DIURETIC VS ACE INHIBITOR AND CALCIUM BLOCKER FOR HYPERTENSION. WHICH IS BETTER?

RATE CONTROL HAS ADVANTAGES OVER RHYTHM CONTROL FOR ATRIAL FIBRILLATION

THE METABOLIC SYNDROME INCREASES MORTALITY IN MIDDLE-AGED MEN

HOT FLUSHES

ALENDRONATE VS ESTROGEN VS BOTH FOR OSTEOPOROSIS

BODY MASS INDEX AND THE RISK OF STROKE IN MEN

SCREENING FOR PROSTATE CANCER. THE DEBATE CONTINUES

CORTICOSTEROID THERAPY FOR PATIENTS WITH ACUTE EXACERBATIONS OF COPD

THYROID-HORMONE SUPPRESSIVE THERAPY IN BENIGN THYROID NODULES – IS IT EFFECTIVE?

EFFECTS OF SUBCLINICAL THYROID DYSFUNCTION ON THE HEART.

ANTIBIOTICS FOR ACUTE PURULENT RHINITIS

LOW DOSE MIFEPRISTONE AND LEVONORGESTREL FOR EMERGENCY CONTRACEPTION
HIGHLIGHTS DECEMBER 2002

12-1 MAJOR OUTCOMES IN HIGH-RISK HYPERTENSIVE PATIENTS RANDOMIZED TO ANGIOTENSIN-CONVERTING ENZYME INHIBITOR OR CALCIUM CHANNEL BLOCKER VS DIURETIC

“Thiazide-type diuretics should be considered first for pharmacologic therapy in patients with hypertension.” They are unsurpassed in lowering BP, in reducing clinical events, and in tolerability. They are much less costly.

Since a large proportion of participants required more than one drug to control their BP, it is reasonable to infer that a diuretic should be included in all multidrug regimens.

12-2 A COMPARISON OF RATE CONTROL AND RHYTHM CONTROL IN PATIENTS WITH ATRIAL FIBRILLATION

None of the presumed benefits of rhythm control by cardioversion were confirmed by this study.

The strategy of restoring and maintaining sinus rhythm had no clear advantage over the strategy of controlling ventricular rate, and allowing the AF to continue.

Patients in the cardioversion group were significantly more likely to be hospitalized and have adverse drug effects. This has some cost considerations.

Rate control (with drugs alone) should be considered a primary approach to therapy and rhythm control (by attempted cardioversion &/or drugs), may be abandoned early if it is not fully satisfactory.

Management of AF by conversion to sinus rhythm by drugs &/or electric shock offered no survival advantage over ventricular rate control by drugs.

12-3 THE METABOLIC SYNDROME AND TOTAL AND CARDIOVASCULAR DISEASE MORTALITY IN MIDDLE-AGED MEN

Middle-aged men with the MET-S had an increased cardiovascular and overall mortality even in the absence of baseline diabetes and CVD. Early identification, treatment, and prevention of the MET-S presents a major challenge.

“The importance of the metabolic syndrome from a clinical and public health perspective may be greatest in its earliest stages, before development of CVD or diabetes.”

Modest lifestyle interventions can improve components of the MET-S.

12-4 HOT FLUSHES

Hormone replacement therapy remains the most effective therapy by far. But some women are now reluctant to take them.

Selective serotonin reuptake inhibitors (SSRIs) are somewhat effective, but a poor second choice.

12-5 SIGNIFICANT DIFFERENTIAL EFFECTS OF ALENDRONATE, ESTROGEN, OR COMBINATION THERAPY ON THE RATE OF BONE LOSS AFTER DISCONTINUATION OF TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS.

At one year, accelerated bone loss was seen after withdrawal of estrogen., but not after withdrawal of alendronate or combined estrogen/alendronate therapy.

Combined alendronate/HRT is likely more beneficial than either alone.

Therapy to preserve BMD must be continued indefinitely.
12-6 BODY MASS INDEX AND THE RISK OF STROKE IN MEN

Overweight and obese men were at increasing risk of stroke. The risk appeared to be independent of hypertension, diabetes, and cholesterol levels.

Increased risk of stroke is another hazard of obesity.

12-7 SCREENING FOR PROSTATE CANCER: AN UPDATE OF THE EVIDENCE FOR THE U.S. PREVENTIVE SERVICES TASK FORCE

Screening can detect PC earlier. A major problem is the heterogeneity of PC. The large discrepancy between PC diagnosis and deaths indicates that some, and probably most, PC detected by screening is clinically unimportant. Because precise evidence regarding the prognosis of various types of PC is lacking, the types of PC that will cause clinical symptoms and death, and that can be treated better if detected early, are not defined. The most appropriate targets of screening are not known. “Since research has not yet clearly defined the characteristics of clinically important prostate cancer, we do not know what the specific target of screening should be.”

“The efficacy of screening for prostate cancer remains uncertain.”

“The USPTF concludes that evidence is insufficient to determine whether the benefits outweigh the harms for a screened population.”

12-8 CORTICOSTEROID THERAPY FOR PATIENTS WITH ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

Short courses of systemic corticosteroids in acute exacerbations of COPD improve spirometric and clinical outcomes.

12-9 THYROID-HORMONE SUPPRESSIVE THERAPY IN BENIGN THYROID NODES –IS IT EFFECTIVE?

Despite the wide use of thyroid hormones in the treatment of thyroid nodules, there is still lack of evidence to generally justify thyroid suppression as a therapy. “It is not known if thyroid-hormone treatment is effective in controlling the size of thyroid nodules, or safe, particularly if suppression of thyroid-stimulating hormone is long-term.”

12-10 EFFECTS OF SUBCLINICAL THYROID DYSFUNCTION ON THE HEART.

“Subclinical thyroid dysfunction is not a compensated biochemical state.” Timely treatment could help prevent cardiovascular involvement.” (Eg, judicious thyroxine replacement for high TSH states and beta-blockers for low TSH states.)

12-11 ANTIBIOTICS FOR ACUTE PURULENT RHINITIS

Guidelines suggest that antibiotics are ineffective. This may not be true. However, the modest benefit for this condition, which is rarely life-threatening, may warrant constraint on their use because of side effects, cost, development of antibiotic resistance, and promotion of use of health services. Perhaps they should consider delayed prescriptions in an attempt to meet demand from patients while maintaining evidence based integrity.

12-12 LOW DOSE MIFEPRISTONE AND TWO REGIMENS OF LEVONORGESTREL FOR EMERGENCY CONTRACEPTION

Single-dose mifepristone, single-dose levonorgestrel and two-dose levonorgestrel were very efficacious and prevented a high percentage of pregnancies. There was no difference in efficacy.

A single dose of levonorgestrel can be substituted for the two-dose regimen.

Efficacy extends, but diminishes, for up to 5 days.
And The Winner Is – Diuretic!

12-1  MAJOR OUTCOMES IN HIGH-RISK HYPERTENSIVE PATIENTS RANDOMIZED TO ANGIOTENSIN-CONVERTING ENZYME INHIBITOR OR CALCIUM CHANNEL BLOCKER VS DIURETIC

What is the optimal first-choice drug therapy for hypertension? Major trials have documented that angiotensin-converting enzyme inhibitors (ACE), and calcium channel blockers (CCB) reduce cardiovascular events in individuals with hypertension.

But, are ACE and CCB more effective than diuretics in reducing incidence of coronary heart disease (CHD) and other cardiovascular events in patients with hypertension?

This trial directly compared the three.

Conclusion: Thiazide-type diuretics were superior to ACE and CCB.

STUDY

1. Multicenter, randomized, double-blind clinical trial entered over 33 000 participants age 55 and older (mean = 67). All had hypertension and at least one other CHD risk factor:
   - Hypertension – stage 1 (140-159/90-99) or stage 2 (160-179/100-109).
   - “Severe” hypertension excluded. Almost all were taking antihypertension drugs. Mean BP of untreated patients at baseline = 156/90
   - Other risk factors: previous myocardial infarction (MI) or stroke, left ventricular hypertrophy, type 2 diabetes, current cigarette smoking, high density cholesterol under 35 mg/dL, documented other CVD.

2. Randomized to:
   - A. Chlorthalidone (Generic) 12.5 to 25 mg daily
   - B. Amlodipine (Generic; Norvasc) 2.5 to 10 mg daily
   - C. Lisinopril (Generic; Prinivil; Zestril) 10 to 40 mg daily.

   (A 4th drug, the alpha-blocker, doxazocin (Cardura), was included in the original study. This arm of the study was terminated early because of an excess incidence of heart failure.)

3. Addition of a 2nd or 3rd drug was permitted. About 40% in each group was taking a step 2 or a step 3 drug at sometime during the observation period.

4. Followed-up frequently for 3+ years to 8 years (mean = 5 years).

5. Primary outcome = fatal CHD or non-fatal MI

RESULTS

1. At 5 years:

<table>
<thead>
<tr>
<th></th>
<th>Chlorthalidone</th>
<th>Amlodipine</th>
<th>Lisinopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mean mm Hg)</td>
<td>134</td>
<td>135</td>
<td>136</td>
</tr>
<tr>
<td>Diastolic BP (mean mm Hg)</td>
<td>75</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Achieved BP goal (&lt;140/90)</td>
<td>68%</td>
<td>66%</td>
<td>61%</td>
</tr>
</tbody>
</table>
Cholesterol (mg/dL at 4 y)  197   196   195  
(Many were taking lipid-lowering drugs.)
Potassium (< 3.5 mEq/L at 4 y) 9%   2%   1%  
Fasting glucose (mean mg/dL) 126   124   122  
Diabetes (FBS > 126) 12%   10%   8%  
(Given the large sample size, almost all differences in follow-up BP and biochemical measurements were statistically significant.)

2. Amlodipine vs chlorthalidone: Secondary outcomes were similar. However, the amlodipine group had a higher risk of heart failure. (10.2% vs 7.7%; absolute difference = 2.5%)

3. Lisinopril vs chlorthalidone: Higher 6-year rates of combined CVD (33.3% vs 30.9%); stroke 6.3% vs 5.6%) and heart failure (8.7% vs 7.7%). [Absolute differences 0.7% to 2.4%]

DISCUSSION
1. Neither the di-hydropyridine calcium blocker amlodipine, nor the ACE inhibitor lisinopril, was superior to the thiazide diuretic chlorthalidone in preventing major coronary events or in increasing survival.
2. Chlorthalidone was superior to amlodipine in preventing HF.
3. Chlorthalidone was superior to lisinopril in preventing HF and aggregate cardiovascular events.
4. The chlorthalidone group had better drug tolerance and BP control.
5. The lower incidence of HF in the chlorthalidone group is consistent with previous reports.
6. No significant differences in end-stage renal disease, glomerular filtration rate, or increase in creatinine levels were noted for the lisinopril vs chlorthalidone comparisons.
7. Benefits of chlorthalidone vs the other drugs were evident despite the higher levels of cholesterol, insulin resistance, and hypokalemia.
8. In black (vs non-black patients), greater benefits were observed for combined CVD and stroke, along with a similar trend for HF. Chlorthalidone resulted in greater BP lowering in blacks.
9. A great number of patients required more than one drug.

CONCLUSION
“Thiazide-type diuretics should be considered first for pharmacologic therapy in patients with hypertension.” They are unsurpassed in lowering BP, in reducing clinical events, and in tolerability. They are much less costly.

Since a large proportion of participants required more than one drug to control their BP, it is reasonable to infer that a diuretic should be included in all multidrug regimens.

JAMA December 18, 2002; 288: 2981-2997 Original investigation by the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT), reported from Case Western Reserve University, Cleveland Ohio. www.jama.com
An editorial in this issue of JAMA (pp 3039 – 42) by Lawrence J Appel, Johns Hopkins University, Baltimore MD comments:

“AllHAT is one of the most important trials of hypertensive therapy” It has enormous clinical, public health, and economic implications. “The most effective therapy is also the least expensive”

Hypertension specialists postulated that diuretic-induced metabolic effects (hypokalemia, dyslipidemia, and insulin resistance) might reduce the otherwise beneficial effects of BP reduction. This led to a shift away from diuretics to ACE and CCB. Because these non-diuretic therapies reduce BP without apparent adverse metabolic consequences, many specialists concluded that such drugs would be superior as a means of preventing coronary heart disease. “The major finding of ALLHAT was a striking and unequivocal null result, namely, that the occurrence of coronary heart disease death and non-fatal myocardial infarction was virtually identical in the amlodipine, lisinopril, and chlorthalidone groups.”

Even though hypokalemia, insulin resistance, and hypercholesterolemia were more common with chlorthalidone, there was no excess of cardiovascular events. (Another example of how surrogate markers can lead clinicians astray. RTJ)

Why should physicians implement an ACE inhibitor-based strategy that commonly leads to use of 2 drugs (ACE and diuretics) when monotherapy with a thiazide diuretic can effectively prevent BP-related cardiovascular outcomes?

What about beta-blockers as first line therapy? Available data suggest that they are no more effective, and quite possibly may be less effective than thiazides. (I believe they would be a good second add-on. RTJ)

What drug should be second-line therapy, since most patients require 2 or more drugs? There are many low cost, off-patent drugs which can be used: a CCB – verapamil; 3 ACE inhibitors – captopril, enalapril, and lisinopril; several beta-blockers. “In short, physicians have the means to effectively control BP with inexpensive medications.”

COSTS: My pharmacy quotes for each tablet:

<table>
<thead>
<tr>
<th></th>
<th>Lisinopril</th>
<th>Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorthalidone</td>
<td>25 mg 9 cents</td>
<td>Generic</td>
</tr>
<tr>
<td>50 mg 10 cents</td>
<td>10 mg $0.70</td>
<td>Could not access</td>
</tr>
<tr>
<td>40 mg $1.00</td>
<td>10 mg $1.15</td>
<td>2.5 mg $1.66</td>
</tr>
<tr>
<td></td>
<td>40 mg $1.73</td>
<td>10 mg $2.43</td>
</tr>
</tbody>
</table>

(Note the savings if you use generics and a pill cutter. Costs vary. Shop around.)
stroke, possibly enable discontinuation of anticoagulation, improve quality of life, and lengthen survival. However, sinus rhythm may be difficult to maintain by drug therapy, and serious adverse drug effects may occur.

Ventricular rate control may simplify therapy and permit use of less toxic drugs. However, continuing anticoagulation is thought to be more important in these patients than in patients who maintain sinus rhythm for a long period.

This study asked – Which approach is better?

Conclusion: Ventricular rate control without attempts at cardioversion had significant clinical advantages.

STUDY
1. Randomized trial compared the two treatment strategies in over 4000 patients (mean age 70) with a history of AF. The great majority had a qualifying episode of AF within the previous 6 weeks, most lasting over 2 days. The majority had recurrent AF. Some were in normal sinus rhythm at start of therapy.
2. The majority had hypertension. Many had a history of coronary disease. Left atrium was enlarged in 2/3, and left ventricular function was depressed in 26%.
3. Criteria for enrollment included the likelihood that AF would cause illness or death; long-term treatment for AF was warranted; and anticoagulant therapy was not contraindicated.
4. Randomized to:
   A. Cardioversion attempt group (Rhythm control):
      The drug selected to attempt reversion to sinus rhythm was chosen by the treating physician.
      (Mainly amiodarone and sotalol.) Electrical cardioversion could be attempted as necessary. (Often attempted more than once.)
      Anticoagulation was continued in most.
   B. Ventricular rate control group (Rate control; no attempt to convert):
      Drugs included beta-blockers, calcium-channel blockers, digoxin, or a combination. A combination was commonly used. Goal was heart rate no higher than 80 at rest, and no higher than 110 on a 6-minute walk.
      Anticoagulation was continued indefinitely.
5. Primary endpoint = death. Follow-up mean = 3.5 years.

RESULTS
1. Ventricular rate control group:
   Reverted to normal sinus rhythm at 5 years 35%
   (Many reverted to normal sinus rhythm while receiving rate control drugs without any attempt at cardioversion,)
   Crossed over to cardioversion attempts 12%
   Adequate rate control 80%
   Death at 5 years 21%
   Stroke (annual rate) 1%
Hospitalizations 73%

2. Cardioversion group (Rhythm control):
   Sinus rhythm at 5 years 63%
   Crossed over to ventricular rate control 38%
   (About 1/3 failed cardioversion and were then treated with rate control.)
   Death at 5 years 24%
   Stroke (annual rate) 1%
   Hospitalizations 80%

2. In both groups, most strokes occurred in patients in whom warfarin had been stopped, or when INR became subtherapeutic.

3. Adverse events:
   Pulmonary events, gastrointestinal events, bradycardia, prolongation of QT interval, and “other” events prompting discontinuation of a drug were significantly more frequent in the cardioversion attempt group.

DISCUSSION
1. None of the presumed benefits of rhythm control by cardioversion were confirmed by this study. The strategy of restoring and maintaining sinus rhythm had no clear advantage over the strategy of controlling ventricular rate, and allowing the AF to continue.
2. All comparisons of subgroups according to the prespecified covariates either showed non-significant differences, or a greater benefit from ventricular rate control.
3. The cross-over rate was greater among persons originally assigned to cardioversion. Drugs aimed at converting AF to normal sinus rhythm and at sustaining normal sinus rhythm frequently fail.
4. The risk of stroke (the most serious clinical consequence of AF) was low in both groups. The majority occurred in patients who had stopped anticoagulation or in those who failed to maintain a therapeutic INR.
5. Patients in the cardioversion group were significantly more likely to be hospitalized and have adverse drug effects. This has cost considerations. The adverse effects of amiodarone, the most commonly used drug, might reasonably be expected to increase with longer use.
6. “Rate control should be considered a primary approach to therapy, and rhythm control, if used, may be abandoned early if it is not fully satisfactory.”
7. Anticoagulation should be continued even if the patient converts to sinus rhythm.

CONCLUSION
Management of AF by conversion to sinus rhythm by drugs &/or electric shock offered no survival advantage over ventricular rate control by drugs. The strategy of attempting to restore and maintain sinus rhythm had no clear advantage over the strategy of controlling ventricular rate, and allowing the AF to continue.
“Rate control should be considered a primary approach to therapy, and rhythm control, if used, may be abandoned early if it is not fully satisfactory.”

NEJM December 5, 2002; 347: 1825-33  Original investigation by the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) investigators, AFFIRM Clinical Trial Center, Seattle, Washington

www.nejm.org

A companion article appeared in this issue of NEJM “A Comparison Of Rate Control And Rhythm Control In Patients With Recurrent Persistent Atrial Fibrillation” NEJM December 5, 2002; 347: 1834-40, first author Isabelle C Van Gelder, University Hospital, Groningen, the Netherlands:

Randomized over 500 patients who had persistent AF after a previous electrical shock cardioversion to:

Rate control group -- received drugs to slow and control ventricular rate. No further attempts at cardioversion.
Rhythm control group -- underwent serial cardioversions and received anti-arrhythmic drugs.
Oral anticoagulation was given to both groups.

After 2+ years, only 39% of those in the rhythm control group (repeated cardioversions) had normal sinus rhythm. A careful treatment protocol failed to maintain sinus rhythm in the majority of those receiving prior cardioversion.

Primary end point, a composite of death, heart failure, pacemaker implantation, thromboembolism, bleeding, and severe adverse effects of drugs occurred more frequently in the rhythm control group than in the rate control group (23% vs 17%).

Prophylactic anti-arrhythmic drugs contributed significantly to incidence of major cardiac endpoints in the rhythm control group, but not in the ventricular rate control group.

Conclusion: “Rate control is not inferior to rhythm control for prevention of death and morbidity from cardiovascular causes, and may be appropriate therapy in patients with a recurrence of persistent atrial fibrillation after electrical cardioversion.”

Comment:

No doubt restoration of sinus rhythm improves efficiency of ventricular function. However, from a clinical standpoint, it conferred no benefit in the patients in these studies.

In younger more healthy patients, especially those with “lone” AF, electrical conversion to sinus rhythm may be the preferred option.  RTJ

Participants in both groups were old and sick. These studies will certainly make life simpler for primary care clinicians and their patients. Relieving them of some of the burden and cost of therapy is most welcome. RTJ

Early Identification, Treatment, And Prevention Of The MET-S Presents A Major Challenge.

12-3 THE METABOLIC SYNDROME AND TOTAL AND CARDIOVASCULAR DISEASE MORTALITY IN MIDDLE-AGED MEN

The metabolic syndrome (MET-S) is a concurrence of disturbed glucose and insulin metabolism, overweight, and abdominal fat distribution, mild dyslipidemia, and hypertension.

It is also termed “the insulin resistance syndrome”. It is associated with a later development of type 2 diabetes and cardiovascular disease (CVD).
The pathogenesis has multiple origins. Obesity and sedentary lifestyle coupled with unfavorable diet, and still largely unknown genetic factors, clearly interact to produce the syndrome. With the epidemic of overweight and sedentary lifestyle world-wide, MET-S is becoming increasingly common. According to the National Cholesterol Education Program (NCEP), about 1/3 of middle-aged men and women in the USA have the MET-S.

Definitions of the syndrome and various cutoffs for its components have varied widely. The NCEP definition\(^1\) differs slightly from the WHO definition.

This study assessed the association of the MET-S with cardiovascular and overall mortality.

Conclusion: Mortality increased in men with the MET-S.

STUDY
1. Population-based prospective cohort study entered over 1200 Finish men, age 42 – 60 (mean = 51) at baseline.
   None had known CVD, cancer or diabetes.
2. Determined prevalence of MET-S at baseline.
   \( \text{(I abstracted data only on those defined by the NCEP definition. RTJ)} \)

RESULTS
1. Prevalence of MET-S ranged from 8% to 14% depending on the definition.
2. 109 deaths occurred: 46 due to CVD, 27 of which were due to coronary heart disease (CHD).
3. Men with the MET-S as defined by NCEP were 3 times more likely to die of CHD after adjustments for traditional cardiovascular risk factors.
4. Estimated overall survival at 14 years:
   90% for those without the MET-S
   79% of those with the MET-S
5. The investigators calculated the effect of other risk factors when added to those of the MET-S.
   Factors such as smoking, elevated LDL-cholesterol, and elevated systolic BP increased risk.

DISCUSSION
1. The increased mortality found in persons with the MET-S was independent of other important and potentially confounding risk factors.
2. The association persisted even when persons with impaired fasting glycemia were excluded.
   (Fasting blood glucose 100- 110 mg/dL.)
3. The prevalence of MET-S in this cohort was likely lower than will be found in the USA.
   It is likely that prevalence of the MET-S will increase and its disease burden will increase.
4. MET-S is associated with an increased mortality for men with MET-S even in its earlier phases, before development of CVD or diabetes.
5. Modest lifestyle interventions can have a major impact in decreasing the risk for diabetes in
glucose-intolerant individuals. Physical activity, weight loss and proper diet favorably affect components of
the MET-S.

6. Early identification, treatment, and prevention of the MET-S presents a major challenge.
7. “The importance of the metabolic syndrome from a clinical and public health perspective may be greatest in
it earliest stages, before development of CVD or diabetes.”

CONCLUSION

Middle-aged men with the MET-S had an increased cardiovascular and overall mortality even in the absence
of baseline diabetes and CVD.

JAMA December 4, 2002; 288: 2709-16 Original investigation based on the Kuopio Ischemic Heart Disease Risk
Factor Study, first author Hanna-Maaria Lakka, University of Kuopio, Finland www.jama.com

1 The NCEP definition -- at least 3 of the following:
   1) Fasting plasma glucose > 110 mg/dL (Blood glucose > 100)
   2) Abdominal circumference > 104 cm
   3) Triglycerides > 150 mg/dL
   4) HDL-cholesterol < 40 mg/dL
   5) BP over 130/85, or on medication.

Comment:

This analysis contains statistical manipulations and terms I did not understand. I doubt that most primary care
clinicians would understand them either. Fortunately, primary care clinicians can understand and apply clinical
applications of studies without fully understanding the statistical implications.

I believe I understood the main message and the degree to which MET-S increases risk. RTJ

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SSRIs -- A Much Less Effective Substitute For HRT

12-4 HOT FLUSHES

Almost every woman will encounter hot flushes (hot flashes) during her lifetime. They may be accompanied
by sweating (including night sweats), palpitations, anxiety, depression, irritability, insomnia, inability to
concentrate, and even panic. Many women find them nearly intolerable. Symptoms last one year or less in most
women. About 1/3 last over 5 years after natural menopause and may persist for up to 15 years. Surgical
menopause is associated with more abrupt and severe symptoms.

The pathophysiology remains unknown. A decline in hormone concentration might lead to alterations in brain
neurotransmitters and to instability of the hypothalamic thermoregulatory setpoint.

Hormone replacement therapy (HRT), especially with estrogens, is the most effective therapy, and is the
mainstay of treatment. It is up to 5 times more effective than placebo. It is more efficacious than any other
therapy. Progestagens alone are also effective. However, many women and their physicians are reluctant to accept hormonal therapy.

Women want non-pharmacological treatments, but they are not very effective. Non-hormonal drugs are often associated with adverse effects.

The placebo effect in reducing symptoms is strong -- 20% to 30% reduction in frequency and severity.

What about selective serotonin reuptake inhibitors (SSRIs)?

SSRIs are one of the most prescribed drugs in the world. They have revolutionized treatment of depression. They can reduce hot flashes in some women. A reduction of symptoms compared with placebo has been reported with venafaxine (Effexor) and fluoxetine (Prozac). Adverse effects are moderate. They are less effective than HRT. Although many questions about their use remain, they are the most promising non-hormonal therapy.

<table>
<thead>
<tr>
<th>Results of randomized trials:</th>
<th>Hot flash reduction</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen</td>
<td>50-110%</td>
<td>--</td>
</tr>
<tr>
<td>Progestagen</td>
<td>71-90%</td>
<td>21-26%</td>
</tr>
<tr>
<td>Soya</td>
<td>35-45%</td>
<td>25-38%</td>
</tr>
<tr>
<td>Clonidine</td>
<td>37-41%</td>
<td>20-27%</td>
</tr>
<tr>
<td>SSRIs</td>
<td>34-65%</td>
<td>27-38%</td>
</tr>
</tbody>
</table>

Lancet December 7, 2002; 360: 1851-61 Review article, first author Vered Stearns, Comprehensive Cancer Center at Johns Hopkins, Baltimore MD. [www.thelancet.com](http://www.thelancet.com)

Comment:

This systematic review was based on a Medline search and Cochrane review. It focused on prospective, randomized, placebo-controlled trials. Those interested in epidemiology, pathophysiology, and details of treatment may wish to consult the original.

SSRIs are a much less effective second choice. I believe most women with distressing menopausal symptoms will willingly accept the adverse effects of dual estrogen/progestin HRT reported by the Women’s Health Study. The increase in risk of coronary heart disease, breast cancer, stroke, pulmonary embolism, and gallbladder disease occurred in only a few women in 10 000 each year. This was partially balanced by a reduction in risk of fractures and cancer of the colon. Other benefits of HRT include reduced risk of osteoporosis, depression, vaginal dryness, and genital atrophy.

========================================================================

_Aлендронат Производит Более Долгосрочные Преимущества_  

**12-5 SIGNIFICANT DIFFERENTIAL EFFECTS OF ALENDRONATE, ESTROGEN, OR COMBINATION THERAPY ON THE RATE OF BONE LOSS AFTER DISCONTINUATION OF TREATMENT OF POSTMENOPAUSAL OSTEOSPOROSIS.**

“Combination therapy with alendronate (Fosamax) and estrogen for 2 years increases bone mineral density (BMD) at the spine and hip more than does therapy with either agent alone.”
This study asked – What is the rate of bone loss when therapy with alendronate, estrogen, or the combination is discontinued? This is a clinically important point. Many women discontinue estrogen within one year. The investigators determined the rate of bone loss after therapy with the three regimens was discontinued.

Conclusion: At one year, accelerated bone loss occurred after estrogen was discontinued, but not after withdrawal of alendronate.

STUDY
1. Double-blind randomized trial entered 244 postmenopausal women (mean age = 64). All were post-hysterectomy. All had osteoporosis. (BMD at lumbar spine over 2.0 standard deviations below peak bone mass in young adults.)
2. Randomized to:
   - Alendronate 10 mg daily
   - Conjugated estrogen 0.625 mg daily
   - Both
   - Placebo
3. All took supplementary calcium.
4. After 2 years, many taking active drugs were switched to placebo. Some continued on the original drug for the 3rd year.
5. Measured BMD at 2 years and at 3 years.

RESULTS
1. Between-treatment differences at 3 years:
   - Lumbar spine
   - Total hip
   - Alendronate 2y then placebo for 1 y vs placebo/placebo +7.0% +4.0%
   - Estrogen for 2 y then placebo for 1 y vs placebo/placebo +2.9% +2.1%
   - Alendronate + estrogen for 2 y then placebo for 1 y vs placebo/placebo +9.5% +3.9%
   - Alendronate + estrogen for 3 y vs placebo for 3 y +11.2% +6.5%
(Ie, some additional evidence that combination therapy is better than either drug alone. Also that patients who take estrogen for 2 years and then discontinue lose BMD more rapidly than those who use alendronate and then discontinue.)
2. All drugs were well tolerated.
3. No difference in clinical outcomes. (Short time period and relatively few patients.)

DISCUSSION
1. Women who took estrogen for 2 years and then discontinued lost significant amounts of BMD during the year after discontinuation. Bone loss after discontinuation of estrogen was accelerated.
2. Women who took alendronate (or alendronate + estrogen) for 2 years and then discontinued, maintained the increases in BMD.
3. Women who took alendronate + estrogen for 3 years had even greater increases in BMD.
4. The Framingham study reported that women who took estrogen during the 2 years before the study had a 66% reduction in hip fracture. The association may be only for current estrogen users. When estrogen is discontinued, BMD decreases and the protective effect is lost.

CONCLUSION

At one year, accelerated bone loss was seen after withdrawal of estrogen, but not after withdrawal of alendronate or combined estrogen/alendronate therapy.


Comment:

The study suggests several important clinical points:

Combined alendronate/HRT is likely more beneficial than either alone.

Therapy to preserve BMD must be continued indefinitely. (Although the study did not extend beyond 3 years, this implication is strong.) RTJ

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An Independent Risk Factor For Stroke

12-6 BODY MASS INDEX AND THE RISK OF STROKE IN MEN

Obesity is an established risk factor for coronary heart disease (CHD). Obesity also contributes to incidence of hypertension, diabetes, and dyslipidemia which are in turn risk factors for CHD

This study asks: Is obesity an independent risk factor for stroke?

Conclusion: Increasing body mass index (BMI) is an independent risk factor for stroke.

STUDY

1. A prospective cohort study (The Physicians Health Study) entered over 21,000 US male physicians (mean age = 53) None had previous cardiovascular disease.
2. Mean BMI = 24.9. 57% had a “normal” weight according to WHO criteria (BMI < 25); 38% were overweight (BMI 25-30); 5% were obese (BMI > 30)
4. Follow-up = 13 years.

RESULTS

1. Over the follow-up period, 747 strokes were documented: 631 ischemic, 104 hemorrhagic, 12 undefined.
2. Association with BMI:
Mean systolic and diastolic BP and prevalence of hypertension increased with increasing BMI. Current smoking highest in the obese. Regular exercise decreased with increasing BMI. Leanest consumed more alcohol.

3. Age and multiple-adjusted relative risks of stroke:

<table>
<thead>
<tr>
<th>BMI</th>
<th>&lt; 23</th>
<th>23-25</th>
<th>25-27</th>
<th>27-30</th>
<th>&gt; 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total stroke</td>
<td>1.00 (referent)</td>
<td>1.09</td>
<td>1.32</td>
<td>1.51</td>
<td>2.00</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.00</td>
<td>1.07</td>
<td>1.33</td>
<td>1.54</td>
<td>1.95</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>1.00</td>
<td>1.30</td>
<td>1.45</td>
<td>1.50</td>
<td>2.25</td>
</tr>
</tbody>
</table>

(Compared with BMI < 23, those with BMI > 30 twice the risk of stroke.)

5. When BMI was evaluated as a continuous variable, each unit increase in BMI was associated with a 6% rise in adjusted relative risk of stroke.

6. Additional adjustments for hypertension, diabetes, and hypercholesterolemia only slightly attenuated the risks for total and ischemic strokes.

DISCUSSION

1. Increasing BMI was associated with a steady increase in risks of total, ischemic, and hemorrhagic stroke.

2. Although concomitant hypertension and diabetes accounted for much of the increase in total and ischemic stroke, a significant increase in risk associated with increased BMI remained after adjustment for these potential biases.

3. What might the mechanism be for this independent association? Some have proposed higher levels of prothrombotic factors and increased levels of C-reactive protein.

4. BMI is an imperfect measure of obesity. Abnormal regional adiposity (abdominal) may further increase risk for stroke.

5. Increased BMI is a modifiable factor.

CONCLUSION

Overweight and obese men were at increasing risk of stroke. The risk appeared to be independent of hypertension, diabetes, and cholesterol levels.

Increased risk of stroke is another hazard of obesity.


Comment:

BMI = weight in kg divided by height in meters squared.

=================================================================
Evidence Is Insufficient For or Against

12-7 SCREENING FOR PROSTATE CANCER: AN UPDATE OF THE EVIDENCE FOR THE U.S. PREVENTIVE SERVICES TASK FORCE [www.preventiveservices.ahrq.gov]

PC is the most common non-cutaneous cancer and the second leading cause of cancer death. Screening is still controversial.

This study examined the evidence of benefits and harms of screening and early treatment of PC. This systematic review entered data from MEDLINE, the Cochrane Library, reviews, and opinions of experts. It sought answers to 8 questions regarding: efficacy of screening; yield of screening; efficacy of radical prostatectomy, radiation therapy, androgen deprivation, and watchful waiting; harms of treatment; and cost-effectiveness.

Accuracy of screening: Currently prognostic markers can distinguish 1) a small number of men with excellent prognosis for long-term survival, and 2) a small number of men with poor prognosis for long-term survival. However, they cannot correctly categorize the prognosis of those in the middle category, which includes most men with PC. “Since research has not yet clearly defined the characteristics of clinically important prostate cancer, we do not know what the specific target of screening should be.”

Large screening programs have reported that about 25% of men in their 70s have a prostate specific antigen (PSA) level over 4.0 ng/dL. Few other screening tests have such a high percentage of positive results. If it is assumed that biopsy is performed on all men with an abnormal result on a screening test, it is estimated that the percentage of all men screened who would have a prostate cancer detected would range from approximately 1.5% for men in their 50s to 10% for men in their 70s.

One observational study reported 10-year disease-specific survival:

<table>
<thead>
<tr>
<th></th>
<th>Radical prostatectomy</th>
<th>Watchful waiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men with well-differentiated PC</td>
<td></td>
<td>No difference</td>
</tr>
<tr>
<td>Men with moderately differentiated PC</td>
<td>87%</td>
<td>77%</td>
</tr>
<tr>
<td>Men with poorly differentiated PC</td>
<td>67%</td>
<td>45%</td>
</tr>
</tbody>
</table>

“Watchful waiting” implies that no treatment is given initially, but that the patient is followed for evidence of progression or symptomatic disease for which treatment might be offered. Men with well-differentiated clinically localized PC have excellent long-term survival, with little or no reduction in survival compared with similar men without PC. Men with poorly differentiated PC have reduced survival. Because most prostate cancer detected today is moderately differentiated, survival of men with this type of tumor is important to the debate about screening.

Fifteen-year survival time of men with clinically localized moderately differentiated PC:

<table>
<thead>
<tr>
<th>Gleason score 7</th>
<th>Age 50-59</th>
<th>30%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age 70-79</td>
<td>58%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gleason score 5</th>
<th>Age 50-59</th>
<th>94%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age 70-79</td>
<td>94%</td>
</tr>
</tbody>
</table>
Harms of treatment include a low, but significant 30-day mortality for radical prostatectomy; impotence; urinary incontinence. The risk varies with expertise of the surgical center. Adjuvant therapy with androgen deprivation therapy is accompanied by hot flashes, breast swelling, lack of vitality, anemia, and osteoporosis.

The bottom line:

Screening can detect PC earlier. A major problem is the heterogeneity of PC. The large discrepancy between PC diagnosis and deaths indicates that some, and probably most, PC detected by screening is clinically unimportant. Because precise evidence regarding the prognosis of various types of PC is lacking, the types of PC that will cause clinical symptoms and death, and that can be treated better if detected early, are not defined. The most appropriate targets of screening are not known.

“The efficacy of screening for prostate cancer remains uncertain.”

Annals Int Med December 3 2002; 137: 917-29 “Clinical Guidelines” review article, first author Russell Harris, University of North Carolina, Chapel Hill [www.annals.org](http://www.annals.org)

An accompanying article (pp 915-16) “Screening for Prostate Cancer: Recommendation and Rationale” summarizes the recommendation of the U.S. Preventive Services Task Force:

“The USPTF concludes that evidence is insufficient to determine whether the benefits outweigh the harms for a screened population.”

Comment:

The debate – to screen or not to screen – seems to have no end. Note that the USPTF does not recommend that screening be discontinued – only that there is insufficient evidence to support generalized screening.

The pubic is quite aware that many men continue to die of PC, and that screening will lead to life-saving treatment in some. The problem is that screening cannot determine which individuals will benefit and who will be harmed. I believe that many men will continue to accept the harms that screening may bring in order to achieve a possible life-extending benefit. Fortunately, the older one becomes, the less difficult is the decision.

Men who contemplate screening must be made aware of the risks as well as the possible benefits of screening, and the surrounding uncertainty, before physicians recommend it. RTJ

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Short Courses Of Systemic Corticosteroids May Improve Clinical Outcomes.

12-8 CORTICOSTEROID THERAPY FOR PATIENTS WITH ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

Chronic obstructive pulmonary disease (COPD) is a heterogeneous group of diseases characterized by airflow limitation that is not fully reversible. (Contrasts to asthma.) The airflow limitation is associated with an abnormal inflammatory response of the lungs to noxious particles or gases.

Pathologic changes are heterogeneous and affect the airways, lung parenchyma, and pulmonary vasculature. Internal airway diameter is reduced as a consequence of structural remodeling, chronic inflammation, and
hyperplasia of mucous-secreting cells. Destruction of lung parenchyma is most often observed as centrilobular
emphysema in which the walls of the airspaces distal to the terminal bronchioles are destroyed.

The clinical picture and symptoms are variable and not perfectly related to measured airway obstruction. The
clinical course is that of chronic stable airway obstruction punctuated by acute episodes of worsening respiratory
function. These “exacerbations” are manifested by increasing cough, change in quantity and color of sputum, and
worsening dyspnea. Exacerbations are common, most often associated with upper respiratory infections.

Historically, treatment has mirrored the treatment of asthma. The majority of patients with COPD who
require treatment for acute respiratory failure receive corticosteroids. Their use has been endorsed by guidelines.
(Patients with stable COPD have minimal response to corticosteroids.)

This study reviewed the literature systematically to determine whether corticosteroids benefit patients with
acute exacerbations.

Conclusion: Corticosteroids improve outcomes.

STUDY
1. Systematic search retrieved 8 studies that met criteria for inclusion. These clinical trials were randomized and
   placebo-controlled. They considered effects of systemic corticosteroids in patients with acute exacerbations
   as well as any adverse effects.
2. Corticosteroids included methylprednisolone, prednisolone, prednisone, and hydrocortisone, given by
   mouth or I.V. for various times.

RESULTS
1. Five of the 8 studies found significant improvements in forced expiratory volume at 1 second (FEV1)
   of over 20%.
2. Two studies found improvement in clinically relevant outcomes.
3. One study did not find significant improvement in spirometric measures.

DISCUSSION
1. Study design factors may lead to underestimation or overestimation of steroid effect. These stem
   from the definition and identification of COPD and the quality and validity of outcome measures.
2. Differentiation from asthma is based on finding minimal reversible airflow obstruction. The
   gold standard for diagnosis of COPD is an objective measure of lung function. In the absence of spirometry,
   the diagnosis is usually based on historical and physical findings.
3. Most COPD exacerbations are due to worsening airflow obstruction caused by respiratory
   tract infections.
4. It is possible that some patients with asthma or asthma combined with COPD were included in
the studies. Nevertheless, the overall implications of the reported trials remains valid. “Patients who present to their physicians with symptoms of a COPD exacerbation are likely to benefit immediately from systemic corticosteroid therapy regardless of whether their true diagnosis is COPD or asthma.”

5. In patients with an exacerbation, corticosteroid therapy modestly reduces treatment failures and duration of hospitalization, and improves FEV1. Benefit is apparent within one day and lasts for at least 5 days of therapy.

6. The total steroid dose given to “average” patients with exacerbations probably does not carry a significantly increased risk of bone loss.

CONCLUSION

Short courses of systemic corticosteroids in acute exacerbations of COPD improve spirometric and clinical outcomes.


Comment:

Good evidence also exists for use of antibiotics in exacerbations. RTJ

Still Lack Of Evidence To Generally Justify Thyroid Suppression

12-9 THYROID-HORMONE SUPPRESSIVE THERAPY IN BENIGN THYROID NODULES — IS IT EFFECTIVE?

Recent studies have revisited this perennial controversy. A meta-analysis\(^1\) included 6 studies which applied strict criteria for inclusion: solitary nodule proven benign by fine needle biopsy; follow-up at least 6 months; documented suppression of thyroid-stimulating hormone (TSH); measurements by ultrasound; volume reduction by more than 50%.

Overall, the study failed to demonstrate a statistically significant treatment effect, although a trend (relative risk 1.9) favored therapy.

Thyroid nodules are common (one of 5 German patients presents with one). Most are unrecognized. The diagnostic challenge is to detect a rare malignancy among the overwhelming majority of benign lesions.

If the nodule is benign, how best to treat it? The answer is not easy because nodules do not represent a single disease entity. They are heterogeneous in various respects, including their histologic classification (neoplasia vs hyperplasia), molecular basis (occurrence of mutations), and clinical manifestations (uninodular or multinodular, small or large, functional or non-functional).

Most nodules tend to grow slowly. However, the growth rate of nodules is apparently higher than non-thyroid tissue in the same gland.
 Remarkably, despite the wide use of thyroid hormones in the treatment of thyroid nodules, there is still lack of evidence to generally justify thyroid suppression as a therapy. “It is not known if thyroid-hormone treatment is effective in controlling the size of thyroid nodules, or safe, particularly if suppression of thyroid-stimulating hormone is long-term.”

Prevention of nodule development is different. Indeed, prevention seems to be far more effective than treatment later on. Long-term use of iodine is preferable to levothyroxine administration. Iodine supplementation programs significantly reduce the prevalence of thyroid nodular disease. In iodine-deficient countries, iodine supplementation may be available to prevent development of additional new nodules.

Preliminary conclusions:
- Most benign nodules exhibit a favorable prognosis.
- They slowly increase in size over years.
- No convincing evidence that growth may be halted by suppressive therapy.

Lancet December 14, 2002; 360: 1899-1900 Editorial by Rudolf Hoermann, Klinikum Luedenscheid, Germany.

www.thelancet.com

1 “Effectiveness of Thyroid Hormone Suppressive Therapy in Benign Solitary Thyroid Nodules” J Clin Endocrinol Metab 2002; 87: 4154-59

Comment:
- How should primary care clinicians in the USA approach this problem?
  - Observe for the signs of the rare cancer. Observe for growth.
  - Consider that TSH suppression with thyroxine must be almost complete to achieve any chance of shrinkage.
  - Efficacy of suppression must be monitored carefully, with frequent clinic visits and TSH determinations, as well as clinical manifestation of hyperthyroidism.
  - I believe the risks of therapy by the primary care clinician outweigh any benefit. Iatrogenic hypothyroidism is common, and can lead to significant harms. (Eg, osteoporosis, atrial fibrillation.)
  - See the following abstract. RTJ

12-10 EFFECTS OF SUBCLINICAL THYROID DYSFUNCTION ON THE HEART.

The cardiovascular system is sensitive to thyroid hormone. Cardiac changes are associated with overt thyroid dysfunction. What effect does subclinical thyroid dysfunction have on the heart?

The investigators hypothesized that subclinical thyroid dysfunction is not in the strict sense a compensated biochemical change. It may lead to dysfunction of the heart and could lead to important clinical effects and prognostic implications.

Conclusion: The heart responds to the minimal but persistent changes in circulating thyroid hormone levels typical of subclinical thyroid dysfunction.
1. Conducted a systematic review of available data on effects of subclinical hypo- and hyper-thyroidism on the cardiovascular system.

2. Subclinical hypo-thyroidism:
   A. Definition: High thyroid stimulating hormone (TSH) with normal free thyroxine (FT4) and normal free triiodothyronine (FT3). It is associated with under-replacement of exogenous thyroxine in patients with overt hypothyroidism; a number of drugs; and thyroiditis. It is common. It predisposes to overt hypothyroidism.
   B. Cardiac manifestations: A number of abnormalities have been described in small studies. Patients may have impaired left ventricular diastolic function at rest and systolic dysfunction on effort. This may result in poor physical exercise capacity. Some studies reported the pre-ejection period and the interval from Q wave to pulse arrival at the brachial artery were prolonged. Low aortic acceleration (index of left ventricular function) reverted to normal with thyroxine therapy. Longer peak filling rate, normalized after thyroxine therapy. (Not all studies have been duplicated; controversy persists)
   C. Coronary artery disease: A recent study reported restoration of euthyroidism in patients with subclinical hypothyroidism reduced both total and LDL-cholesterol levels, lipoprotein(a), and homocysteine levels. (All beneficial changes.) The large Rotterdam epidemiological study reported subclinical hypothyroidism is associated with greater prevalence of aortic atherosclerosis, and myocardial infarction in elderly women.
   D. “Subclinical hypothyroidism should be considered a mild form of thyroid failure . . . that is associated with initial signs of cardiovascular hypothyroidism.”
   E. Benefits of thyroxine treatment include improved lipid profiles, possible lowered risk of atherosclerosis and coronary artery disease, prevention of cardiac morphologic and functional abnormalities, prevention of progression to overt hypothyroidism, a modest symptom benefit, and prevention of goiter in some patients.

   The thyroxine dose must be lower than in those with overt disease. Dosage must be monitored to achieve optimal replacement dose. Aim for TSH of 1.0 to 2.0 mU/L. Start with 12.5 ug in the elderly and 25 ug in younger patients.

   An interesting observation: changes in cardiovascular measures can also be found in subclinical hypothyroid patients with TSH values less than 10 mU/L. “Persistent clinical hypothyroidism with TSH values which are stable above 4.0 should be treated, particularly if associated with thyroid antibodies.

3. Subclinical hyper-thyroidism:
   A. Definition: Low TSH (< 0.1 mU/L or undetectable) with normal FT4 and FT3. It may be due to endogenous or exogenous factors.
   1) Endogenous: This may be due to early Graves disease, multinodular goiter, and an autonomously functioning thyroid nodule)
2) Exogenous: usually due to overtreatment with thyroxine. The most common cause of subclinical hyperthyroidism is thyroxine therapy. Appropriate dosage to maintain normal TSH levels is necessary to avoid adverse cardiovascular effects of mild hormone excess or deficiency.

B. Various cardiac abnormalities have been described: shorter isovolumetric contraction time and pre-ejection period; increased heart rate; increased number of atrial premature beats; increased left ventricular mass; impaired left ventricular diastolic function (impaired relaxation); reduced exercise performance; reduced peak workload and peak oxygen uptake; increased peak aortic flow; increased left ventricular mass; and an increase in prevalence of atrial fibrillation.

C. Subclinical hyperthyroidism is also associated with an increased mortality, especially from cardiovascular disease.

4. Despite the high prevalence of subclinical thyroid dysfunction in the general population, treatment of this condition is controversial. This review concluded that minimal “persistent” changes in thyroid hormone levels cause significant changes in the heart.

5. “Subclinical thyroid dysfunction is not a compensated biochemical state.” Timely treatment could help prevent cardiovascular involvement.” (Eg, judicious thyroxine replacement for high TSH states; beta-blockers or low-dose anti-thyroid drugs for low TSH states.)

Annals Int Med December 3, 2002; 137: 904-14 Review article, fist author Bernadette Biondi, University of Naples Federico II School of Medicine, Naples, Italy. www.annals.org

Comment:
The authors state that not all of the cited cardiovascular abnormalities have been confirmed. They have chosen studies which support their enthusiastic point of view. Nevertheless, I believe that primary care clinicians will encounter patients with these subclinical states and then will be faced with a decision to treat, ignore, or follow. Testing for autoantibodies in patients with high TSH may aid decision.

I would favor judicious treatment of the subclinical hypothyroid state with low-dose thyroxine and careful titration and follow-up. Overt hypothyroidism may be prevented. Care not to over treat! For low TSH states, an individual decision based on symptoms may lead to beta-blocker therapy. RTJ

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Another Indication For The “If” Prescription

12-11 ANTIBIOTICS FOR ACUTE PURULENT RHINITIS

Muco-purulent rhinitis is a component of the common cold for which antibiotics are often prescribed, but are generally ineffective. Guidelines specifically recommend against using antibiotics to treat rhinitis. “Nevertheless, the color of the nasal discharge doubles the odds of being prescribed antibiotics.” A recent study reported that, while no general practitioners would prescribe antibiotics for clear rhinitis, about ¾ would prescribe them for purulent rhinitis.
A recent study led to a reassessment of efficacy. It reported that amoxicillin was associated with a reduction in purulent symptoms from 14 days to 9 days. Other studies have also reported benefit, including a Cochrane review of purulent rhinitis lasting over 10 days which reported a benefit from antibiotics with a number needed to treat (NN T) of 6.

Guidelines suggest that antibiotics are ineffective. This may not be true. However, the modest benefit for this condition, which is rarely life-threatening, may warrant constraint on their use because of side effects, cost, development of antibiotic resistance, and promotion of use of health services.

What should primary care clinicians do?

Perhaps they should consider delayed prescriptions in an attempt to meet demand from patients while maintaining evidence-based integrity. “Hopefully, increasing numbers of patients will accept that infections of the upper respiratory tract are typically self-limiting, or as we often tell patients “bodies are much cleverer than doctors”. We may tell them that the benefits of antibiotics for purulent rhinitis range from no benefit to a one in 10 chance that they will work. If they are prepared to wait, the condition is likely to get better on its own.

BMJ December 7, 2002; 325: 1311-12 Editorial by Bruce Arroll and Timothy Kenealy, University of Auckland, New Zealand. www.bmj.com/cgi/content/full/325/7376/1311

Comment:

Give the patient a prescription for the antibiotic with the advice not to fill it unless the symptoms do not improve or worsen within 2 to 3 days.

I believe we should give, with judicious clinical judgment, an “if” prescription more frequently to primary care patients. Many will never fill them. I believe the most important reason we can give (at least in the USA) is the likelihood of adverse reactions. RTJ

Simplifying The Regimen, And Extending The Protection Period

12-12 LOW DOSE MIFEPRISTONE AND TWO REGIMENS OF LEVONORGESTREL FOR EMERGENCY CONTRACEPTION

The old standard emergency contraception (ER; the Yuzpe regimen) consisted of two doses of ethinylestradiol and levonorgestrel 12 hours apart. Recently, two doses of 0.75 mg of the progestogen levonorgestrel, administered 12 hours apart, up to 48 hours after unprotected intercourse, has been found effective and is approved in more than 80 countries.

A single low-dose of 10 mg of, mifepristone (RU 486; an anti-progesterone), is also effective.

This study compared effectiveness of a single dose of mifepristone with a single 1.5 mg dose of levonorgestrel and two doses of 0.75 mg 12 hours apart.

Conclusion: The three regimens were similarly efficacious. A single dose of levonorgestrel can be substituted for the two-dose regimen.
STUDY
1. Randomized, double blind multi-country trial entered over 4000 women. All were healthy and had regular menses. All requested EC within 120 hours of one unprotected coitus. All had a normal menstrual cycle before the current cycle. A sensitive test ruled out pregnancy. None wished to continue a pregnancy should EC fail.
2. Randomized to:
   A. 10 mg single dose mifepristone.
   B. 1.5 mg single dose of levonorgestrel.
   C. Two doses of 0.75 mg levonorgestrel 12 hours apart.
3. Primary outcome = unintended pregnancy.

RESULTS
1. Pregnancy rates and prevented pregnancy:

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Pregnancies</th>
<th>Expected pregnancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mifepristone</td>
<td>1359</td>
<td>21 (1.55%)</td>
<td>108</td>
</tr>
<tr>
<td>One dose levonorgestrel</td>
<td>1356</td>
<td>20 (1.47%)</td>
<td>111</td>
</tr>
<tr>
<td>Two dose levonorgestrel</td>
<td>1356</td>
<td>24 (1.77%)</td>
<td>106</td>
</tr>
</tbody>
</table>
2. Delay in treatment after intercourse:
   1 – 3 days – 79% to 82% of expected pregnancies prevented.
   4 – 5 days – 60% to 63% of expected pregnancies prevented.
   (This extends the protective period to 5 days, although efficacy diminishes with time.)
3. Adverse effects:
   Nausea occurred in 15% and vomiting in 1% of groups; diarrhea in 3% to 5%.
   (No significant difference between groups.)
   Fatigue, dizziness headache, lower abdominal pain, and breast tenderness reported in up to 15% with no differences between groups.
   Lower abdominal pain occurred in 31% of the levonorgestrel groups and in 19% of the mifepristone group. Delay in menses occurred in 9% of mifepristone group, slightly more frequent than the other 2 groups. Bleeding within the first week occurred in 19% of the mifepristone group and in 31% of the levonorgestrel groups.
4. Many more women in developed countries reported side effects than in developing counties.
   (This is certainly a provocative comment. RTJ)

DISCUSSION
1. There was no significant difference in efficacy between the 3 regimens.
2. Mifepristone delays ovulation. This results in a longer cycle and later return of menses. A delay in menses adds to anxiety. There is a continued risk of pregnancy if women have unprotected coitus after
mifepristone as compared with levonorgestrel.

3. The levonorgestrel dose need not be split. A single dose simplifies treatment and does not increase side effects.

4. Although efficacy declines, EC still prevented a high percentage of pregnancies for up to 5 days.

CONCLUSION

Single-dose mifepristone, single-dose levonorgestrel and two-dose levonorgestrel were very efficacious and prevented a high percentage of pregnancies. There was no difference in efficacy.

A single dose of levonorgestrel can be substituted for the two-dose regimen.

Efficacy extends, but diminishes, for up to 5 days.


www.thelancet.com

Comment:

Mifepristone and uncombined levonorgestrel and are difficult to obtain in the USA.

Many preparations combining levonorgestrel/ethinyl estradiol are available in tablets. (Birth control pills)

These preparations are probably the most frequently used for EC in the USA. The USA lags behind much of the rest of the world in making EC freely available.

The definition of pregnancy and abortion varies between advocates. I believe most persons in the USA believe that pregnancy begins with implantation. If so, EC is not abortion. It prevents implantation. This can be most reassuring to many. What if the patient is already pregnant when the EC is taken? I believe anomalies would be rare. But if a fetal malformation did occur, even though not related to the EC, both the patient and clinician would probably feel some guilt. RTJ

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