PRACTICAL POINTERS

FOR
PRIMARY CARE

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JUNE 2006

AMBULATORY BLOOD PRESSURE MONITORING A better estimate of risk in the individual

CYCLO-OXYGENASE-2 INHIBITORS AND TRADITIONAL NSAIDs Increase risk of atherothrombosis

LIFE WITHOUT COX-2 INHIBITORS Always offer acetaminophen first

SHOULD WE LOWER CHOLESTEROL AS MUCH AS POSSIBLE Adverse effects of stains are underreported. Benefits of high doses may be exaggerated.

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COFFEE MAY INDEED HELP KEEP YOU AWAKE FOR NIGHT DRIVING

ACE INHIBITORS INCREASE RISK OF CONGENITAL ABNORMALITIES EVEN WHEN GIVEN IN THE FIRST TRIMESTER.

SUPPOSE YOU COULD HAVE LIVED AT ANY TIME IN HISTORY When would it be? And why?

THE PATIENT'S JOURNEY: PALLIATIVE CARE—A parent's pain during her son's illness and death

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This document is divided into two parts

1) The **HIGHLIGHTS AND *EDITORIAL COMMENTS***

   HIGHLIGHTS condenses the contents of studies, and allows a quick review of pertinent points of each article.

   EDITORIAL COMMENTS *are the editor's assessments of the clinical practicality of articles based on his long-term review of the current literature and his 20-year publication of Practical Pointers.*

2) The main **ABSTRACTS** section is designed as a reference. It presents structured summaries of the contents of articles in much more detail.

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 5 years can be accessed at www.practicalpointers.org

Richard T. James Jr. M.D.
Editor/Publisher.

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HIGHLIGHTS AND *EDITORIAL COMMENTS* JUNE 2006

Better Estimate of Risk in the Individual

6-1 AMBULATORY BLOOD PRESSURE MONITORING

Our knowledge about risks of hypertension and the benefits of treatment is based on taking a small number of readings with the traditional auscultatory technique in a medical setting. Such measurements have been of enormous value on a population basis, but often provide a poor estimate of risk of an individual. This may be due in part because of poor technique of the observer, the "white coat" effect, and the inherent variability of blood pressure **(BP**).

Any clinical measurement of BP may be regarded as a surrogate measure for the "true" BP of the patient, defined as the mean level over prolonged periods.

Two techniques have been developed to improve the estimate of the "true" BP: 1) ambulatory BP monitoring (**ABPM**), and 2) home BP monitoring. Home monitoring may be used to supplant ABPM, but it is not included in most studies documenting the superiority of ABPM over traditional BP measurements.

This review considers ABPM only.

ABPM can provide: 1) the mean 24-h BP, 2) diurnal rhythm of BP, and 3) BP variability.

ABPM in other clinical conditions:

White coat hypertension

Labile BP

Resistant hypertension

Masked hypertension

Postural hypotension

Evaluating response to drugs

Predictions of clinical outcomes.

This is a concise, informative, and readable review. You may wish to read the full abstract and the original.

In my experience as a patient, determination of BP in doctor's offices is often done improperly. There may be little opportunity to relax before the BP is taken. Usually, only one determination is made, and the observer then states "Your blood pressure is X/Y " Accurate BP determinations are essential for the well being of all.

I believe many patients with "high blood pressure" receive drug therapy unnecessarily—mainly those with WCH. Home measurements will allow many patients to discontinue drugs.

Lifestyle interventions are essential in patients with WCH

I believe all patients with elevated BP should be monitored at home. Accurate automated machines are available of $100 or less. They provide easily repeated and reasonably accurate observations. Patients may fully relax and take several readings to obtain an average. They will help diagnosis of WCH. They will monitor response to therapy. In general practice, repeated home BP measurements are more revealing and practical than ABPM. Home BP may reduce number of doctor visits and pay for the machine.

If a machine is available at home, persons who do not have hypertension may check their BP once or twice a year. I would advise patients to avoid BP machines such as those available in pharmacies where readings may be similar to clinic readings.

ABPM should be reserved for special circumstances.

Monitors cost about $3000.

All, Except Possibly Naproxen, Carry Some Risk of Atherothrombosis.

6-2 DO SELECTIVE CYCLO-OXYGENASE-2 INHIBITORS AND TRADITIONAL NON-STEROIDAL ANTI-INFLAMMATORY DRUGS INCREASE THE RISK OF ATHEROTHROMBOSIS?

A Meta-analysis of Randomised Trials

. This meta-analysis included 138 randomized trials comparing selective COX-2 inhibitors versus 1) placebo, and 2) traditional non-selective NSAIDs. All studies included information about serious vascular complications (myocardial infarction [**MI**], stroke, and vascular death).

Selective COX-2 inhibitors vs placebo:

An increased risk associated with the former (1.2% per year vs 0.9% per year) [Absolute difference = 0.3%; NNT to harm one patient over 1 year = 333.]. This was chiefly attributed to an increase in risk of MI (0.6 per year vs 0.3 per year) with little apparent difference in other vascular outcomes.

"There was no significant heterogeneity among the different selective COX-2 inhibitors."

Traditional NSAIDs versus placebo:

	Rate ratio for vascular events
Naproxen vs placebo	0.92 (Ie, less risk than placebo)
Ibuprofen vs placebo	1.5
Diclofenac vs placebo	1.6

Selective COX-2 inhibitors vs traditional NSAIDs:

Overall, there was no significant difference in incidence of serious vascular events between 1) selective COX-2 inhibitors and 2) traditional NSAIDs—340 vascular events during over 33 000 person years of exposure to 1), and 211 vascular events in over 22 000 person-years of exposure to 2). [1% per person-years vs 0.9% per person-years.

Selective COX-2 inhibitors were associated with a 1.4-fold increased risk of serious vascular events largely due to a two-fold increase in myocardial infarction.

High doses of ibuprofen and diclofenac were associated with a similar increased risk.

High doses of naproxen were *not* associated with increased risk.

Traditional NSAIDs also inhibit the enzyme COX-2. If selective COX-2 inhibitors are associated with increased risk, it would seem reasonable to assume that traditional NSAIDs would also increase risk.

Do patients with higher baseline risks of MI have higher risk of MI associated with COX-2 inhibitors? If so, would not reduction of other risk factors (smoking, dyslipidemia, hypertension) reduce the risk of MI associated

with COX-2 inhibitors and higher-risk traditional NSAIDs? Would it be more dangerous to prescribe NSAIDS to these patients?

All NSAIDs except naproxen (Generic; Naprosin) carry risk of atherothrombotic disease, especially when used for long periods at high doses. We should not forget that NSAIDs have adverse effects on the kidney, blood pressure and heart (increasing risk of congestive failure).

I believe the widespread acceptance and use of COX-2 inhibitors is a tribute to the marketing skills of drug companies.

"Patients Should Always Be Offered Acetaminophen Before Resorting To Other Analgesics."

6-3 LIFE WITHOUT COX-2 INHIBITORS *Doctors Need To Broaden Their Approach To Pain In Older Patients*

Several selective COX-2 inhibitors have been withdrawn from the market. Use of others is being limited because of increased risk of myocardial infarction in long-term users.

"Have we lost a truly superior option? Probably not. Other pharmacological and non-drug options may be reasonably effective, equally safe, and less costly."

Acetaminophen (eg, *Tylenol*) offers effective and safe treatment for general musculoskeletal pain, including osteoarthritis. "Patients should always be offered acetaminophen at sustained doses before resorting to other analgesics." It has a relatively high safety margin except in overdose. It should be limited to 4 g daily, and less if the patient has liver disease or has high alcohol intake.

Opioids can be used as a last pharmacological resort. "Concerns about addiction are largely unfounded." Dependence—withdrawal symptoms if drugs are withdrawn—can be expected. "Fear of dependency and addiction is not sufficient justification to fail to relieve pain."

The editorialists comment on other pain-relieving measures: topical diclofenac; braces; exercise; glucosamine.

"Rather than lamenting the loss of COX-2 inhibitors—an intervention more popular than proved—we will best serve our patients by thinking creatively about other approaches to their pain." Presenting a menu of possible treatments and working with patients to choose those that best suit their lifestyle and health beliefs is the optimal way to find solutions to their chronic pain.

Some drugs are available combined with acetaminophen. Many variations are available allowing for personal choice. None offers complete relief. All have some degree of placebo effect.

I believe most older people with osteoarthritis pain accept, and live with some degree of discomfort. Many go on to consider joint injections and replacement therapy.

"Adverse Effects Of Statins are Underreported, and Benefits of Higher Doses May Be Exaggerated."

6-4 SHOULD WE LOWER CHOLESTEROL AS MUCH AS POSSIBLE?

The National Cholesterol Education Program suggests that persons at high risk of cardiovascular disease should be treated more aggressively. "Aggressive" means that LDL-cholesterol levels should be lowered to less

than 70 mg/dL (1.81 mmol/L). This recommendation, if strictly followed, would put most of the Western world's adult population on statin therapy.

These editorialists believe the benefit/risk ratio of more drastic lowering of LDL-c is not known. They question the wisdom of this advice. They believe the adverse effects of statins are underreported in clinical trials, and that benefits of higher doses may be exaggerated.

I believe patients and primary care clinicians have focused too exclusively on cholesterol levels, and consider it the major risk factor for cardiovascular disease, while ignoring other risk factors which are equally important.

Statins may reduce risk to a minor extent in smokers, but high risk remains. One might ask—what is the benefit of lipid control if the patient continues to smoke? The same applies to poorly controlled hypertension, diabetes, obesity (especially abdominal obesity), and sedentary lifestyle.

Conversely, for patients without risk factors other than LDL-c, I believe that lowering it to below 70 is not likely to materially improve prognosis unless LDL-c is excessively high.

Remember that most satins are metabolized in the liver by the cytochrome P450 system, and thus are liable for interactions with other drugs.

The adverse effects of statins are likely underreported. High doses are related to a greater number of adverse effects. I believe in a general rule: Adverse effects of drugs are more related to dose than to idiosyncrasy. Start with what is defined as the standard dose (or lower, especially in the elderly whose creatinine clearance gets lower with age, and in patients with renal and liver disease). If a standard dose does not result in the desired effect, adding a second and a third drug will likely be safer than increasing the dose of the first drug.

Cost is also an important factor. Patients should be told they can save hundreds of statin dollars yearly if they choose a low cost generic statin, buy a $3 pill cutter, and purchase the high dose pills and cut them to the desired dose. Statins have a high therapeutic index.

I also believe that generic statins (eg, Simvastatin) will provide about as much protection as other statins if other risk factors are treated at the same time and if the dose is adjusted.

We have also failed to fully implement dietary measure to control lipids.

"Caution in Lowering Diastolic Pressure in Hypertensive Patients with CAD."

6-5 CAN AGGRESSIVE LOWERING BLOOD PRESSURE IN HYPERTENSIVE PATIENTS WITH CORONARY ARTERY DISEASE BE DANGEROUS?

Several reports have shown that low diastolic BP (as well as high diastolic) is associated with an increased risk in patients with coronary artery disease **(CAD**). ("J-shaped curve".) *(Ie, when diastolic becomes very low, events may be more frequent. When diastolic becomes relatively normal, events may occur less frequently. When diastolic becomes high, events may again increase in frequency.)*

This relationship would apply especially to diastolic BP since the heart, in contrast to other organs, is perfused mainly during diastole. If the J-shaped curve does exist, it should be most evident in patients with limited coronary perfusion.

This was secondary analysis of over 22 000 patients enrolled in the International Verapamil -Trandolapril

Study (INVEST). All patients (mean age 66) had hypertension and CAD. All were clinically stable. All received either verapamil (*Generic*; a calcium blocker**)** or an atenolol (a generic beta-blocker) based strategy.

Diastolic BP:

Lower diastolic pressure (60 and under) led to an almost double to triple risk of primary outcomes.

The diastolic related to the least risk was between 70 and 90.

Those with diastolic of 70 and under made up only 1% of the cohort, but accounted for 20% of the primary outcome events.

Primary outcomes occurred in over 30% in those with diastolic 60 and under, and in about 35% of those with diastolic over 110. (Ie, risk increased as diastolic fell below 70, and rose as it increased above 90.)

Stroke incidence was not related to low diastolic.

For systolic pressure the J-shaped curve was much shallower.

The hazard ratios for the primary outcome showed a nadir (least risk) of 119/84.

Because perfusion occurs mostly during diastole, physiological features of myocardial perfusion are unique, and directly related to diastolic pressure. An inappropriately low diastolic pressure beyond a certain critical level could compromise myocardial perfusion.

A rapid pulse rate shortens diastolic time and perfusion. A slower pulse rate increases diastolic time and perfusion. Would not slowing the pulse rate be an additional indication for use of beta-blockers in some patients with CAD?

"Include A Regulatory Time Bomb"

6-6 THE FDA'S NEW LABELING REGULATIONS: Highlights and A Hidden Hazard

The FDA is trying to make the official descriptions (package inserts, or labeling) of prescription drugs—which are notoriously user-hostile—more helpful. Labeling constitutes the formal, government-approved definition of a drug's benefits and risks. They are written by the manufacturer and require FDA approval.

The FDA has announced new rules to go into effect on June 30, 2006. It is hoped that the changes will simplify the prescribing process for physicians, decrease medication errors, and improve patient safety. The new rules will require manufacturers to add a "highlights" section at the top of the label that summarizes key information about indications, risks, and doses.

The Hidden Hazard:

The most troubling aspect of the FDA's new plan has nothing to do with providing information to prescribers. The agency used the passage of the new labeling regulations to add quietly (without opportunity to debate) a new section to its preamble that will make it extremely difficult for anyone to bring legal action against a drug manufacturer for harm caused by one of its products which has been approved by the FDA.

I applaud this attempt at clarification. Seeking specific information about a drug in the fine print of the PDR can be irritating. All of us would welcome drug information presented in a more concise and easy-to-read labels, particularly regarding adverse effects.

I would be willing to wager that the "Hidden Hazard", the effort of a government agency in effect to change the law, will be overturned.

"At 12 Months, Only 25% Of The Original Sample Were Still Keeping Their Allocated Diets"

6-7 RANDOMIZED TRIAL OF FOUR COMMERCIAL WEIGHT LOSS PROGRAMS IN THE UK

The BBC "Diet Trials"

"Most adults in the United States diet at some time." Long-term success rates are poor.

This randomized unblinded trial considered 4 diets available in the UK vs a control group:

A. Dr Atkins' new diet revolution (a self-monitored low carbohydrate diet.)

B. Weight Watchers (an energy controlled diet with weekly group meetings.)

C. Slim-Fast (a meal replacement approach.)

D. Rosemary Conley's eat yourself slim diet and fitness plan (a low fat diet and a weekly group exercise class.)

All 4 diets resulted in about an equal weight loss over 6 months: (Intention-to-treat basis)

	Atkins	WW	Slim-Fast	Rosemary	Controls
Loss (kg)	6	7	5	6	Gain of 0.6 kg

People who kept their allocated diet lost about 10% of their weight despite some weight rebound. "These results provide information about the 'best effect' that the most highly motivated subjects may hope to achieve over one year. "

Would adopting a revolving diet plan (ie, switching from one to another after a month) benefit some people?

The only proven remedy for obesity is bariatric surgery.

Weight Gain Exacerbates Symptoms; Weight Loss May Improve Symptoms

6-8 BODY-MASS INDEX AND SYMPTOMS OF GASTROESOPHAGEAL REFLUX IN WOMEN

Gastroesophageal reflux disease (**GERD**), with hallmark symptoms of heartburn and acid regurgitation, affects up to 60% of persons some time during the course of a year, and up to 30% weekly.

This study explores more fully the relation between body mass index (BMI; weight in kg / square of the height in meters) and symptoms of GERD in women.

Of 10 545 women (mean age 66), 2310 (22%) reported having symptoms at least once a week.

Women who had frequent symptoms were more likely than women without symptoms to have a higher BMI, to have a higher daily caloric intake, and to be less active.

There was a dose-dependent relationship between increasing BMI and frequent reflux symptoms.

Odds ratio compared with "reference" BMI 20 to 22.4:

BMI	< 20	20-22.4	22.5-24.9	25 -27.4	27.5-29.9	30-34.9	$\geq$35

Odds ratio	0.67	1.00	1.38	2.20	2.43	2.35	2.93

Women with a BMI < 20 seemed to have some protections against symptoms.

Among women who gained weight during the previous 14 years, a dose-dependent increase in risk of symptoms was observed. Those gaining a BMI of 3.5 or more increased risk of frequent symptoms by more than a factor of two.

Among women who *lost* weight during the same period, there was a *reduction* in risk of symptoms. Those losing a BMI of 3.5 or more decreased risk of frequent symptoms by more than a factor of two as compared with women who had no change in BMI.

This may be helpful to some patients. I believe we can, with some assurance, tell patients with GERD that losing weight may be one factor that relieves symptoms

Lose Weight; Eat One Less Portion Of Meat Or Fish A Day; If You Drink, Drink Wine Instead Of Beer; Drink A Glass Of Skim Milk Daily.

6-9 DIAGNOSIS AND MANAGEMENT OF GOUT

Thirty clinical points. Read the full abstract.

L-ABAs Increase Severe Life-Threatening Asthma Exacerbations and Deaths.

6-10 EFFECT OF LONG-ACTING BETA-AGONISTS ON SEVERE ASTHMA EXACERBATIONS AND DEATH: *Meta-analysis*

Regular use of L-ABAs is associated with an adaptive response, with tolerance to the drug's effects, and a worsening of disease control.

This meta-analysis included 19 placebo-controlled trials (over 33 000 patients) that lasted at least 3 months. which included long-term use of two L-ABAs: salmeterol (*Advair; Serevent*) and formoterol (*Foradil*).

All trials permitted use of as-needed short acting beta-agonists, including the placebo groups. The trials therefore compared L-ABAs + short acting beta-agonists *vs* placebo + short-acting beta-agonists. Many patients were also receiving long-term inhaled corticosteroids.

Odds ratios L-ABAs vs placebo:

Severe exacerbations	2.6
Life-threatening exacerbations	1.8
Deaths	3.5

Difference in absolute terms (*My calculations from figure 2 and figure 3 page 908. RTJ*)

Hospitalizations	110/10 000 / year
Life threatening	15/10 000 / year

Asthma-related deaths: about 1 per 1000 person-years of life

Salmeterol is one of the most frequently prescribed medications in the world--an estimated 3.5 million users in the US. "This indicates that salmeterol may be responsible for about 4000 of the 5000 asthma-related deaths that occur in the United States each year."

Use of L-ABAs is widespread and frequent. Certainly, they give relief to many patients with asthma. I believe the message is not to discontinue regular use, but to monitor use more carefully.

Caffeine May Indeed Help To Keep You Awake

6-11 THE EFFECTS OF COFFEE AND NAPPING ON NIGHTTIME HIGHWAY DRIVING

Double-blind, randomized crossover study of 12 young adults, mean age 21. All had been driving for at least 2 years and drove between 10 000 and 20 000 km per year. None were professional drivers.

Compared effects on nighttime driving performance of 125 mL (half a cup of coffee) containing 200 mg of caffeine vs decaffeinated coffee (placebo) containing 15 mg caffeine given at 1:00 AM. Recorded inappropriate (center) line crossings by video during highway driving and compared self-rated fatigue and sleepiness.

Participants drove 125 miles one time between 6:00 PM and 7:30 PM (daytime reference condition); and two times between 2:00 AM and 3:30 AM (after placebo, and after caffeine). All drank the caffeine or the placebo 30 minutes before the nighttime drive.

Participants were instructed to maintain a constant speed of 80 miles per hour on a straight highway, and to drive in the center of the lane and not cross the painted lines.

After the intervention, participants returned to the laboratory to sleep and polysomnographic study.

Line crossings during daytime were infrequent. Line crossings at night after caffeine were equally infrequent. After placebo, line crossings at night were frequent.

Coffee containing caffeine at night reduced driving impairment without altering subsequent sleep.

Admittedly, a surrogate outcome, but, I believe a reasonable one. There must be a variation in response to caffeine between individuals. Some say that drinking caffeinated coffee in the evening keeps them awake. Some say no effect on sleep.

Angiotensin II Blockers as Well

6-12 ACE INHIBITORS AND CONGENITAL ABNORMALITIES

When ACE inhibitors (**ACE**; eg, *Captopril*; the prototype) are used in the second half of pregnancy, they can cause major congenital abnormalities. These effects result from blockade of conversion of angiotensin I to angiotensin II in the developing fetal kidneys. A similar pattern has been reported after treatment with angiotensin II- receptor-antagonists.

A study in this issue of NEJM reports that major congenital abnormalities may also occur if ACE are taken during the *first* trimester of pregnancy.

All drugs are foreign to the body. All drugs should be avoided in pregnancy. This essentially means that all women of child-bearing age should avoid drugs unless they are considered essential, or it is established without a doubt that they will not become pregnant. No tobacco; no alcohol; no drugs.

Almost half of all pregnancies are unintended.

Primary care clinicians must be among the major prescribers of ACE. Acting on this information may prevent a major catastrophe.

Suppose You Could Have Lived At Any Time In Human History. When Would It Be?

6-13 THE WESTERN MEDICAL TRADITION 1800 to 2000: *Book Review*

Suppose you could have lived at any time in human history. When would it be? The age of Pericles? The dawn of Christianity? Renaissance Europe? The Enlightenment? Victorian Britain? Take your pick.

A Canadian radio discussion of this possibility fell distinctly flat when all the panelists instantly agreed that our time is the best time to come into the world. The reason: modern health care and the capacity of the modern state to make it available to ordinary people.

The Western Medical Tradition 1800 to 2000 (Cambridge University Press, 2006) is authored by 5 editors associated with the *Wellcome Trust Centre for the History of Medicine.*

Read the full abstract or the original.

Adequate and Timely Communication with Patients Is One of the Great Lacks of the Medical Profession

6-14 THE PATIENT'S JOURNEY: PALLIATIVE CARE—A PARENT'S VIEW

This is an account of the pain a family endured during the painful illness and death of a son. Read the full abstract and the original article.

A mother, Stephanie, recounts the emotional struggle she, her family, and her 17-year old son Andrew endured during his extensive treatment and death from a brain tumor. They were finally told that the end was near. "Although the progress of the illness—the months of anxiety, hospital admissions, treatments, improvements, relapses—does to a certain extent prepare you for such news, it is difficult to describe the effect of it. I think crushing, stunning defeat after a prolonged painful struggle sums it up. And, of course, it is the end of all hopes for recovery when treatment stops and palliative care takes over."

So what did the experience of the son's last weeks show the mother?

It would have been good to have someone in overall charge of palliative care.

It would have been useful to discuss all possible options and contingencies for palliation.

The philosophy of acceptance is not enough for siblings. Attempts to prepare the sisters were insufficient. Preparation should have been started earlier with professional help.

Despite the excellent medical care and loving nursing the cancer unit offered, dying in such a unit is not the best choice if one has a choice.

Palliative care in the community offers an extra option for the last weeks of a child's life. This is especially beneficial to families with terminally ill children, enabling the child to remain at home in familiar surroundings and with the people who love them most.

I sensed that the family, at last, did achieve a degree of peace.

Church and clergy were not mentioned. Hospice was not mentioned. Those of us who have suffered the loss of a loved one with the help of church and Hospice care know how supportive and reassuring they are.

I wonder why greater pain relief could not have been accomplished at home. I believe most families can be taught to administer morphine safely.

Communication1 Communication! Communication! Adequate and timely communication with patients is one of the great lacks of the medical profession. The family did not have access to a specific person (eg, a primary care clinician) who knew the situation and could act immediately to counsel and support. Their support was fragmented.

ABSTRACTS JUNE 2006

Better Estimate of Risk in the Individual

6-1 AMBULATORY BLOOD PRESSURE MONITORING

Our knowledge about risks of hypertension and the benefits of treatment is based on taking a small number of readings with the traditional auscultatory technique in a medical setting. Such measurements have been of enormous value on a population basis, but often provide a poor estimate of risk of an individual. This may be due in part because of poor technique of the observer, the "white coat" effect, and the inherent variability of blood pressure **(BP**).

Any clinical measurement of BP may be regarded as a surrogate measure for the "true" BP of the patient, defined as the mean level over prolonged periods.

Two techniques have been developed to improve the estimate of the "true" BP: 1) ambulatory BP monitoring (**ABPM**), and 2) home BP monitoring. Home monitoring may be used to supplant ABPM, but it is not included in most studies documenting the superiority of ABPM over traditional BP measurements.

This review considers ABPM only.

ABPMs are typically programmed to take readings every 15 to 30 minutes throughout day and night. Readings are then downloaded into a computer. Approved devices are usually accurate to within 5 mm Hg of readings taken with a mercury sphygmomanometer.

ABPM can provide: 1) the mean 24-h BP, 2) diurnal rhythm of BP, and 3) BP variability.

1) Mean 24-h BP:

Currently, clinical guidelines exist for estimating only mean BP levels. The daytime level considered the upper limit of normal is 135/85, corresponding to the clinic level of 140/90. Cardiovascular risk appears to increase markedly above these thresholds.

2) Diurnal rhythm:

Subjects with normotension can have a pronounced diurnal rhythm of BP. It falls to its lowest level during the first few hours of sleep. There is a marked surge in the morning hours during the transition from sleep to wakefulness. The average difference between the two is 10 to 20 percent. Nighttime BP can be assessed only by ABPM. Patients with hypertension usually have the same pattern, but the diurnal profile of BP is set at a higher level. A failure of BP to fall at night may be associated with an adverse prognosis.

3) BP variability:

There are several ways of measuring variability: beat to beat, and changes over weeks or months. ABPM can yield only a crude estimate of the true variation of BP other than sleep as compared with wakefulness. The clinical significance of variability is not known.

ABPM in other clinical conditions:

A. White coat hypertension (**WCH**): This is the only indication for ABPM approved for reimbursement by Medicare. Suspected WCH is defined as a clinic BP of 140/90 or higher on at least 3 occasions, with at least 2 sets of measurement of less than 140/90 in non-clinic settings—plus the absence of target-organ damage. This

diagnosis is important because it is generally accepted that patients with WCH are at relatively low risk and are unlikely to benefit from anti-hypertension drug therapy. Several studies have shown that drug therapy of WCH reduces the clinic BP, but has a negligible effect on the ambulatory BP, which by definition is normal. Sustained hypertension may develop in some patients with WCH, and the risk of stroke may increase after 6 years. Long-term follow-up with repeated ABPM or home monitoring is essential. Although ABPM is expensive, its role in the diagnosis of WCH is invaluable, and may reduce health costs.

B. Labile BP: This is something of a misnomer, since all hypertension is labile. ABPM may be helpful in monitoring BP in some patients with a history of paroxysmal hypertension. Pheochomocytoma may be suspected. (Although the elevated BP in this condition is not always labile.) Panic attacks are a much more common cause.

C. Resistant hypertension: An exaggerated white coat effect may be suspected in patients with clinic hypertension which remains high despite taking 3 or more drugs. Some of these patients may have normal ambulatory BP, and a benign prognosis. They likely could be identified by home BP monitoring.

D. Masked hypertension: Is the reverse of white coat hypertension. Clinic BP is normal and ambulatory BP is high. One study reported that, over a 5-year period, the risk of cardiovascular events in these patients was double that of patients with adequately controlled hypertension. “The prevalence of masked hypertension in the general population could be as high as 10%.” However, the role of ABPM for diagnosing masked hypertension is uncertain.

E. Postural hypotension: Is not uncommon in older patients. Patients become dizzy and may faint when standing for long periods. Their BP is unusually labile. When supine, the BP may be high, particularly during the night. Treatment with vasopressor drugs and antigravity stockings is a compromise between permitting the BP to go too low, and making it go too high. ABPM is essential in evaluating optimal control in these patients.

F. Evaluating the response to drug treatment: ABPM is not commonly used in routine clinical practice for evaluating response. It is inconvenient to make repeated recordings, and cost is high. (*Home BP measurements are helpful for evaluating response*.)

G. Predictions of clinical outcomes: The general findings of studies indicates that ABPM predicts cardiovascular events better than clinic BP. Regression of left ventricular hypertrophy is more closely associated with changes in ambulatory BP than clinic BP. It is not certain which component of the 24-hour profile gives the best prediction of risk. The most widely used predictor has been the 24-hour mean.

Most patients find ABPM acceptable. It is typically performed on a work-day, when the BP is often higher than when the patient stays at home. Use is gradually increasing. ABPM can be regarded as the gold standard for prediction of risk related to BP. “A good case can be made for using this technique in all patients in whom hypertension has been newly diagnosed by means of clinic blood pressure measurements.”

NEJM June 1, 2006; 354: 2368-74 Review Article, “Current Concepts”, first author Thomas G Pickering, Columbia Presbyterian Medical Center, New York.

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All, Except Possibly Naproxen, Carry Some Risk of Atherothrombosis.

6-2 DO SELECTIVE CYCLO-OXYGENASE-2 INHIBITORS AND TRADITIONAL NON-STEROIDAL ANTI-INFLAMMATORY DRUGS INCREASE THE RISK OF ATHEROTHROMBOSIS?

A Meta-analysis of Randomised Trials

The anti-inflammatory effects of non-steroidal anti-inflammatory drugs (**NSAIDs**) are believed to be mediated by inhibition of the enzyme cyclo-oxygenase-2 (**COX-2**). COX-2 is induced by inflammation. It results in the febrile-aching aspect of inflammation. The COX-1 enzyme is protective. It largely protects the stomach against adverse effects of NSAIDs.

The selective COX-2 inhibitors (selective NSAIDs) were developed, hypothesizing that selective inhibition of COX-2, leaving the protective effects of COX-1 intact, would provide a safer alternative to traditional NSAIDs.

Studies have reported a lower incidence of upper gastrointestinal complications with selective cyclo-oxygenase-2 inhibitors. Recent concern about their cardiovascular safety has limited use.

Several questions remain unanswered: 1) What is the magnitude of the excess risk of myocardial infarction, stroke, and vascular mortality due to NSAIDs? 2) Is the excess risk dose-related? 3) Are traditional NSAIDs (which inhibit both COX-1 and COX-2) associated with increased risks of vascular events?

This meta-analysis assessed the risk of NSAIDs, both selective COX-2 inhibitors, and traditional NSAIDs on risk of vascular events.

Conclusion: Selective COX-2 inhibitors are associated with a moderate increase in risk of vascular events. High doses of the traditional NSAIDs (ibuprofen and diclofenac) are also associated with an increase in risk. Naproxen is not.

STUDY

1. Meta-analysis included 138 randomized trials compared selective COX-2 inhibitors versus 1) placebo, and 2) versus traditional non-selective NSAIDs. All studies included information about serious vascular complications (myocardial infarction [**MI**], stroke, and vascular death).
2. Selective COX-2 inhibitors vs placebo:

   An increased risk associated with the former (1.2% per year vs 0.9% per year) [Absolute difference = 0.3%; NNT to harm one patient over 1 year = 333.]. This was chiefly attributed to an increase in risk of MI (0.6 per year vs 0.3 per year) with little apparent difference in other vascular outcomes.

   "There was no significant heterogeneity among the different selective COX-2 inhibitors."
3. Traditional NSAIDs versus placebo:

	Rate ratio for vascular events
Naproxen vs placebo	0.92 (Ie, less risk than placebo)
Ibuprofen vs placebo	1.5
Diclofenac vs placebo	1.6

4. Selective COX-2 inhibitors vs traditional NSAIDs:

   Overall, there was no significant difference in incidence of serious vascular events between 1) selective COX-2 inhibitors and 2) traditional NSAIDs—340 vascular events during over 33 000 person years of

exposure to 1), and 211 vascular events in over 22 000 person-years of exposure to 2). [1% per person-year vs 0.9% per person-year.

5. Dose: There was sufficient data to assess a dose-response to celecoxib (*Celebrex*) only. There was a significant trend toward an increased incidence of serious vascular events with higher doses.

DISCUSSION

1. Selective COX-2 inhibitors were associated with a 1.4-fold increased risk of serious vascular events largely due to a two-fold increase in myocardial infarction.
2. Some investigators have suggested (on the basis of survival curves) that the hazard emerges only after a year or 18 months. Long-term exposure may be associated with increased risks.
3. Traditional NSAIDs also inhibit the enzyme COX-2. *(If selective COX-2 inhibitors are associated with increased risk, it would seem reasonable to assume that traditional NSAIDs would also increase risk RTJ.)*
4. High dose ibuprofen (*Generic; Motrin*); 800 mg three times daily), and high dose diclofenac (75 mg three times daily) were each associated with increased risk. High dose naproxen (*Generic*; 500 mg twice daily) was associated with substantially smaller risk.
5. In absolute terms, selective COX-2 inhibitors were associated with about 3 extra vascular events per 1000 per year. The annual excess incidence associated with full compliance would be expected to be higher. (Many patients discontinued therapy early.)

CONCLUSION

Selective COX-2 inhibitors were associated with a moderate increase in vascular events, largely due to an increased risk of myocardial infarction.

High doses of ibuprofen and diclofenac were associated with a similar increased risk.

High doses of naproxen were *not* associated with increased risk.

BMJ June 3, 2006; 332: 1302-05 Original Meta-analysis, first author Patricia M Kearney, University of Oxford. UK

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"Patients Should Always Be Offered Acetaminophen Before Resorting To Other Analgesics."

6-3 LIFE WITHOUT COX-2 INHIBITORS

Doctors Need To Broaden Their Approach To Pain In Older Patients

Several selective COX-2 inhibitors have been withdrawn from the market. Use of others is being limited because of increased risk of myocardial infarction in long-term users.

"Have we lost a truly superior option? Probably not. Other pharmacological and non-drug options may be reasonably effective, equally safe, and less costly."

COX-2 inhibitors rose to market prominence on the basis of studies showing less gastrointestinal tract ulceration on endoscopy. "However, ulceration is neither intrinsically harmful, nor a surrogate marker for harm

associated with use of NSAIDs." Gastroduodenal damage found on endoscopy does not lead, in most patients, to the serious effects of bleeding, perforation and obstruction. The presence of gastroduodenal ulcers is not related to symptoms of dyspepsia. Many ulcers are asymptomatic. Patients with dyspepsia associated with drug treatment often do not have signs of mucosal damage.[1]

"The common assumption that COX-2 inhibitors are safer than other NSAIDs has not been borne out."

If older people with pain need NSAIDs, misoprostol (*Cytotec)*[2], reduces NSAID-induced gastric injury and is effective in preventing serious adverse effects. It should be offered as co-treatment to patients at high risk. Histamine-2 antagonists and proton pump inhibitors are not consistently effective at preventing serious adverse effects,

Diclofenac used topically offers short-term pain relief for knee arthritis.

Acetaminophen (eg, *Tylenol*) offers effective and safe treatment for general musculoskeletal pain, including osteoarthritis. "Patients should always be offered acetaminophen at sustained doses before resorting to other analgesics." It has a relatively high safety margin except in overdose. It should be limited to 4 g daily in adults and less if the patient has liver disease, or has a high alcohol intake.

Opioids can be used as a last pharmacological resort. "Concerns about addiction are largely unfounded." Dependence— symptoms if drugs are withdrawn—can be expected. "Fear of dependency and addiction is not sufficient justification to fail to relieve pain." Low potency opioids such as dextropropoxyphene (*Darvon*) and tramadol (Generic; *Ultram*) offer little analgesic advantage over acetaminophen.

Non-drug options: Braces—unloader braces which bend knees outward from the midline (valgus position) and therapeutic taping are effective in relieving pain. Exercise—may reduce hip and knees pain while improving function.

"Dietary supplements": Glucosamine sulfate is superior to placebo in treatment of osteoarthritic pain.

"Rather than lamenting the loss of COX-2 inhibitors—an intervention more popular than proved—we will best serve our patients by thinking creatively about other approaches to their pain." Presenting a menu of possible treatments and working with patients to choose those that best suit their lifestyle and health beliefs is the optimal way to find solutions to their chronic pain.

BMJ June 3, 2006; 332: 1287-88 Editorial, first author Allen F Shaughnessy, Tufts University, Boston, Mass.

1 *I believe the editorialists are too dismissive of the potential harms of traditional NSAIDs. It takes only one major upper-gi hemorrhage to cause havoc.*

2 A synthetic prostaglandin analogue which inhibits gastric acid production.

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"Adverse Effects Of Statins are Underreported, and Benefits of Higher Doses May Be Exaggerated."

6-4 SHOULD WE LOWER CHOLESTEROL AS MUCH AS POSSIBLE?

"Statins are portrayed as harmless drugs that almost everyone would benefit from, but little is known about the side effects at the high doses now being suggested."

The National Cholesterol Education Program suggests that persons at high risk of cardiovascular disease should be treated more aggressively. “Aggressive” means that LDL-cholesterol levels should be lowered to less than 1.81 mmol/L (70 mg/dL). This recommendation, if strictly followed, would put most of the Western world’s adult population on statin therapy.

These editorialists believe the benefit/risk ratio of more drastic lowering of LDL-c is not known. They question the wisdom of this advice.

A recent trial[1] reported that even 80 mg of atorvastatin (*Lipitor; Caduet*) was unable to lower mean LDL-c below 70 mg/dL. Atorvastatin 80 mg was associated with a greater increase in adverse events, withdrawals, and increased liver enzymes.

Another large trial[2] (secondary prevention) of 1) atorvastatin 80 mg vs 2) simvastatin 20 mg over 5 years, reported no statistically significant reduction in major coronary events. And adverse events leading to discontinuation of 9.6% vs 4.2%

“Clinical experience has taught us that a dose increase of that size of any drug will inevitably increase both the number and seriousness of side effects.”

The authors suggest that statin therapy (especially high dose) may increase incidence of myalgia and rhabdomyolysis, liver dysfunction, heart failure, mental and neurological symptoms, and cancer. (*With no references and little information other than comment. RTJ*)

They believe the adverse effects of statins are underreported in clinical trials, and that benefits of higher doses may be exaggerated. High doses may not be related to lowering mortality.

BMJ June 3, 2006; 332: 1330-32 Editorial, first author Uffe Ravnskov, Lund, Sweden.

1 “ Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease” NEJM 2005; 352: 1425-35

2 “High Dose Atorvastatin vs Usual-dose Simvastatin for Secondary Prevention after Myocardial Infarction” JAMA 2005; 294: 2437-45

The editorial staff of BMJ makes the interesting comment at the end of the editorial that three of the authors have argued in the scientific press that high cholesterol is not the cause of atherosclerosis and coronary disease Nevertheless, I believe their comments have merit.

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“Caution in Lowering Diastolic Pressure in Hypertensive Patients with CAD.”

6-5 CAN AGGRESSIVE LOWERING BLOOD PRESSURE IN HYPERTENSIVE PATIENTS WITH CORONARY ARTERY DISEASE BE DANGEROUS?

Several reports have shown that low diastolic BP (as well as high diastolic) is associated with an increased risk in patients with coronary artery disease **(CAD**).. (“J-shaped curve”.) *(Ie, when diastolic becomes very low, events may be more frequent. When diastolic becomes relatively normal, events may occur less frequently. When diastolic becomes high, events may again increase in frequency.)*

This dichotomy may “leave a clinician with the uncomfortable choice of whether to prevent stroke or renal disease at the expense of coronary heart disease”.

Some authorities consider the J-shaped curve a real possibility. This relationship would apply especially to diastolic BP since the heart, in contrast to other organs is perfused mainly during diastole. If the J-shaped curve does exist, it should be most evident in patients with limited coronary perfusion.

This study assessed whether low BP could be associated with excess mortality and morbidity in patients with CAD.

Conclusion: The risk of all-cause death and myocardial infarction **(MI**) progressively increased as diastolic BP became lower (below 70). There was no adverse effect on risk of stroke.

STUDY

1. This was secondary analysis of over 22 000 patients enrolled in the International Verapamil -Trandolapril Study (INVEST). All patients (mean age 66) had hypertension and CAD. All were clinically stable.
2. All patients received either verapamil (a generic calcium blocker) or an atenolol (a generic beta-blocker) based strategy.
3. BP goals were: < 140/90 (or <130/85 if the patient had diabetes or renal dysfunction)—the Joint National Committee recommendations. Trandolapril or hydrochlorothiazide could be added when necessary to reach target BP.
4. Assessed patients periodically until the last patient enrolled was followed for 2 years. (Median = 2.7 years / patient.)
5. Evaluated the relationship between average on-treatment BP and risk for the primary outcome (all-cause death, non-fatal MI, and non-fatal stroke).

RESULTS

1. Over 2250 patients (10%) had a primary outcome.
2. Systolic BP:
   - There was a shallow J-shaped curve for systolic BP. The lowest point for the fewest outcomes was 120 mm Hg. Incidence rose slightly as pressure declined to 110, and as pressure rose to 160 and above. Risks increased dramatically from 180 to 220.
3. Diastolic BP:
   - Lower diastolic pressure (60 and under) led to an almost double to triple risk of primary outcomes.
   - The diastolic related to the least risk was between 70 and 90.
   - Those with diastolic of 70 and under made up only 1% of the cohort, but accounted for 20% of the primary outcome events.
   - Primary outcomes occurred in over 30% in those with diastolic 60 and under, and in about 35% of those with diastolic over 110. (Ie, risk increased as diastolic fell below 70, and rose as it increased above 90.)
   - Stroke incidence was not related to low diastolic.
4. The hazard ratios for the primary outcome showed a nadir (least risk) of 119/84.

DISCUSSION

1. “Clearly, the diastolic J-curve was much more pronounced than the systolic J-curve.”
2. Because perfusion occurs mostly during diastole, physiological features of myocardial perfusion are unique, and directly related to diastolic pressure. An inappropriately low diastolic pressure beyond a certain critical level could compromise myocardial perfusion.
3. As in the Framingham study, pulse pressure (systolic minus diastolic) was a powerful determinant of risk of the primary outcome in INVEST. When pulse pressure was added to the diastolic pressure model, pulse pressure plus diastolic BP was significantly associated with the primary outcome.[1]
4. These findings indicate that in this sample of patients, diastolic pressure below 70 could potentially be harmful.
5. Patients who had coronary revascularization seemed to tolerate lower diastolic pressures relatively better than those without revascularization.
6. Both INVEST drug strategies have been shown to protect the heart, perhaps because they reduce heart rate, prolong diastole, and (at least for verapamil) may have a direct effect in dilating the coronary arteries. Antihypertension medications which increase heart rate (and shorten length of diastolic filling of the coronary arteries) may have the potential to compromise myocardial perfusion.
7. “Although elevated systolic pressure, one of the most powerful risk factors for stroke and MI, remains undertreated in many patients, our data suggest caution in lowering diastolic pressure in hypertensive patients with CAD.”
8. The Joint National Committee in 2003 noted that “patients with occlusive CAD are put at risk for coronary events if diastolic blood pressure is low”.

Annals Int Med June 30 2006; 144: 884-93 Original investigation, first author Franz H Messerli, St Luke’s-Roosevelt Hospital, New York

1 As diastolic falls and systolic is stable, pulse pressure automatically increases.

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“Includes A Regulatory Time Bomb”

6-6 THE FDA’S NEW LABELING REGULATIONS: Highlights and A Hidden Hazard

The FDA is trying to make the official descriptions (package inserts, or labeling) of prescription drugs—which are notoriously user-hostile—more helpful. Labeling constitutes the formal, government-approved definition of a drug’s benefits and risks. They are written by the manufacturer and require FDA approval.

Package inserts are lengthy listings of drug indications, effects, and associated risks that are routinely included with medications when they are shipped to pharmacies. They are just as routinely discarded before the drug is dispensed. Physicians are more likely to see the labeling in the fine print of *The Physician’s Desk Reference* (PDR).

The FDA now admits what most clinicians have known for decades: the current labeling is poorly organized; it is studded with often irrelevant information; it may include an important fact about safety in any number of places (“warning” “adverse effect” “precaution”) .

The FDA has announced new rules to go into effect on June 30, 2006. It is hoped that the changes will simplify the prescribing process for physicians, decrease medication errors, and improve patient safety. The new rules will require manufacturers to add a "highlights" section at the top of the label that summarizes key information about indications, risks, and doses.

The revised format will be required for new medications. Drugs already on the market will have 3 to 7 years to implement the changes. Most products approved before mid-2001 will not have to modify their labels at all.

"There is not much evidence that a revised label format will have much of an effect on patient safety, despite the FDA's claims." Data on risks included in the official label often lag by as much as several years—a reflection on the FDA's problem with post-marketing surveillance and of manufacturer's reluctance to accelerate the inclusion of new data about side effects. "Studies of the effects of printed warnings on practice show that physicians frequently prescribe drugs despite important contraindications, even when spelled out in the label."

"Ultimately, the most attractive and best-organized labels will not influence behaviors if physicians do not read them."

The Hidden Hazard:

The most troubling aspect of the FDA's new plan has nothing to do with providing information to prescribers. The agency used the passage of the new labeling regulations to add quietly (without opportunity to debate) a new section to its preamble that will make it extremely difficult for anyone to bring legal action against a drug manufacturer for harm caused by one of its products which has been approved by the FDA. After the comment period for the new labeling regulations had closed, language was added which would preempt nearly all action against drug manufacturers for unanticipated injuries resulting from use of their products. This immunity would apply even if a company failed to warn prescribers or patients adequately about a known risk, unless a patient could prove that the company intentionally committed fraud—a very hard test to meet.

"In other words, along with the very modest alterations of drug labeling to be phased in over the next seven years, the changes the FDA will begin implementing . . . include a regulatory time bomb that could severely limit the accountability of companies that fail to adequately evaluate or report the risks associated with their products."

"Court challenges are likely."

NEJM June 8, 2006; 354: 2409-11 "Perspective", Commentary, first author Jerry Avorn, Harvard Medical School, Boston, Mass.

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"At 12 Months, Only 25% Of The Original Sample Were Still Keeping Their Allocated Diets"

6-7 RANDOMIZED TRIAL OF FOUR COMMERCIAL WEIGHT LOSS PROGRAMS IN THE UK

The BBC "Diet Trials"

"Most adults in the United States diet at some time." Long-term success rates are poor, with 50% of the weight loss being regained within one year.

Commercial diets provide consumers with a plethora of choice.

This study (231 patients) compared 4 popular commercial weight loss programs available in the UK with a control group.

Conclusion: Clinically useful weight loss can be achieved in adults who are motivated to follow the diets for a substantial period.

STUDY

1. Randomized unblinded trial considered 4 diets available in the UK vs control group:
   A. Dr Atkins' new diet revolution (a self-monitored low carbohydrate diet.)
   B. Weight Watchers (an energy controlled diet with weekly group meetings.)
   C. Slim-Fast (a meal replacement approach.)
   D. Rosemary Conley's eat yourself slim diet and fitness plan (a low fat diet and a weekly group exercise class.)
2. Determined changes in weight over 6 months.
3. Described dieting behavior and weight change at 12 months.

RESULTS

1. All 4 diets resulted in about an equal weight loss over 6 months: (Intention-to-treat basis)

	Atkins	WW	Slim-Fast	Rosemary	Controls
Loss (kg)	6	7	5	6	Gain of 0.6 kg

2. Waist circumference decreased by 6 to 8 cm.
3. Glucose concentrations fell over time, but only in the WW group was fasting glucose significantly lowered. Blood pressure fell slightly.
4. About ¼ of participants had withdrawn at 6 months.
5. At 12 months, only 58 participants (25%) of the original sample were still keeping their allocated diets. More participants in the two unsupported diets (Atkins and Slim-Fast) withdrew, and their weight rebound was greater after 6 months

DISCUSSION

1. Clinically beneficial weight loss is possible through commercially available strategies.
2. The range of absolute weight loss in participants who completed the study was wide. Compliance with each diet varied greatly.
3. Currently, we cannot predict the dietary approach best suited to each person, but it is clear that "one size does not fit all".
4. Behavior from 6 to 12 months points toward an advantage of programs based on group support.
5. People who kept their allocated diet lost about 10% of their weight despite some weight rebound. "These results provide information about the 'best effect' that the most highly motivated subjects may hope to achieve over one year. "

BMJ June 3, 2006; 332: 1309-11 Original investigation, first author Helen Truby, University of Surry, UK.

Weight Gain Exacerbates Symptoms; Weight Loss May Improve Symptoms

6-8 BODY-MASS INDEX AND SYMPTOMS OF GASTROESOPHAGEAL REFLUX IN WOMEN

Gastroesophageal reflux disease (**GERD**), with hallmark symptoms of heartburn and acid regurgitation, affects up to 60% of persons some time during the course of a year, and up to 30% weekly.

This study explores more fully the relation between body mass index (BMI; weight in kg / square of the height in meters) and symptoms of GERD in women.

Conclusion: BMI is associated with symptoms GERD in both normal-weight and overweight women. Even a moderate weight gain among persons of normal weight may cause or exacerbate GERD.

STUDY

1. A supplement of the Nurses' Health Study, in 2000, asked over 10 000 women about frequency, severity, and duration of symptoms of heartburn and acid regurgitation; 2310 (22%) reported they had symptoms at least once a week. Of these, the majority considered the symptoms as moderate or severe.
2. Categorized women according to BMI as measured in a previous study done in 1998. A 1980 questionnaire was used to obtain participant's weight at age 18.
3. Determined the association between BMI and symptoms of GERD.
4. Used BMI of 20 to 22.4 as the reference population.
5. Excluded women with symptoms less frequent than weekly in order to improve specificity of the study.
6. Evaluated the effect of weight change on symptoms by calculating the change in BMI between age 18 and 1998.

RESULTS

1. Of 10 545 women (mean age 66), 2310 (22%) reported having symptoms at least once a week.
2. Women who had frequent symptoms were more likely than women without symptoms to have a higher BMI, to have a higher daily caloric intake, and to be less active.
3. There was a dose-dependent relationship between increasing BMI and frequent reflux symptoms.

   Odds ratio compared with "reference" BMI 20 to 22.4:

BMI	< 20	20-22.4	22.5-24.9	25 -27.4	27.5-29.9	30-34.9	≥35
Odds ratio	0.67	1.00	1.38	2.20	2.43	2.35	2.93

4. Women with a BMI < 20 seemed to have some protections against symptoms.
5. Among women who gained weight during the previous 14 years, a dose-dependent increase in risk of symptoms was observed. Those gaining more than 3.5 increased risk of frequent symptoms of more than a factor of two.
6. Among women who *lost* weight during the same period, there was a *reduction* in risk of symptoms. Those losing a BMI of 3.5 or more decreased risk of frequent symptoms by more than a factor of two as compared with women who did not lose weight.

7. Findings did not vary significantly when dietary factors (such as citrus, onions, tomatoes, other fruits and vegetables, and total fat) were included in the model.

DISCUSSION

1. "We found a strong positive association between BMI and symptoms of GERD in a large cohort of women. This association extended across all categories of BMI from 'normal' to overweight." "This suggests that moderate amounts of weight gain, even among normal-weight persons, may result in the development or exacerbation of symptoms of gastroesophageal reflux disease."
2. The association was not altered significantly after controlling for multiple potential confounding variables.
3. A similar dose-response relationship was observed for both frequent and infrequent symptoms, nocturnal symptoms, and all degrees of severity and duration of symptoms.
4. Weight gain was associated with an increase in risk. And weight loss was associated with a decrease in risk.

CONCLUSION

Symptoms of GERD rise progressively with increasing BMI among normal weight persons.
Even moderate weight gain may cause or exacerbate symptoms of GERD
Notably, weight loss was associated with a decrease in risk.

NEJM June 1, 2006; 354: 2340-48 Original investigation, first author Brian C Jacobson, Boston University School of Medicine, Boston Mass

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Lifestyle Changes Are Basic

6-9 DIAGNOSIS AND MANAGEMENT OF GOUT

- Podagra—literally "foot catch".
- Gout is much more common in men. Incidence increases with age.
- The clinical syndrome arises from deposition of urate crystals in joints, where they cause inflammation. Maximum inflammation develops within one day.
- Deposition in soft tissues also occurs, but does not cause inflammation there.
- Crystals deposit when the serum becomes saturated with urate, a breakdown product of purine metabolism.
- Gout occurs only when serum is saturated with urate—concentrations greater than 0.42 mmol/L (7.0 mg/dL). But, only a minority of people with hyperuricemia develop gout. Even when urate concentration reaches 10 mg/dL, the annual incidence of gout is only 6%.
- The most commonly affected joints are in the extremities. Urate is more likely to deposit in cooler parts of the body.
- Most patients with idiopathic gout have a genetically reduced renal excretion of urate. Decreased

excretion alone does not usually lead to hyperuricemia.

- Many other factors affect urate concentrations—meat, fish, alcohol (particularly beer—not wine), obesity, weight gain, drugs (eg, diuretics), and diseases associated with increased purine turnover.
- Gout is usually diagnosed by clinical features—plus hyperuricemia.
- In the acute situation, it is reasonable to treat patients with suspected gout as if they had gout.
- Inadvertent treatment for gout is unlikely to be problematic.
- Hyperuricemia is associated with increased cardiovascular risk. Patients with gout should be screened for cardiovascular risk factors.

Treatment of acute attacks

- Acute gout usually resolves within 7-10 days, even without treatment.
- After an initial attack, patients may be without symptoms for years. Some attacks are more frequent.
- Few develop chronic tophaceous gout.
- Serum urate may fall during an acute attack. A normal urate at this point does not rule out gout.
- NSAIDs (specifically indomethacin) are the most popular treatment for acute gout.
- Colchicine is popular therapy in some countries. Diarrhea and vomiting may occur before pain relief.
- Corticosteroids are effective therapy. Occasional short courses of oral steroids may be preferable to NSAIDs and colchicine because of a lower incidence of adverse effects.
- Applications of ice, elevation, and rest may be helpful.
- Urate lowering drugs should not be started during an acute attack.

Prophylactic treatment

- Asymptomatic hyperuricemia does not require treatment.
- For most people with occasional gout, risks of prophylactic treatment probably outweigh the benefits. Urate lowering drugs are usually needed only for patients with frequent attacks.
- An NSAID should be prescribed for the first 3 months of urate lowering treatment to prevent a rebound increase in acute gout.
- The target for urate lowering is 0.36 mmol/L (6.0 mg/dL), well below the level at which urate crystallizes.
- Allopurinol (*Generic*) a xanthine oxidase inhibitor, has been the mainstay of preventive therapy. Dose may be titrated up to 900 mg/d to achieve serum urate concentrations below 6.0 mg/dL.
- Some patients cannot tolerate allopurinol, especially those with renal impairment. A potentially fatal hypersensitivity syndrome has been reported.
- Sulfinpyrazone, (*Generic*) a uricosuric, increases excretion of urate, but increases risk of stone formation. It is not suitable for patients with renal impairment.
- Lifestyle changes are basic:

  Lose weight

Eat one less portion of meat or fish a day

If you drink, drink wine instead of beer

Drink a glass of skim milk daily. Low fat dairy is protective.

BMJ June 3, 2006; 332: 1315-19 Clinical Review by Martin Underwood, University of London, UK

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L-ABAs Increase Severe Life-Threatening Asthma Exacerbations and Deaths.

6-10 EFFECT OF LONG-ACTING BETA-AGONISTS ON SEVERE ASTHMA EXACERBATIONS AND DEATH: *Meta-analysis*

Inhaled corticosteroids are first choice maintenance therapy for asthma. For patients whose condition is not adequately controlled by inhaled corticosteroids alone, the addition of long-acting beta agonists (**L-ABAs**) is recommended. Prior studies reported that L-ABAs can improve control of symptoms and reduce the risk of exacerbations.

However, there is controversy. L-ABAs may increase the risk for fatal and non-fatal asthma complications.. Regular use is associated with an adaptive response, with tolerance to the drug's effects, and a worsening of disease control.

A large study reported early in 2006 reported a four-fold increase in asthma-related deaths associated with the L-ABA salmeterol therapy. However, life-threatening and fatal asthma deaths were relatively rare—2 per 1000 patient-years of salmeterol use.

An FDA advisory panel recently concluded that a strong warning of increased risk should be placed on the labeling of all L-ABAs.

The objective of this meta-analysis was to more precisely assess the effect of L-ABAs on severe asthma exacerbations, life-threatening attacks, and deaths.

Conclusion: L-ABAs increase severe life-threatening asthma exacerbations and deaths.

STUDY

1. Meta-analysis included 19 placebo-controlled trials (over 33 000 patients) that lasted at least 3 months which included long-term use of two L-ABAs: salmeterol (*Advair; Serevent*) and formoterol (*Foradil*)
2. All trials permitted use of as-needed short acting beta-agonists, including the placebo groups. The trials therefore compared L-ABAs + short acting beta-agonists *vs* placebo + short-acting beta-agonists. Many patients were also receiving long-term inhaled corticosteroids.
3. Determined odds ratio (compared with placebo) of severe exacerbations requiring hospitalization, life-threatening exacerbations requiring intubation and ventilation, and asthma–related deaths.

RESULTS

1. Odds ratios L-ABAs vs placebo:

Severe exacerbations 2.6

Life-threatening exacerbations 1.8

Deaths 3.5

2. Difference in absolute terms (*My calculations from figure 2 and figure 3 page 908. RTJ*)

Hospitalizations 110/10 000 / year

Life threatening 15/10 000 / year

3. Asthma-related deaths: about 1 per 1000 person-years of life.

4. No significant difference between salmeterol and formoterol.

DISCUSSION

1. L-ABAs increased risks of hospitalizations, life-threatening attacks, and deaths among adults and children.

2. Inhaled corticosteroids partially protect against adverse effects of beta-agonists. But, even when used concomitantly with corticosteroids, regular beta-agonist use results in substantial tolerance over time. The FDA has required a strong warning when salmeterol is used with or without inhaled corticosteroids.

3. Salmeterol is one of the most frequently prescribed medications in the world--an estimated 3.5 million users in the US. "This indicates that salmeterol may be responsible for about 4000 of the 5000 asthma-related deaths that occur in the United States each year."

4. African Americans may be at especially high risk.

5. Absent L-ABAs, inhaled corticosteroids and inhaled anticholinergics agents would be the main options for treatment of asthma.

6. Treatment with inhaled anticholinergic drugs results in bronchodilation and protection against bronchoconstriction without evidence of tolerance over time. It is associated with a 15% improvement in asthma symptoms and a 7% increase in peak flows compared with placebo.

7. Inhaled beta-agonists are also widely used in COPD, although inhaled anticholinergics such as ipratropium have been shown to have equal or superior efficacy. A recent meta-analysis of patients with COPD found that inhaled anticholinergics reduced respiratory deaths by 70% while inhaled beta-agonists increased deaths by more than 2-fold compared with placebo.

CONCLUSION

L-ABA use increases the risk of hospitalization, life-threatening exacerbations, and death from asthma.

Annals Int Med June 20, 2006; 144: 904-12 Meta-analysis, first author Shelly R Salpeter, Santa Clara Valley Medical Center, San Jose, California.

An editorial in this issue (pp 936-37) by Jeffrey Glasroth, Tufts University School of Medicine, Boston Mass. asks—Considering all the available data, what should physicians do?

1. Use inhaled corticosteroids as first line treatment for patients with mild to moderate persistent asthma symptoms. Do not use L-ABAs as initial therapy for any asthma patient.
2. Systemic corticosteroids may be used for exacerbations.
3. For patients who do not achieve at least good control (defined as minimal daily or nocturnal symptoms and

infrequent exacerbations requiring systemic corticosteroids or emergency department visits):

A. Escalate dose of inhaled corticosteroids alone.

B. Escalate dose of inhaled corticosteroids combined with L-ABAs. The combination may result in greater rate and level of control than inhaled corticosteroids alone, and permit a lower dose of inhaled corticosteroid.

C. Patients must be carefully monitored to identify those who are not responsive, or whose condition deteriorates in response to L-ABA therapy.

D. If L-ABAs fail, the physician should withdraw the drug either abruptly or by tapering (some uncertainty on this point). Be prepared to provide an alternative if the L-ABA fails. An anticholinergic has theoretical appeal based on suggestive data that African-Americans (who are the most disadvantaged by adverse effects of L-ABAs) may respond better to anticholinergics than other groups. This is based on their genotype which predisposes to less favorable control by L-ABAs and more favorable response to anticholinergics.[This may be a foretaste of pharmacogenomic profiling which will tailor drug therapy to the individual.]

E. An especially vexing problem is the African-American patient who is not controlled by maximum doses of inhaled corticosteroids alone. It seems reasonable then to add an anticholinergic.

L-ABAs are powerful and complex medications that must be used with care even as we await additional information to help refine the decisions to use them.

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Caffeine May Indeed Keep You Awake.

6-11 THE EFFECTS OF COFFEE AND NAPPING ON NIGHTTIME HIGHWAY DRIVING

"Sleep-related accidents represent up to 20% of all traffic accidents." Driving between 2:00 and 5:00 AM increases risk of accidents by a factor of 6. Many people repeat this dangerous behavior because of economic rewards. The age group most often involved is 18 to 25.

Epidemiologic studies report that 65% of sleep-related accidents occur after inappropriate highway line crossings.

Countermeasures include napping and awakening agents such as caffeine.

This study tested effect on driving of coffee containing caffeine vs decaffeinated coffee on nighttime driving performance. The study also tested the effect of napping.

Conclusion: Both caffeinated coffee and napping[1] at night reduced driving impairment.

STUDY

1. Double-blind, randomized crossover study of 12 young adults, mean age 21. All had been driving for at least 2 years and drove between 10 000 and 20 000 km per year. None were professional drivers.
2. Compared effects on nighttime driving performance of coffee containing 200 mg of caffeine vs decaffeinated coffee (placebo) containing 15 mg caffeine given at 1:00 AM

3. Compared self-rated fatigue and sleepiness; recorded inappropriate (center) line crossings by video during highway driving.
4. Participants drove 125 miles one time between 6:00 PM and 7:30 PM (daytime reference condition); and two times between 2:00 AM and 3:30 AM (after placebo, and after caffeine). All drank the caffeine or the placebo 30 minutes before the nighttime drive.
5. Participants were instructed to maintain a constant speed of 80 miles per hour on a straight highway, and to drive in the center of the lane and not cross the painted lines
5. After the intervention, participants returned to the laboratory to sleep and polysomnographic study.

RESULTS

1. Line crossings:	% of participants
Daytime 0 to 1 crossings	75%
Nighttime 0 to 1 crossings after caffeine	75%
Nighttime 0 to 1 crossings after placebo	13%

(Ie, after caffeine, nighttime line crossings were similar to daytime crossings.)

2. Rate ratio of line crossings after placebo (compared with after caffeine) was 3.7.
(Ie, risk was much lower when participants drank caffeine.)
3. Sleep latencies and efficiency were similar (after driving and return to laboratory) between caffeine and placebo.
4. Self-evaluation of sleepiness at the wheel was lower in the caffeine group compared with the placebo group

DISCUSSION

1. There was a significant increase in line crossings during nighttime driving compared with daytime driving when subjects drank the placebo.
2. Caffeine significantly reduced inappropriate line crossing at nighttime.

CONCLUSION

Coffee containing caffeine at night reduced driving impairment without altering subsequent sleep.

Annals Int Med June 6, 2006; 144: 785-91 Original investigation, first author Pierre Philip, Clinique du Sommeil, Bordeaux, France.

1 I omitted the data on napping. It resulted in a benefit equal to that of caffeine.

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Angiotensin II Blockers as Well

6-12 ACE INHIBITORS AND CONGENITAL ABNORMALITIES

When ACE inhibitors (**ACE**; *Captopril*; the prototype) are used in the second half of pregnancy, they can cause major congenital abnormalities including fetal growth retardation, pulmonary hypoplasia, joint contractures,

neonatal renal failure, and death. These effects result from blockade of conversion of angiotensin I to angiotensin II in the developing fetal kidneys. A similar pattern has been reported after treatment with angiotensin II-receptor-antagonists (the "sartans"; eg, losartan) drugs that block the system at a different point.

In this issue of NEJM[-1] a study reports that major congenital abnormalities may also occur if ACE are taken during the first trimester of pregnancy. Of over 200 children whose mothers had taken ACE during the first trimester (but not later in the pregnancy), 9% had major congenital abnormalities. This rate was 3 times that of over 29 000 unexposed children.

Ten ACE are availably in the USA. Over 42 million prescriptions are written each year. Almost no data are available regarding possible teratogenic risks in humans at the time when most new drugs receive FDA approval. A system of voluntary reporting of adverse effects is notoriously inefficient.

Therapeutic doses of 8 antihypertension drugs are considered unlikely to pose a substantial teratogenic risk (hydrochlorothiazide, chlorothiazide, chlorthalidone, atenolol, acebutolol, pindolol, nifedepine, and reserpine.) But each has other adverse effects.

NEJM June 8, 2006; 354: 2498-2500 Editorial by J M Friedman, University of British Columbia, Canada.
1 NEJM June 8, 2006; 354: 2443-51 "Major Congenital Abnormalities after First-Trimester Exposure to ACE Inhibitors", first author William O Cooper, Vanderbilt University School of Medicine, Nashville, TN

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Suppose You Could Have Lived At Any Time In Human History. When Would It Be?

6-13 THE WESTERN MEDICAL TRADITION 1800 to 2000: *Book Review*

Suppose you could have lived at any time in human history. When would it be? The age of Pericles? The dawn of Christianity? Renaissance Europe? The Enlightenment? Victorian Britain? Take your pick.

A Canadian radio discussion of this possibility fell distinctly flat when all the panelists instantly agreed that our time is the best time to come into the world. The reason: modern health care and the capacity of the modern state to make it available to ordinary people.[1]

"Yes, today's children are menaced by deadly new viruses, by weapons of mass destruction and global warming, by drug companies wanting to hook them on pills for daily living, by doctors who sometimes do more harm than good, and by feckless and predatory politicians." Nonetheless, the fact is that, if you were to come alive in the past, the chances are that you would die at a young age, probably of infectious disease. If you survived infancy you would have to work grindingly hard most days of your life. You would be malnourished. Your body would give out. Even if you survived to reach retirement, your old age would be a short wait in death's departure lounge.

If you are born today into any one of about half of the nation states in the world, the odds are that you will have the opportunity to live 80 years or more, and you will live most of those years in physical comfort. "In most of the world, especially the 'west', life is no longer nasty, brutish, and short." "We often fail to see and celebrate our past achievements because we are so anxious for more progress that we keep on raising the bar of our

expectations. We declare the present intolerable. In health care we see nothing but shortcomings, problems, and new challenges." [2]

"We seldom get into the mind set that celebrates how full the glass has become in western countries, mostly thanks to the achievements of modern medicine."

The Western Medical Tradition 1800 to 2000 (Cambridge University Press, 2006) is authored by 5 editors associated with the *Wellcome Trust Centre for the History of Medicine* who "sometimes seem not to appreciate that they are writing one of history's great success stories".

"The scope of the global medical enterprise in our time has been so great and complex that it almost overwhelms." [3]

Given all our social injustice, [4] all our desire for a better world, and all the shortcomings of the western medical tradition, the present is much better for most people because of our historical determination to blend science and human art and idealism in bettering our health.

"Most of us, if pressed, would confess that our own lives have already been saved, or at least made more comfortable, by doctors, drugs, or both." [5]

Lancet June 24, 2006; 367: 2051-52 "Perspectives, book review and commentary by Michael Bliss, University of Toronto, Canada.

1 Obviously not the only, or even the premier reason. Western heath care is fostered by our stable political, social, and economic systems. What great gifts our forebears gave us!

2 This is good! Never be satisfied by the status quo. Things can always be improved.

3 It is indeed almost unbelievable—the progress in medicine in the past 60 years. When I graduated from medical school, penicillin was not generally available.

4 I believe our chief challenge is now to ensure social justice by providing affordable health care to all.

5 Those of us who live in retirement communities are well aware that the lives of <u>all</u> <u>residents</u> (no exceptions) have been prolonged and made much more comfortable by modern medicine and surgery. Think about how many have been spared infections by vaccines, how many lives have been saved by antibiotics, how many productive lives have been extended by lipid and blood pressure control, how many see better because of cataract surgery and lens replacement, and how many whose comfort has been enhanced by joint replacements. The list goes on.

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Adequate and Timely Communication with Patients Is One of the Great Lacks of the Medical Profession

6-14 THE PATIENT'S JOURNEY: PALLIATIVE CARE—A PARENT'S VIEW

The mother, Stephanie, recounts the emotional struggle she, her family, and her 17-year old son Andrew endured during his extensive treatment and death from a brain tumor. They were finally told that the end was near. "Although the progress of the illness—the months of anxiety, hospital admissions, treatments, improvements, relapses—does to a certain extent prepare you for such news, it is difficult to describe the effect of

it. I think crushing, stunning defeat after a prolonged painful struggle sums it up. And, of course, it is the end of all hopes for recovery when treatment stops and palliative care takes over."

The mother experienced many urgent and conflicting demands—the need to prepare her other children and loving relatives and friends; the practical considerations demanded by his condition, which centered about the prompt supply of pain relief, and the huge and overwhelming desire to make his last weeks as happy as possible.

How does one prepare a 17-year old for death? Stephanie did not know the right way. What she did impress on her son, his sisters and herself was acceptance. "Don't fight it. Everything that could be done medically had been done. We fought for life as hard as we could; now we will accept what comes next." The son faced his last weeks with serenity and dignity.

It was clear that pain relief would be a major concern. There was no need for him to be in the hospital. He was discharged with a pharmacy of painkillers, pump syringes, and needles. However, there was no community nursing service available for support. Unbearable pain usually occurred in the middle of the night when all she had was the telephone number of a nurse at the local hospital. The nurse could not leave her post to come to their aid.

The son returned to the hospital when oral medications no longer brought relief.

Other issues made it difficult—lack of advice on how to adapt the home to the son's needs; no clear direction as to who was actually medically in charge. As he was treated in two different hospitals, the family was never 100% sure where they should turn for answers. In order to keep the son at home longer, they could have used the care of their general practitioner who had made the original diagnosis. They did not want to bother him since he had not been involved in the ongoing care.

The family received insufficient information. Much had been passed between the various medical bodies throughout the illness. But, reports were not updated or consulted. Discharge letters were not read, and sometimes were illegible.

The mother did know that in an emergency, when her son's pain became too great, they could go to the hospital. This is what they ended up doing.

Toward the end, the son was transferred to a special cancer unit. At one point there was some talk of sending him home again, but the pain issue seemed insurmountable, and he felt safer in the hospital.

So what did the experience of the son's last weeks show the mother?

It would have been good to have someone in overall charge of palliative care.

It would have been useful to discuss all possible options and contingencies for palliation.

The philosophy of acceptance is not enough for siblings. Attempts to prepare the sisters were insufficient. Preparation should have been started earlier with professional help.

Despite the excellent medical care and loving nursing the cancer unit offered, dying in such a unit is not the best choice if one has a choice.

Palliative care in the community would have offered an extra option for the last weeks of the son's life. This is especially beneficial to families with terminally ill children, enabling the child to remain at home in familiar surroundings and with the people who love them most.

BMJ June 24, 2006; 332: 1494-95 Commentary by Stephanie Darnell, the mother