information provided includes data on sleep parameters, respiration, leg movements, ECG, and descriptions of any abnormalities noted in the various parameters that are recorded. Understanding the information provided in the sleep study report and knowing how to use it is crucial for accurate diagnosis and effective treatment. The combined information from the sleep history and the sleep report allows diagnosis of all sleep disorders.*

Sleep Architecture

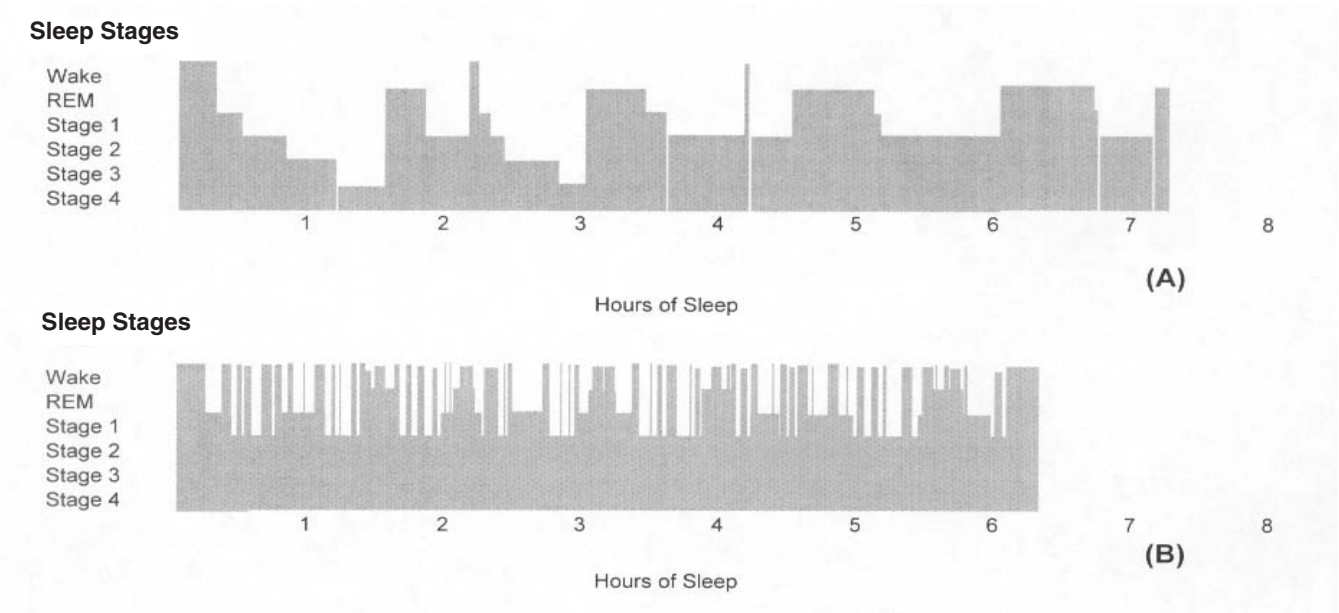
Sleep architecture refers to the temporal pattern of sleep and wake across the sleep period. The generation of sleep follows a consistent progression of sleep stages and repetitive cycles that are represented by the sleep architecture. Sleep stages are based on the EEG and consist of 5 stages (Stages 1, 2, 3, 4, and rapid eye movement [REM] sleep). Stages 1-4 are collectively called non-REM sleep (NREM). Adults usually cycle through the NREM stages in consecutive order and then into REM about every 90 minutes throughout sleep. REM periods get longer across the night, while stage 3 and 4 get shorter and occur primarily in the first half of the night. Stages of sleep are usually sustained in normal sleep architecture without frequent brief awakenings that characterize disturbed sleep.

The sleep report may contain a graphic representation of the stages of sleep across the night called a hypnogram. This is a visual representation of the sleep architecture. A neat stepwise graph reflects normal uninterrupted sleep while a ragged, comb-like appearance depicts disturbed sleep with frequent stage changes and awakenings (*see Figure 1*). This fragmented sleep is unlikely to be restorative. The general appearance of the hypnogram gives a quick impression of the amount of sleep as well as the degree of sleep disruption present. The numerical data represented by the hypnogram is usually provided in the sleep report (*see Table 1*).

Total Sleep Time

The total sleep time (TST) in minutes or hours must be reported (*see Table 1*). Typically patients are recorded for 8 hours and they will sleep between 6-8 hours. TST divided by the time in bed (TIB) is called the sleep efficiency, and it is expressed as a percent. A normal adult sleeper would be expected to have a sleep efficiency > 90% at home, but in the

Figure 1



The sleep architecture demonstrated in the top hypnogram (A) demonstrates a pattern of normal sleep stage progression across the night. The lower hypnogram (B) demonstrates a very disrupted pattern of sleep with frequent brief awakenings throughout the night.

laboratory > 80% may be considered good since sleep time in the laboratory is usually shorter and more disrupted than sleep at home. Sleep efficiencies greater than 95% are suspicious in adults. This may represent the effects of sleep deprivation due to insufficient sleep, idiopathic hypersomnia or possibly narcolepsy. An MSLT is useful in the differential diagnosis of these problems.

Reports should document an adequate amount of sleep time on the back and side, to evaluate a positional component in the diagnosis of sleep apnea. Often sleep apnea is worse in the supine position as the tongue lapses back to occlude the airway. In some patients, apnea may occur only in the supine position so an effective treatment option is simply a behavioral technique to avoid the supine sleep position (eg, use of a tennis ball in a back pocket at the mid-scapular level on a sleep shirt). If a patient always avoids a certain sleep position, then recording from that position is unnecessary.

Recent revisions by the Centers for Medicare and Medicaid Services (CMS) require a minimum of 2 hours of sleep time as a basis for computing the apnea and hypopnea index for sleep apnea.[1] (*See Table 2*.) Shorter sleep times can inflate the index—especially with sleep times of less than 1 hour. This CMS requirement primarily affects split night studies. To meet CMS requirements, the technician performing a split night study must accurately estimate whether 2 hours of sleep, not recording time, have occurred and judge whether there will still be adequate sleep time to titrate the patient.

Sleep Latency

Sleep latency is the time from lights out to the first 30-second epoch of scored sleep (sleep onset). Sleep latency must be interpreted in the context of the patient's sleep history and medication use. Sleep latencies longer than 30 min-

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utes warrant further investigation. A common cause of a long latency is situational insomnia due to difficulty sleeping in an unfamiliar laboratory setting. This is a likely explanation if the patient's sleep history or if sleep logs do not indicate a problem with sleep onset insomnia. If the patient's history does indicate chronic difficulty falling asleep, then physiological causes such as pain or restless legs may be identified from the sleep history. In the absence of an identifiable physiological cause for a long sleep latency as reported in the PSG and indicated in the sleep history, a diagnosis of psychophysiological insomnia is supported.

Latencies to other stages of sleep may be reported, and these are measured from sleep onset to the first epoch of that stage of sleep. Only the latency to stage REM is diagnostically useful. Normal REM latency is 90 minutes or longer in adults. Shorter REM latencies of 30-50 minutes are classic findings in untreated depressed patients.[2] Very short REM latencies (< 15 min) are common in narcolepsy patients and support the diagnosis.[3] However, a short REM latency may also be induced in otherwise normal individuals who are partially sleep deprived, depressed, or withdrawing from stimulant medication or alcohol. In these cases, the shortened REM latency is also accompanied by an increase in the percent of REM sleep, a phenomenon called REM-rebound. Whenever the REM percent is very high, REM-rebound should be suspected. A REM-rebound phenomenon must be excluded as an explanation for a shortened REM latency before attributing diagnostic meaning to it.

Sleep Stages

Sleep stages are determined for each 30 seconds of EEG activity based on standard scoring criteria.[4] The minutes and percent of stages 1-4 and REM are usually reported (*see Table 3*). The minutes of each stage are divided by the TST to give the percentage of each stage. The percentage of stages is more useful for comparison than sleep time, since it corrects for variations in TST. Normal sleep stage percentages vary with age. The percent of each sleep stage is useful in evaluating the degree of sleep disturbance and can help in the differential diagnosis of some sleep disorders.

Stage 1 is a transitional stage between wake and sleep. In normal sleepers it would comprise a few minutes of TST. The higher the percentage of stage 1, the more disrupted the patient's sleep. The cause of increased stage 1 is often due to repetitive sleep apnea episodes or leg movements that cause brief arousals or awakenings that are followed by a retransition to sleep.

Stage 2 sleep normally follows stage 1 sleep. Stage 2 occupies 50% or more of TST in adults. It is a "filler" stage that will decrease when other stages rebound or increase in their absence. The percent of stage 2 is not useful for diagnostic purposes or as an indication of sleep disruption.

Stages 3 and 4 are characterized by increasing delta waves in the EEG and are collectively called delta sleep or slow wave sleep (SWS). Delta sleep decreases dramatically with age and is often absent or minimal in normal sleepers older than age 40. In patients still capable of generating delta sleep, the presence of frequent arousals or awakenings, as occur in sleep apnea, may not allow enough time between awakenings for delta sleep to occur since it follows stage 2 sleep. With initiation of effective PAP treatment, arousals are eliminated and there may be a rebound of delta sleep during the titration night. In patients without frequent sleep disruptions, the amount of delta sleep is useful for diagnostic purposes since some parasomnias such as sleepwalking and night terrors only occur during stage 3 or 4. If there is little or no stage 3 or 4 recorded, parasomnias can be ruled out as the cause of abnormal behaviors during sleep.

The presence of REM sleep is very useful for diagnostic

Table 1. Summary of Sleep Parameters and Scoring of Sleep Stages in Polysomnograms Demonstrating Normal Sleep Architecture (A) and Disturbed Sleep Architecture (B)

Sleep Architecture (A)			**Sleep Architecture (B)**		
1. Total time in bed:		7.2 hr	Total time in bed:		6.6 hr
2. Total sleep time:		6.6 hr	Total sleep time:		5.2 hr
3. Sleep efficiency Index:		92%	Sleep efficiency Index		79%
4. Latency to sleep:		16 min	Latency to sleep:		3 min
5. Latency to REM onset:		100 min	Latency to REM onset:		210 min
6. Sleep time on back:		4.2 hr	Sleep time on back:		3.2 hr
7. Sleep time on side:		2.3 hr	Sleep time on side:		2.0 hr
8. Number of REM periods:		4	Number of REM periods:		2
9. Arousal Index:		8	Arousal Index:		19
Sleep Stage	**Min**	**%**	**Sleep Stage**	**Min**	**%**
Stage Wake	20	5	Stage Wake	72	17
Stage 1	16	4	Stage 1	220	52
Stage 2	215	54	Stage 2	101	24
Stage 3	25	6	Stage 3	0	0
Stage 4	44	11	Stage 4	0	0
Stage REM	78	20	Stage REM	27	6

Table 2. Requirements Adopted by the Center for Medicare and Medicaid Services for Coverage of CPAP Devices in Adults with Obstructive Sleep Apnea

The use of CPAP devices are covered under Medicare when ordered and prescribed by a licensed treating physician to be used in adult patients with obstructive sleep apnea. Obstructive sleep apnea will be covered under Medicare in adult patients with obstructive sleep apnea if either of the following criteria is met:

1. AHI = 15 events per hour, or

2. AHI = 5-14 events per hour with documented symptoms of excessive daytime sleepiness, impaired cognition, mood disorders or insomnia, or documented hypertension, ischemic heart disease, or history of stroke.

The AHI is equal to the average number of episodes of apnea and hypopnea per hour and must be based on a minimum of 2 hours of sleep recorded by polysomnography using actual recorded hours of sleep (ie, the AHI may not be extrapolated or projected). Apnea is defined as a cessation of airflow for at least 10 seconds. Hypopnea is defined as an abnormal respiratory event lasting at least 10 seconds with at least a 30% reduction in thorocoabdominal movement or airflow as compared to baseline and with at least a 4% oxygen desaturation. The polysomnography must be performed in a facility-based sleep study laboratory and not in the home or in a mobile facility.

purposes. REM sleep is physiologically different from NREM. REM sleep is characterized by muscular atonia (eg, paralysis of volitional muscles), irregular breathing, and hypoventilation that may result in lower oxygen values compared to wake. Due to these changes, the type of disordered breathing events may be different in REM (eg, central rather than obstructive apnea), the events may be longer, and the oxygen desaturation may be greater. In some patients, disordered breathing events may only appear in REM sleep. Baseline or diagnostic studies without REM sleep may miss the presence of sleep apnea or underestimate its severity. In addition, disorders such as petit mal epilepsy are activated by REM sleep, and REM behavior disorder only occurs during REM sleep. If however, a significant disorder can be documented without REM sleep, the recording of REM is not crucial. The percentage of REM sleep is typically around 20-25% in normal adults. However, dramatic increases (called REM-rebound), can be seen following withdrawal of REM-suppressant medications, recovery from sleep deprivation and during the initiation of PAP. REM sleep is often decreased when sleep is frequently disrupted.

Respiration

Data concerning sleep-related breathing disorders are usually of most concern. The 2 types of breathing events scored are apneas and hypopneas. Apnea refers to a complete cessation of airflow while hypopnea refers to a decrease in airflow. These are further defined as obstructive, central, or mixed events. In obstructive apnea events, there is continued respiratory effort without airflow. In central apnea events, there is an absence of respiratory effort and airflow. A mixed apnea event is a combination of central and obstructive apnea. Hypopneas may be similarly classified depending on the relationship between the decreased airflow and the amount of respiratory effort. There can be variations in the definitions of these terms between sleep programs, so definitions of the terms must be provided to accurately compare reports from different facilities.

Recently, CMS has adopted standardized definitions that are used to determine qualification for CPAP coverage for Medicare patients.[1] (*See Table 2*.) According to CMS recommendations, apnea is defined as a cessation of airflow for at least 10 seconds. Hypopnea is defined as an abnormal respiratory event lasting at least 10 seconds with at least a 30% reduction in thorocoabdominal movement or airflow as compared to baseline, and with at least a 4% oxygen desaturation. However, airflow and chest movement are usually measured qualitatively in the PSG; therefore, the percent of decrease in flow or effort depends on the judgment of the scorer and interpreting physician (scoring bias).

The total number and type of apneas and hypopneas scored should be included in the report. When the number of apneas and hypopneas is divided by total sleep time, the

Table 3. Summary of Scoring of Apneas and Hypopneas, Indices for Sleep Position and State, and Minimum Oxygen Saturation Levels by State

Respiration

Type of Apnea	# events	Apnea + Hypopnea Indices
Obstructive apneas	70	Apnea + Hypopnea Index/hr of sleep: 19
Mixed apneas	0	Apnea + Hypopnea Index on back: 38
Central apneas	1	Apnea + Hypopnea Index on side: 4
Hypopneas	28	Apnea + Hypopnea Index in NREM: 1
		Apnea + Hypopnea Index in REM: 23

Oximetry

Baseline Oxygen Saturation:	98%
Minimum Oxygen Saturation in NREM:	84%
Minimum Oxygen Saturation in REM:	75%

Table 4. Respiratory and Oximetry Data from a CPAP Titratio Study Report

Respiratory Events

		CPAP cm/H_20			
Type of Apnea	**Baseline Study**	**4**	**6**	**8**	**10**
Obstructive	70	11	26	20	0
Mixed	0	0	0	0	0
Central	1	0	2	2	0
Hypopnea	28	4	6	14	0

Apnea + Hypopnea Indices

		CPAP cm/H_20			
Apnea + Hypopnea Indices	**Baseline Study**	**4**	**6**	**8**	**10**
Apnea + Hypopnea Index	19	52	30	16	0
Apnea + Hypopnea Index on back	38	NA	35	18	0
Apnea + Hypopnea Index on side	4	52	20	11	0
Apnea + Hypopnea Index in REM	18	NA	NA	17	0
Apnea + Hypopnea Index in NREM	23	52	66	9	0
Total sleep time (hours)	5.2	.3	1.2	2.3	3.8

Oximetry

		CPAP cm/H20			
	Baseline Study	**4**	**6**	**8**	**10**
Baseline oxygen saturation	97%				
Minimum oxygen saturation in NREM	84%	78%	80%	88%	96%
Minimum oxygen saturation in REM	75%	na	na	84%	94%

Results from the previous baseline study are shown in the first column. Respiratory data show the number of apneas and hypopnea from the baseline study and each CPAP level in the titration study. The apnea + hypopnea index (AHI) for back and side sleep positions and REM and NREM are shown by PAP levels with total sleep time noted for each condition. Oximetry data show the minimum percent oxygen saturation at each CPAP level tested in REM and NREM sleep.

result is the Apnea Hypopnea Index (AHI). An index can be computed in the same way for each type of breathing event (*see Table 3*). An Apnea Index (AI) includes only apneas per hour of sleep while the Hypopnea Index (HI) is based on total hypopneas divided by total sleep time. The Respiratory Disturbance Index (RDI) is a term used in some reports, and it is generally considered the same as the AHI. However, the more general term "respiratory disturbance" may include other breathing irregularities in addition to apneas and hypopneas depending on the definition used by the laboratory. The indices are used as a measure of the severity of sleep apnea, with higher indices reflecting increasing severity.

Terms such as mild, moderate, or severe are not as useful as the actual index. In fact, no standards for mild, moderate, or severe exit. Since the effect of sleep-disordered breathing depends on factors other than the AHI (such as degree of sleep disturbance, amount of oxygen desaturation, and duration of sleep-disordered breathing events), it is simplistic to infer the severity of sleep-disordered breathing based on the AHI alone.

The use of an index controls for variations in number of events due to differences in TST and provides a more reliable measure for comparison. However, the index is extremely inflated when computed for sleep times less than 1 hour. CMS

Table 5. Multiple Sleep Latency Test

Nap time	Sleep Latency	REM Latency
0900	4.0 min	no REM
1100	2.0 min	6 min
1300	3.5 min	4.0
1500	1.5 min	no REM

Mean sleep latency: 2.8 min

Impression: The multiple sleep latency test indicates pathological daytime sleepiness associated with REM onset sleep suggestive of narcolepsy.

347—Narcolepsy

A Multiple Sleep Latency Test report showing sleep latencies and REM latencies from 4 naps. The test results are abnormal showing a mean sleep latency of 3 minutes and REM onsets in 2 naps.

requires a minimum of 2 hours of sleep before accepting an AHI for determining treatment coverage. Generally an AHI < 5 is considered within normal limits.

Apnea and hypopnea indices can be computed for sleep position (side or back) as well as sleep state (REM vs NREM) by counting events in each condition and dividing by the total sleep time for that condition. An AHI by position is useful for treatment purposes. If the index is > 5 on the back but < 5 on the side, techniques to help avoid back sleep can be extremely effective. By contrast, a REM-related AHI > 5 with a NREM index < 5 is not useful for treatment purposes as treatment cannot be confined to the REM state. A high REM index underscores the effect of differential control of breathing during REM and the associated atonia that results in loss of rib cage musculature to aid respiration. REM sleep occurring in the supine position usually results in the most severe apnea episodes, with the longest duration and the greatest oxygen desaturation.

Oxygen Saturation

Apnea and hypopneas can be associated with severe drops in oxygen saturation. The minimum oxygen saturation occurring during the night should be noted in the report. (*See Table 3*.) This value may be reported for the REM and NREM states independently. However, for treatment purposes, only the lowest value is needed. If oxygen during sleep falls below 88% at any time and is not associated with apneas or hypopneas, nocturnal oxygen administration may be warranted. Significant oxygen desaturation associated with apneas or hypopneas should be eliminated with effective PAP treatment in individuals without respiratory compromise. Treatment of any underlying pulmonary disease must be achieved before CPAP or oxygen therapy is initiated.

The CMS definition of hypopnea requires an associated drop of 4% or more in oxygen saturation. However, not all hypopneas are associated with oxygen desaturation. Some hypopneas produce arousals without oxygen desaturation. PAP treatment of hypopneas associated with arousals using CPAP is effective in eliminating disturbed sleep and daytime sleepiness. A definition of hypopnea that requires a degree of oxygen desaturation results in a lower reported AHI.

Arousals

Arousals refer to brief awakenings (≥ 3 seconds) during sleep. They typically occur at the termination of apnea events as the patient awakens to breathe. Arousals may also be triggered by events such as PLMS or they may occur spontaneously. Sleepiness increases as the number of arousals increase.[5-7] The sleepiness occurs even without changes in TST or stages of sleep.[8] The sleep fragmentation is considered the cause of excessive sleepiness regardless of the trigger for the arousal. The number of arousals per hour of sleep is computed and reported as the arousal index. (*See Table 1*.) Indices greater than 20 are generally considered elevated.

Cardiac Parameters

Cardiac information including rate, rhythm, and general morphology is collected during the sleep study. The cardiac rhythm during sleep is similar to wake although the heart rate is slower. Relative bradycardia and tachycardia (that may not be abnormal) typically occurs in association with apneas, with heart rate decreasing during the apnea and then increasing during the arousal that follows. Due to the slower heart rate during sleep and apnea events, escape beats are more likely to occur. Some patients may have cardiac arrhythmias or conduction disturbances only during sleep. These will be described in the sleep study report and may require further cardiac evaluation.

EEG Activity

Sleep can activate epileptiform discharges or seizures. However, epileptiform activity may be difficult to detect in the sleep study EEG recordings since typically only 2 EEG placements are used. If epilepsy is suspected, a full EEG montage should be performed and specified in the PSG order. Any EEG abnormalities noted in the study will be included in the sleep study report. Significant findings may require further neurologic evaluation, including a seizure-montage EEG, interpreted by a neurologist.

Diagnoses

Diagnostic impressions or provisional diagnoses are included at the end of the report. These are used in the context of all other clinical information, to make final diagnoses. Often patients will have more than 1 sleep diagnosis when sleep study findings and sleep history information are both carefully evaluated.

The list of diagnoses on the report may also include the corresponding ICSD and International Classification of Disease (ICD) codes. The ICSD lists more sleep disorders than the ICD, so some sleep disorders diagnoses will not have a corresponding ICD code. Codes for common sleep disorders, such as sleep apnea, are similar.

Treatment Recommendations

Treatment recommendations should be included with the

report. In sleep centers accredited by the American Academy of Sleep Medicine (AASM), all sleep study reports must include treatment recommendations. These may be found at the end of the report following diagnoses or in a separate summary letter to the referring physician.

Specialized Sleep Tests

Titration Studies

Titration reports for PAP or bilevel PAP include the same information as the baseline studies in addition to the AHI for the various pressures used from 4 to 20 cm/H_2O. (*See Table 4*.) Generally, the AHI decreases with increasing pressure. However, if pressure is raised too high for a patient, an increase in the AHI may occur. Generally, the pressure producing the lowest AHI is recommended for treatment, but this is not always the case. The pressure with the lowest AHI may not include supine sleep or REM sleep, the conditions when breathing problems are usually worse. If the baseline study indicated that the breathing problem was REM-related or only occurred in the supine position, then titration indices that include those periods are needed to determine the most effective pressure. PAP may not always eliminate all apneas and hypopneas, but the recommended pressure should result in an AHI less than 5. In some cases, the effective pressure may eliminate apneas and hypopneas but oxygen saturation may remain low. In these cases, supplemental nocturnal oxygen can be bled into the PAP mask and this may be also titrated during the sleep study. Information concerning supplemental oxygen will be included in the sleep study report.

Multiple Sleep Latency Test

Performance of MSLT is generally indicated when narcolepsy is suspected. It is not part of the routine evaluation of sleep apnea. The MSLT is used as an objective measure of daytime sleepiness and to aid in the diagnosis of narcolepsy. The MSLT is performed following a polysomnogram to assure that an adequate amount of normal sleep was obtained in the sleep period prior to the MSLT. In the MSLT, the mean sleep latency is determined from a series of naps and is used as a quantitative measure of sleepiness (*see Table 5*.)

The MSLT consists of 4-5 naps given 2 hours apart, beginning 1.5-3 hours after awakening. The MSLT requires the patient to lie down in a quiet, dark room and try to fall asleep. The patient is given 20 minutes to fall asleep or the nap is terminated. If the patient does fall asleep, the nap is terminated 15 minutes after sleep onset. The mean sleep latency is computed across all naps using 20 minutes if no sleep occurs in a trial. A mean sleep latency < 5 minutes is considered abnormal while a latency > 10 minutes is considered normal. Latencies between 5 and 10 minutes represent borderline pathological sleepiness. The cause of the sleepiness needs to be determined for latencies < 10 minutes. If no physiological cause can be found for latencies < 5 minutes then a diagnosis of idiopathic hypersomnia is made and stimulant medication is recommended.

The presence of REM sleep or latency to REM in each nap is also reported. If REM sleep occurs in 2 or more naps (REM onsets), a diagnosis of narcolepsy is supported. A final diagnosis of narcolepsy is made if the sleep history is also consistent with narcolepsy and other causes of REM onsets are ruled out. REM onset sleep is characteristic of narcolepsy, but the presence of REM in the MSLT is not always indicative of narcolepsy. REM onset sleep can also be caused by withdrawal of medications, sleep deprivation, depression, and disturbed nocturnal sleep, such as that caused by sleep apnea.[2,9] A preceding night study is used to document adequate sleep time without sleep-related physiological abnormalities to eliminate these as possible causes for the REM onsets. Medication use is documented and drug screens are often performed on the day of the MSLT to help assure an interpretable MSLT study. If other conditions are found that may produce REM onsets, the diagnosis of narcolepsy is uncertain. Consequently, strict guidelines are imposed on the patients and the procedure for the MSLT to assure validity for diagnostic purposes.

In some cases, the MSLT is used for objective documentation of the degree of daytime sleepiness when an underlying sleep disorder is known to exist. This commonly occurs when patients are involved in hazardous work activities that put them or others at risk due to job malperformance from sleepiness. Objective testing is needed since subjective estimates of sleepiness may be overestimated or underestimated and because the subjective estimates are not always related to objective measurements.[10]

Common Sleep Disorders

Narcolepsy

Narcolepsy is a usually inherited sleep disorder with symptoms typically beginning between 15 and 30 years of age.[11] Age of onset is useful in differentiating narcolepsy from sleep apnea. Narcolepsy is estimated to affect .02-.15% of the US population.[12,13] It is characterized by sudden attacks of irresistible sleepiness, cataplexy, sleep paralysis, and hypnogogic hallucinations. These symptoms may occur in varying combinations and severity. Some symptoms such as sleep paralysis and hypnogogic hallucinations may occur in individuals without narcolepsy, but cataplexy is believed to be specific. Very short naps of 10-20 minutes are usually extremely refreshing in narcoleptic patients and often consist of REM sleep. REM onset sleep periods occur because of impaired sleep-wake regulation rather than an excessive need for REM sleep.[14] This particular characteristic of narcolepsy is useful for diagnosis since the MSLT will often demonstrate REM onset sleep in 2 or more nap trials in narcoleptics. This finding, along with an appropriate clinical history, is the basis for diagnosing narcolepsy.

Patients with narcolepsy have a decrease in hypocretin (orexin) production as a result of decreased functioning in hypocretin-producing cells of the hypothalmus.[15,16] Activity of these cells are also associated with arousal and hunger.

Use of new drugs that selectively target the hypothalamus, such as a modafanil, have been found to be effective in narcolepsy without the side effects of amphetamine and without significant changes in sleep architecture. Modafanil affects specific cells in the hypothalamus rather than producing general activation throughout the brain.[17] Other common treatments

include amphetamines, methylphenidate, and pemoline.[18] Methylphenidate and dextroamphetamine, that have been shown to produce the most improvement in patients' alertness compared to modafanil, pemoline, protriptyline, ritanserin, and gamma-hydroxybutyrate.[19] Selegeline and modafanil have fewer adverse effects and less abuse potential than the amphetamine-containing compounds.[20-23]

Severe cataplexy may require additional treatment. Tricyclic antidepressants, such as imipramine, as well as serotonin reuptake inhibitors, such as fluoxetine and citalopram, have been found to be effective.[24] Roboxetine has been found to be effective for both excessive sleepiness and cataplexy.[25]

Although narcolepsy has a genetic basis and is HLA-DR2 linked, about one third of the general population has the "narcolepsy gene," which makes genetic testing useless for screening.

Insomnia

Insomnia without obvious physiological causes is called "psychophysiological insomnia." Psychophysiological insomnia is due to increased sympathetic arousal that is present throughout the 24-hour day.[26] The dysphoria of being hyperaroused throughout the day and night results in the insomnia symptom complex of "fatigue, tiredness, sadness, and general malaise" as well as accounting for the paradoxical inability to sleep despite being very tired. Treatment that focuses on decreasing activation only at bedtime may be ineffective in promoting sleep in a strong hyperaroused system or eliminating the subjective complaints associated with insomnia. In patients without strong hyperaroused systems, treatment with hypnotics such as benzodiazepines, zolpidem tartrate, or zeleplon, generally provide fast and effective short-term treatment but not long-term effectiveness. The use of cognitive behavioral therapy (CBT) including sleep hygiene, stimulus control, cognitive restructuring, and sleep restriction have longer response times than using sedating hypnotics but the effects are longer lasting.[27-29] Combined treatment of hypnotics and CBT is more efficacious in the short term, but not as good as CBT alone in the long term.

Shift work

An estimated 3 million Americans are involved in shift work.[30] When sleep time is altered so that sleep occurs during another part of the 24 hours cycle, there can be a misalignment of body rhythms. Alterations of the sleep wake cycle affect sleep and performance. Sleep time during the daylight hours is shorter by 2-4 hours with more awakenings compared to night sleep, even in permanent night shift workers.

Hypnotics and behavioral interventions can improve the amount and quality of daytime sleep. Typically, hypnotics with short or intermediate half lives such as temazepam, sonata, or ambien are used when sleep periods are initially shifted. This reduces the possibility of residual drug effects called "drug hangover" during the subsequent wake period. Nonpharmacological treatments are preferred long term. A 2-3 hour prophylactic nap prior to a nocturnal work shift significantly reduces sleepiness. Prophylactic naps in combination with caffeine at intervals during the work shift can maintain performance through the wake period.

Restless Legs Syndrome

The restless legs syndrome (RLS) is a common cause of sleep disturbances and affects an estimated 10-15% of the population.[31] The unpleasant sensory symptoms are typically described as a crawling or tingling sensation. It is temporarily relieved by moving the affected limbs. Symptoms usually occur at rest and commonly when an individual lays down to sleep. RLS contributes to long sleep latencies and can prolong awakenings during the night. This is reflected in a low sleep efficiency. RLS is diagnosed only through a sleep history. The underlying pathophysiology is not known, although it is believed due to an alteration in neuronal dopaminergic or opioidergiec pathways since treatment with opioidergic or dopaminergic agonists is often beneficial.[32-34] Mirapex and neurontin have become commonly used medications to treat RLS. Iron deficiency is associated with RLS, and iron replacement can improve symptoms of those patients with a low serum ferritin, so it is useful to screen for iron deficiency in RLS patients.[35]

Sleep Apnea

Sleep apnea refers to pauses in breathing during sleep. It is characterized by loud snoring, punctuated with pauses during the cessation of airflow. The prevalence of sleep-disordered breathing increases with age ranging from 5% to 25% in middle age to about 24% in healthy older adults.[36,37] In addition to age, the prevalence of sleep apnea and hypopnea is greater in individuals with hypertension, obesity, and other medical conditions including cardiac arrhythmias.

Obstructive apnea or hypopnea is due to a complete or partial collapse of the upper airway while central apnea reflects a loss of CNS stimulation causing an absence of diaphragmatic effort. The exact cause of the collapse or disruption in neural control is not known.

Individuals with sleep apnea often present with complaints of daytime sleepiness and loud snoring. A bed partner is often able to give an accurate account of witnessed apneas. On awakening, the patient often has a dry mouth and may experience morning headaches. Examination of the oral pharynx often reveals a crowded oral airway due to any number of factors including large tonsils and/or adenoids, thick or large tongue relative to the size of the oral cavity, narrowed opening between palatal pillars, long uvula, or soft palate.

A PSG is needed for diagnosis in patients presenting with symptoms of sleep apnea. The AHI indicates the frequency of the sleep-related respiratory events and is a measure of the severity of the sleep apnea along with the minimum oxygen saturation associated with events. Treatment is typically initiated with indices more than 5, but cardiovascular sequellae have been demonstrated with even lower levels of sleep-disordered breathing.[38]

The most common treatment recommended is PAP, including CPAP and BiPAP. PAP treatment requires that the patient undergo a titration study to determine the effective pressure. Other treatment options include surgery such as UPPP, LAUP, somnoplasty, hyoid advancement or the use of dental appliances to pull the lower jaw forward during sleep, thereby moving the tongue forward and increasing the clearance between the base of the tongue and the oral pharynx. If the apnea occurs only in the supine position, behavioral measures to avoid the supine posi-

tion are very effective. The use of a tennis ball sewn into a sleep shirt is a common recommendation but has never been subjected to rigid scrutiny and should not be recommended for people with significant sleep-disordered breathing or symptoms. In overweight patients, weight loss is recommended to reduce or eliminate sleep-related breathing problems as well as aid other treatments undertaken. Repeat sleep studies should be performed to evaluate the effectiveness of surgical interventions or dental appliances to treat sleep apnea. Surgical approaches have a success rate of less than 50% and were actually less effective than oral appliances in a recent head-to-head trial.[39]

Sleep Disorders Centers

Referral to a sleep disorder center is appropriate when sleep testing is needed and usually is valuable in the diagnosis and treatment of patients with challenging clinical symptoms. At sleep programs accredited by The American Academy of Sleep Medicine (AASM), an individual boarded in sleep medicine is required to review the raw data of every sleep study and provide diagnosis, interpretation, and treatment recommendations to the referring physician. Mechanisms for treatment and long-term follow-up are also available at accredited programs if needed.

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Physician CME Questions

56. Which of the following sets of apnea/hypopnea indices is indicative of position-dependent obstructive sleep apnea?
    a. AHI on back: 45; AHI on side: 54
    b. AHI on back: 19; AHI on side: 0
    c. AHI on back: 33; AHI on side: 49
    d. AHI on back: 39; AHI on side: 30

57. According to CMS recommendations, the AHI must be calculated based on a minimum of which one of the following hours of sleep time?
    a. 2
    b. 3
    c. 4
    d. 5

In Future Issues:

Identifying and Treating Seizures and Epilepsy—Michael D. Privetera, MD

PHARMACOLOGY WATCH

High-Dose Rofecoxib Confirmed Prothrombotic, Study Shows

Debate over the cardiovascular effects of COX-2 inhibitors has raged for more than a year since a special communication was published in *JAMA* last August (*JAMA*. 2001;286: 954-959) suggesting an increase in cardiovascular events with rofecoxib (Vioxx). As the argument goes, unlike nonselective NSAIDs, COX-2 inhibitors have no effect on thromboxane thus they do not inhibit platelet aggregation. However they do inhibit vascular prostacyclin—an effect that may be prothrombotic. Nonselective NSAIDs inhibit both thromboxane and prostacyclin. Whether COX-2 inhibitors are prothrombotic or merely lack the antiplatelet action of nonselective NSAIDs is at the crux of the debate. Now a large retrospect, the cohort study from the Tennessee Medicaid program seems to confirm the prothrombotic effects of rofecoxib, at least in high dose. Researchers from Vanderbilt University reviewed the records of 202,916 patients who did not use anti-inflammatories, 151,728 patients who used "other" anti-inflammatories, and 24,132 patients on rofecoxib over the 18 months between January 1999 and June 2001. Participants were between 50 and 84 years of age and had no life-threatening noncardiovascular illnesses. Users of high-dose rofecoxib (50 mg/d) were 1.7 times more likely than nonusers to have serious CHD (95% CI, 0.98-2.95; $P = 0.058$). Among new users of high dose rofecoxib, the rate increased to 1.93 (1.09-3.42, $P = 0.058$). There was, however, no increase risk of CHD with lower doses of rofecoxib or with use of other NSAIDs (*Lancet*. 2002;360:1071-1073). This study supports the hypothesis that high-dose COX-2 inhibition may be prothrombotic. This evidence is supported by a study in genetically engineered mice. Mice that lack the prostacyclin receptor (a defect that is similar to the effects of COX-2 inhibitors) overproduce thromboxane A2—and are likely to form arterial clots (*Science*. 2002;296:539-541). A recent "Clinical Implications of Basic Research" elegantly depicts the eicosanoid balance and the effects of these drugs on clotting (*N Engl J Med*. 2002;347:1025-1026).

Losartan Better Than Atenolol for LVH Treatment

Losartan is a better option than atenolol for treating isolated systolic hypertension in patients with left ventricular hypertrophy according to a new study. More than 1300 men and women with systolic hypertension and ECG evidence of LVH were randomized to treatment with losartan or atenolol with hydrochlorothiazide added as a second agent as needed. The main outcome measure was a composite end point of cardiovascular death, stroke, or myocardial infarction. After a mean of 4.7 years of follow-up, the main outcome was reduced by 25% with losartan compared with atenolol. There were 25.1 events per 1000 patients years in the losartan group vs. 35.4 in the atenolol group (relative risk [RR] 0.75; 95% confidence interval, 0.56-1.01; $P = 0.6$). There was no difference in the rate of myocardial infarction; however, cardiovascular mortality was significantly decreased in the losartan group as was nonfatal and fatal stroke. Total mortality was also significantly lower than the losartan group (21.2 vs 30.2 events per thousand patient-years; RR, 0.72; 95% CI, 0.53-1.00; $P = .046$). New onset diabetes was also significantly reduced in

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the losartan group, a finding that has been seen in other studies of ARBs. Losartan was also better tolerated than atenolol (*JAMA*. 2002;288:1491-1498).

Lisinopril, Not Losartan, Improves Myocardial Perfusion

In a related study of patients with hypertension and LVH, long-term treatment with lisinopril but not losartan improved myocardial perfusion in maximal coronary blood flow. In this small study, 17 patients with hypertension and LVH (9 treated with lisinopril, 8 treated with losartan) were evaluated with positron emission tomography at baseline and after coronary vasodilation with dipyridamole. The same studies were done on 8 normotensive control patients. After treating with lisinopril, maximal coronary blood flow and myocardial perfusion reserve increased significantly compared with pretreatment values ($P = 0.02$, and $P = 0.002$ respectively). Post-treatment hyperemic flow in patients treated with lisinopril was not significantly different from corresponding measurements and control patients. No difference in either measure was noted with losartan. The authors postulate that angiotensin converting enzyme inhibitors potentiate endogenous bradykinins, which in turn improve myocardial perfusion reserve. Losartan, like other angiotensin receptor blockers, has no effect on bradykinins, which may explain the lack of improvement in this measure. The authors postulate that ACE inhibitors may be more effective in repairing the coronary microangiopathy associated with hypertension-induced LVH (*J Am Coll Cardiol*. 2002;40:703-709).

New Fluoroquinolone Study

It seems that every year there is a new study linking antibiotic use with a reduction in coronary disease. The most recent is a Dutch study of Type 2 diabetics. Using a national hospitalization database from 8 cities, researchers found a significantly reduced risk of CHD in patients who had used at least 14 days of a fluoroquinolone in the 3-year study period (odds ratio = .30; 95% CI, 0.12-0.75). No other antibiotic was associated with a reduction in CHD including tetracyclines, macrolides, cephalosporins, or penicillin derivatives (*Eur Heart J*. 2002;23:1575-1579). And while the explanation for such improvement is still elusive, ongoing research is looking into the CHD/inflammation/infection connection.

Warfarin After MI Better Than Aspirin Alone

Warfarin, with or without aspirin, is better than aspirin alone in preventing vascular events after myocardial infarction according to a new study. In a randomized, multicenter trial, 1216 patients received warfarin (target INR 2.8 to 4.2), 1206 received aspirin 160 mg per day, and 1208 received aspirin 75 mg per day combined with warfarin (target INR 2.0 to 2.6). The mean duration of the study was 4 years and the primary outcome was a composite of death, nonfatal reinfarction, or thromboembolic cerebral stroke. The results showed a recurrence rate of 20% in the aspirin group (241 of 1206), 16.7% in the warfarin group (203 of 1216), and 15% in the combined warfarin in aspirin group (181 of 1208). The difference between the warfarin and warfarin/aspirin group was not statistically significant. There was a statistically significant increase in major, nonfatal bleeding in both warfarin groups compared to the aspirin group (0.62% vs 0.17%, respectively [$P < 0.001$]). The authors conclude that warfarin given alone or in combination with aspirin is superior to aspirin alone in reducing the incidence of composite vascular end points after myocardial infarction; however warfarin therapy is associated with a higher risk of bleeding. No difference in mortality was noted between the 2 groups (*N Engl J Med*. 2002; 347:969-974).

FDA News

Valacyclovir (Valtrex-GlaxoSmithKline) has been approved for the treatment of cold sores (herpes labialis). The approval was based on to studies that showed that valacyclovir 2 g twice a day for 1 day shortens the duration of cold sore outbreaks by about 1 day.

The FDA is one step closer two approving tiotropium (Spiriva-Boehringer Ingelheim), a new long-acting anticholinergic agent for the treatment of COPD. The drug was reviewed by the FDA's Pulmonary Allergy Drugs Advisory Committee and endorsed for the treatment of bronchospasm, however there was no support for the proposed indication of dyspnea.

The agency has strengthened its warnings on mefloquine (Larium-Roche) because of concerns of CNS side effects. Mefloquine is used in the treatment and prevention of malaria. The FDA specifically stated that mefloquine is contraindicated in patients with psychiatric disorders including active depression, recent history depression, generalized anxiety disorder, psychosis, schizophrenia, or other major psychiatric disorders, or with a history of convulsions. The FDA also warns that patients taking the drug for prophylaxis should discontinue it immediately if psychiatric symptoms should develop. Roche has recently issued a "Dear Dr. letter" regarding these warnings. ■

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MRC/BHF Heart Protection Study of Antioxidant Vitamin Supplementation in 20,536 High-Risk Individuals

Source: Heart Protection Study Collaborative Group. *Lancet*. 2002;360: 23-33.

Observational studies have indicated that intake of antioxidant vitamins (AOV), such as vitamins E, C, and beta-carotene, is inversely related to incidence of vascular disease. It has been postulated that this favorable relationship might be mediated, at least in part, through the demonstrated in vitro inhibition of LDL oxidation afforded by AOV. Oxidized LDL is known to be more atherogenic than native LDL. Though the positive potential for AOV benefits is intellectually appealing, want of a randomized, placebo-controlled interventional trial confirming AOV benefit has limited the enthusiasm of the scientific community. The Heart Protection Study Collaborative Group performed such a trial in the largest ever prospective randomized trial of antioxidants (n = 20,536).

Subjects in the trial were at high risk for vascular disease end points, since all had suffered either previous vascular morbidity or were diabetic. The AOV regimen was 600 mg vitamin E, 250 mg vitamin C, and 20 mg beta-carotene daily for 5 years.

There was no significant effect of AOV on any measured end point. To the contrary, there was a small increase in LDL and triglyceride levels in persons receiving AOV compared to placebo recipients. This study concluded that recommendation of AOV supplementation is not justified. ■

Prolonged Erections Produced by Dihydrocodeine & Sildenafil

Source: Goldmeier D, Lamba H. *BMJ*. 2002;324:1555.

Unless used concomitantly with nitrates, the clinical safety profile of the PDE5 inhibitor sildenafil has been generally very good. Another popular method of erectile dysfunction (ED) treatment, intracavernosal injection, has been associated not uncommonly with the adverse effect of priapism, but this adversity has been noted only in anecdotal case reports with sildenafil. Goldmeier and Lamba report on 2 cases of patients with prolonged erections associated with the combination of dihydrocodeine and sildenafil.

In case 1, a man treated for ED with sildenafil 100 mg had been achieving adequate erections that detumesced appropriately with orgasm. After a minor shoulder injury, for which he was prescribed dihydrocodeine 30 mg, administration of the same sildenafil dose resulted in an erection that persisted 5 hours post-ejaculation. Four days later the patient experienced a 4-hour erection with the same combination. Omission of the dihydrocodeine subsequently restored his previous pattern of appropriate detumescence.

Case 2 describes a patient receiving 100 mg sildenafil for psychogenic ED, who also received dihydrocodeine for soft tissue injury. During the first week of narcotic administration, the patient experienced erections persisting 2-3 hours postejaculation, but this effect disappeared in the next 2 weeks, despite continued concomitant sildenafil-opioid administration. Goldmeier and Lamba state that acute opiate intake heightened cyclic GMP concentrations, resulting in prolonged erections. They suggest that persons receiving sildenafil be cautioned regarding this potential interaction. ■

Effect of Magnesium Supplementation of Blood Pressure

Source: Jee SH, et al. *Am J Hypertens*. 2002;15:691-696.

Magnesium (MAG) participates in vascular tone and reactivity by its involvement in Na-K transport. Parenteral high-dose MAG has been shown to reduce blood pressure (BP) in eclampsia and glomerulonephritis. Whether dietary intake of magnesium effects BP in healthy populations remains uncertain, since interventional trials have produced conflicting results. Jee and colleagues performed a meta-analysis of interventional MAG supplementation trials (n = 20 trials, with 1220 total subjects) to seek further clarification of the relationship between MAG and blood pressure.

Overall, MAG supplementation reduced BP by 0.6/0.8 mm Hg. There was a dose-response relationship, however, with BP

reductions of 4.3/2.3 for each 10-mmol increase/day in MAG dose. This meta-analysis encourages the performance of an adequately powered interventional trial for ultimate confirmation of the potential role of MAG supplementation. ■

Homocysteine-Lowering Therapy with Folic Acid, Vitamins, and Clinical Outcome after Percutaneous Coronary Intervention

Source: Schnyder G, et al. *JAMA*. 2002;288:973-979.

HOMOCYSTEINE (HCST) HAS RECENTLY obtained substantial attention as a modifiable cardiovascular risk factor. Elevated levels of HCST have been associated with adverse cardiovascular outcome in a linear fashion, similar to cholesterol. It is suggested that elevations of HCST alter patterns of vascular smooth muscle cell growth and migration, endothelial function, lipoproteins, and coagulability. Hence, modification of HCST might favorably affect outcomes in high-risk CAD patients, such as those undergoing coronary angioplasty.

Schnyder and associates studied patients who underwent PCTA on at least 1 vessel for underlying stenosis > 50%, evaluating the effect of treatments known to reduce HCST: a combination of folic acid, vitamin B_{12}, and vitamin B_6. After PCTA, subjects were randomly assigned to the supplements or placebo, administered for 6 months. The primary study outcome was a composite of death, MI, and need for repeat revascularization for as long as 6 months after administration of the supplements.

At baseline, no patients had severe elevations of HCST, but mild-moderate increases were found in 29% of subjects. HCST-lowering therapy was associated with a risk reduction of 32% in the composite end point, mostly due to a 38% relative reduction in need for revascularization. This inexpensive multiple vitamin intervention holds promise in reducing cardiovascular risk among persons undergoing PCTA. ■

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Effect of Cataract Surgery on Motor Vehicle Accidents in Older Adults

Source: Owsley C, et al. *JAMA*. 2002;288:841-849.

OLDER ADULTS SUFFER VISUAL impairment due to cataract (CAT) more often than any other single cause. More than half of adults older than age 65 have cataract, which is slightly more frequent in African Americans. Retrospective reviews have shown that among older drivers, presence of CAT was associated with an increased frequency of a recent motor vehicle accident (MVA) when compared with persons free of CAT.

The per capita MVA rate in older licensed drivers (40/1000) is substantially less than in persons younger than 25 (140/1000), but this is largely a result of the many fewer miles driven by older persons than younger. Hence, the per-mile driven rate of MVA among older drivers is actually comparable to that of the highest risk younger drivers. Whether correction of CAT results in improvements of MVA risk was the subject of this report.

Owsley et al prospectively compared patients (n = 277) with CAT who underwent intraocular lens implantation after CAT excision to untreated CAT patients, followed 4-6 years. During follow-up, the MVA rate/million miles traveled in the surgically treated group was less than half that seen in the untreated group. Though the trial was not randomized, the data are highly supportive of the potential favorable effect of CAT surgery on highway safety. ■

Inflammatory Biomarkers, Hormone Replacement Therapy, and Incident Coronary Heart Disease

Source: Pradhan AD, et al. *JAMA*. 2002;288:980-987.

THE ROLE OF HORMONE REPLACEMENT therapy (HRT) in menopausal women is an area of current controversy, primarily due to the discordance between observational data that suggested cardiovascular benefits associated with HRT, and recently completed interventional trials that have shown increases in venous and arterial thrombotic end points early after HRT initiation. Among the possible mechanisms for deleterious effects of HRT upon cardiovascular risk, changes in C-reactive protein (CRP) and interleukin (IL-6) might play a role.

Pradhan and associates studied subjects from the Women's Health Initiative (n = 75,343) who had suffered an incident coronary heart disease event (n = 304). In their analysis, they compared CRP and IL-6 levels in persons with incident CHD vs. controls.

Although both baseline CRP and IL-6 were found to predict (independently) CHD events, only CRP levels were increased by the use of HRT. Comparatively, baseline CRP and IL-6 levels demonstrated greater effect on subsequent CHD events than did use or nonuse of HRT. Pradhan et al observe that it is the CRP level, rather than use of HRT, which is the primary determinant of subsequent risk for CHD events. ■