PRACTICAL POINTERS

FOR

PRIMARY CARE

ABSTRACTED MONTHLY FROM THE JOURNALS

AUGUST 2001

SYSTOLIC HYPERTENSION, UNDERDIAGNOSED AND UNDER TREATED.

CONTROL OF SYSTOLIC HYPERTENSION, A NATIONAL PRIORITY

HORMONE REPLACEMENT REDUCES PROGRESSION OF HYPERTENSION

HAND HYGIENE, NOW EASIER AND MORE CONVENIENT

NEW BOLUS THROMBOLYTIC AGENTS

EFFICACY OF CLOPIDOGREL + ASPIRIN FOR ACUTE CORONARY SYNDROMES

SELECTIVE COX-2 INHIBITORS AND RISK OF MYOCARDIAL INFARCTION

STATIN DRUGS REPORTED TO REDUCE RISK OF MACULAR DEGENERATION

SCREENING COLONOSCOPY PREFERABLE TO SIGMOIDOSCOPY AND FBOT

MANAGEMENT OF THE NODULAR THYROID

HRT INCREASES BONE DENSITY IN FRAIL ELDERLY WOMEN

PROGNOSTIC IMPORTANCE OF ELEVATED JUGULAR PULSE AND 3RD HEART SOUND

MACKENZIE'S DESCRIPTION OF JUGULAR VENOUS PULSE 100 YEARS AGO

POSTTRAUMATIC STRESS DISORDER, COMMON, DISABLING, AND TREATABLE

SUBCLINICAL HYPERTHRYOIDISM.

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HIGHLIGHTS AUGUST 2001

8-1 CHARACTERISTICS OF PATIENTS WITH UNCONTROLLED HPERTENSION IN THE U.S.

Most cases of uncontrolled hypertension consist of isolated systolic hypertension in older adults, most of whom have access to health care.

Treatment of systolic hypertension does not remove the cause. (Ie, does not improve compliance of large vessels.) This risk factor remains. Nevertheless, reducing the systolic load probably slows progression of the stiffening, and lowers risk of endothelial rupture and arterial thrombosis.

Practical point: Primary care clinicians have the opportunity and responsibility of diagnosing and treating systolic hypertension in their elderly patients. Treatment should begin low and continue slow. There is no urgency. It is most important to avoid adverse effects lest the patient become discouraged and discontinue treatment.

8-2 CONTROL OF HYPERTENSION — AN IMPORTANT NATIONAL PRIORITY

Epidemiologic data indicate that systolic BP is more important than diastolic as a determinant of cardiovascular risk. In patients with isolated systolic BP, antihypertensive therapy has been shown to reduce mortality and the incidence of stroke, myocardial infarction, and heart failure.

Practical point: The National Heart, Lung, and Blood Institute recommends that systolic BP become the major end point for the detection, evaluation, and treatment of hypertension. "Clearly, a shift needs to occur in clinical practice to focus more on the management of systolic rather than diastolic hypertension."

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8-3 HORMONE REPLACEMENT THERAPY AND LONGITUDINAL CHANGES IN BLOOD PRESSURE IN POSTMENOPAUSAL WOMEN

Postmenopausal women taking HRT had a smaller increase in systolic BP over time than non-users. The difference increased with age.

Practical point: Primary care clinicians may consider this another mechanism for the protective effect of HRT. For those clinicians who believe the benefits of HRT outweigh the harms, another reason to prescribe it.

8-4 HAND HYGIENE

Proper hand hygiene could reduce the incidence of transmission of infection. Washing with soap and water is not the only (or even the most effective) way of reducing transmission of organisms.

The Hand Hygiene group now recommends use of a alcohol-glycerol hand rubs between patients. They are quick to use (10 to 20 seconds) and can be used while walking or talking. This overcomes the objections to soap and water washing which takes time and requires presence of sinks.

Practical point: Clinicians — use this convenient, quick hand wash between patients

8-5 EFFICACY AND SAFETY OF TENECTEPLASE IN COMBINATION WITH ENOXAPARIN, ABCIXIMAB, OR UNFRACTIONATED HEPARIN: The ASSENT-3 Randomised Trial in Acute Myocardial Infarction

Tenecteplase is a new genetically engineered variant of alteplase (tPA; tissue plasminogen activator). It provides a new standard of fibrinolytic therapy by virtue of its equivalent efficacy with regard to 30-day mortality, its reduced propensity for bleeding complications, and its simple administration as a bolus.

“In view of the present data and the ease of administration, enoxaparin might be regarded an attractive alternative anticoagulant given in combination with tenecteplase.”

Taking into account efficacy and safety, the combination of full-dose bolus tenecteplase + enoxaparin for 7 days emerged as the best treatment in this trial. Because of ease of administration and the lack of monitoring of anticoagulation, this combination should be regarded as an attractive alternative pharmacological reperfusion strategy deserving further study.

Practical point: Primary care clinicians will soon have the opportunity and responsibility to apply immediate (bolus)

out-of-hospital thrombolysis.

8-6 EFFECTS OF CLOPIDOGREL IN ADDITION TO ASPIRIN IN PATIENTS WITH ACUTE CORONARY SYNDROMES WITHOUT ST-SEGMENT ELEVATION

The anti-platelet agent clopidogrel (*Plavix*) given in addition to aspirin, had significant benefits in patients with acute coronary syndromes without ST elevation. The risk of major bleeding was increased.

Practical point: Primary care clinicians and their patients should consider the benefit/harm/cost ratio of clopidogrel. Harms are significant, costs high. but benefits may be life saving. The stakes are high.

8-7 RISK OF CARDIOVASCULAR EVENTS ASSOCIATED WITH SELECTIVE COX-2 INHIBITORS.

The new selective COX2 inhibitors (rofecoxib *Vioxx*; celecoxib *Celebrex*) are pro-thrombotic. Meta-analyses thus far indicate an association with increased incidence of cardiovascular events compared with non-selective NSAIDs and placebo.

Practical point: COX-2 inhibitors should be used with caution in patients with established coronary disease and those at high risk of atherosclerosis.

8-8 RISK OF MACULAR DEGENERATION IN USERS OF STATINS

An exciting, but preliminary report of considerable lowering of risk of macular degeneration in older persons taking statin drugs.

8-9 ONE-TIME SCREENING FOR COLORECTAL CANCER WITH COMBINED FECAL OCCULT-BLOOD TESTING AND EXAMINATION OF THE DISTAL COLON

One-time screening of asymptomatic subjects with FBOT plus sigmoidoscopy failed to identify about 1 of every 4 subjects with advanced neoplasia.

Practical point: Primary care clinicians should advise all patients over 50 to undergo periodic colonoscopy and omit FBOT and sigmoidoscopy.

8-10 MANAGEMENT OF NODULAR THYROID DISEASE

Although the optimum diagnostic strategy for euthyroid patients with nodular thyroid disease is still a matter of debate, there is agreement that fine needle aspiration cytology and tests of thyroid function are cornerstones of investigation.

The challenge remains identifying which palpable nodules are malignant.

The advice regarding investigation of nodules to detect cancer differs from the old tradition in several ways:

1. Radionuclide scanning and ultrasound may not reliably differentiate malignant from benign nodules.
2. TSH suppression with thyroxine is not indicated.
3. Differentiating single and multinodular goiters is not helpful in assessing risk of cancer.
4. Overt thyroid dysfunction effectively rules out malignancy

8-11 BONE MINERAL DENSITY RESPONSE TO ESTROGEN REPLACEMENT IN FRAIL ELDERLY WOMEN

In physically frail women, mean age 82, 9 months of HRT significantly increased BMD.

Traditional thought has been that the estrogen-dependent compartment of bone becomes depleted approximately 15 years after menopause. This concept has been challenged by those who believe that estrogen deficiency is also primarily responsible for the continuing decline in BMD that previously had been attributed to aging.

It was once commonly believed that bone turnover remained elevated for only a few years after menopause and that bone loss subsequently slowed or ceased in older women. Recent studies provide evidence that bone turnover remains elevated into old age and that bone loss may accelerate rather than slow in the elderly. (Subjects in this study had high rates of bone turnover as indicated by serum and urine markers.)

Practical point; Primary care clinicians should inform their elderly female patients of the possibility that bone sparing therapy is effective regardless of age, and allow them to make an informed choice to accept or reject.

8-12 PROGNOSTIC IMPORTANCE OF ELEVATED JUGULAR VENOUS PRESSURE AND A THIRD HEART SOUND IN PATIENTS WITH HEART FAILURE.

Detection of elevated jugular venous pressure or a third heart sound in patients with HF was associated with adverse outcomes including progression of HF.

Practical point: The physical examination identifies a subset of patients with a poor prognosis who would benefit from heightened therapeutic interventions.

8-13 THE JUGULAR VENOUS PULSE AND THIRD HEART SOUND IN PATIENTS WITH HEART FAILURE

Read the description of the jugular venous pulse described by Mackenzie in 1903.

8-14 RECOGNITION AND TREATMENT OF POSTTRAUMATIC STRESS DISORDER.

PTSD is a worldwide problem which is reaching alarming proportions. It is associated with persistent disability and comorbidity. Treatment can produce a meaningful reduction in distress. The condition must first be recognized.

Practical point: Primary care clinicians will be seeing more patients with PTSD. Certainly they can elicit patient's experiences and feelings and listen empathetically. Compassionate understanding and treatment with selective serotonin reuptake inhibitors will benefit. There is no reason PTSD cannot be treated effectively in primary care.

8-15 SUBCLINICAL HYPERTHYROIDISM

"Subclinical hyper-thyroidism". (**SCHyperT**) is defined as — the combination of an *undetectable* serum thyrotropin concentration (**TSH**), as measured by an assay with a threshold of detection that is 0.1mU per liter or less, and *normal* serum thyroxine and triiodothyronine concentrations (usually at the upper end of the normal range).

For the many with endogenous SCHyperT who do not have multinodular goiter, and no complications from excess endogenous thyroxine production, treatment is not necessary. Thyroid function tests should be done every 6 months. Recognize that serum T3 may become elevated before T4.

Treatment of patients with SCHyperT due to nodular goiter is more routinely justified given the expected progression to overt hyperthyroidism. "It would be surprising if the complications of overt hyperthyroidism were not seen, albeit at a reduced frequency, in a condition that is effectively the mildest form of thyrotoxicosis."

Practical point: These patients should be followed for development of osteoporosis and atrial fibrillation.

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Focus on the Elderly With Isolated Systolic Hypertension

8-1 CHARACTERISTICS OF PATIENTS WITH UNCONTROLLED HYPERTENSION IN THE UNITED STATES

The percentage of hypertensive patients in whom the hypertension is controlled (defined as <140/90) is widely viewed as unsatisfactory. Many individuals are not aware that they have hypertension. Many are aware, but are not receiving treatment. Many more are being treated, but remain poorly controlled. It is estimated that only about 1/4 of patients are adequately controlled.

Control of hypertension is one of primary care clinicians' most common responsibilities.

This study analyzed data from a national survey (1995-96) to assess the role of access to, and the use of, health care in the control of hypertension.

Conclusion: Most cases of uncontrolled hypertension in the US consist of isolated systolic hypertension in older adults who have access to health care.

STUDY

1. The National Health and Nutrition Survey included over 16 000 adults at least 25 years of age.
2. From this base, estimated the prevalence of hypertension (> 140/90) and the number of those unaware of their hypertension, those untreated, those treated but uncontrolled, and those adequately controlled.

RESULTS

1. Estimated total number with hypertension in the US = 42 million
2. In millions:

	Age 25-44	Age 45-64	Age >64
Distribution by age	8	16	19
Unaware of hypertension	3	4	6
With hypertension known but not treated	2	3	2
With inadequately treated hypertension	1	4	7
Treated and controlled	2	5	4

3. About 75% of all subjects who were unaware that they had hypertension had a diastolic under 90; about 75% of those with uncontrolled, treated hypertension had a diastolic under 90; and about 60% of those with acknowledged untreated hypertension had a diastolic under 90.
4. The systolic BP elevation was mild in these 3 groups as assessed on the basis of historical standards.
5. Thus, "hypertension" in the US predominates as isolated systolic hypertension in the elderly. The pattern of an elevation of systolic and a normal diastolic was dominant in those over age 45. Only in the younger age group with hypertension was the average diastolic over 90.
6. Several factors were associated with lack of awareness of hypertension and acknowledged uncontrolled hypertension: Age > 65 (associated with the largest attributable risk for both outcomes); male sex; not having visited a physician in the past year; and black race.

DISCUSSION

1. The analysis yielded 4 important observations underlying poor control of hypertension:
   1) Undiagnosed, as well as treated but uncontrolled hypertension, occurs largely under the watchful eye of the health care system.
   2) Problems with lack of control are largely concentrated among older members of our society.
   3) Lack of control is *not* confined to the poor, the uninsured, or minorities;
   4) The pattern of an elevation in systolic (> 140) and a diastolic less than 90 predominates not only in the elderly, but among the middle-aged as well.
2. This dispels the stereotype that the typical patient with uncontrolled hypertension is a young man (typically black) who does not visit the physician or who will not take antihypertensive drugs regularly.
3. The increased prevalence in the elderly occurs despite that older Americans have the most frequent contact with the health system, and is the group most likely to have medical insurance.
4. There is persistent controversy about the appropriateness of the current treatment goal — a systolic under 140 in the elderly. More clinical trials are needed, particularly in view of the National High Blood Pressure Program calling for use of systolic as the chief diagnostic and management criterion. Randomized trials however, do provide evidence of the benefit of antihypertension drugs in elderly persons with systolic over 160 and a diastolic under 90. There is no such evidence regarding persons with only a mild elevation of systolic (140 - 160).

CONCLUSION

Most cases of uncontrolled hypertension consist of isolated, mild systolic hypertension in older adults, most of whom have access to health care.

NEJM August 16, 2001; 345: 479-86 Original investigation, first author David J Hyman, Baylor College of Medicine, Houston TX **www.nejm.org**

Comment:

The National High Blood Pressure Program calls for use of systolic BP as the chief diagnostic and management criterion. The realization that isolated systolic hypertension is the chief risk factor for complications of hypertension is a sea change from the old teaching that diastolic was the offender.

Primary care clinicians should treat isolated systolic hypertension in the elderly as well as in middle age. Treatment is lifelong and includes life-style changes as well as drugs. Drugs should be started at low dose and gradually increased. A combination of drugs is often required to attain a goal of at least under 160. Low dose diuretics + a beta-blocker, or a low dose diuretic + a *long acting* dihydropyridine calcium blocker are preferred combinations in the elderly with isolated systolic hypertension. (There are 7 "dipine" drugs on the market. [Eg, amlodipine, felodipine.] Diltiazem and verapamil are non-dihydropyridine and should not be used for this purpose.)

Some clinicians still advocate beginning with one drug and titrating up to maximum dose, and only then adding a second if adequate control is not achieved. I believe this is a bad approach since adverse effects are usually related to higher doses, not to idiosyncratic reactions to the drug. Better to add a second and third low-dose drug to a first low-dose drug.

The goal of achieved BP depends on the totality of risk factors. Those with lipid problems, diabetes, obesity, sedentary life styles should receive more aggressive BP-lowering therapy. RTJ

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NIH recommends systolic become the major endpoint for detection and treatment

8-2 CONTROL OF HYPERTENSION — AN IMPORTANT NATIONAL PRIORITY

Epidemiological data indicate that systolic BP is more important than diastolic as a determinant of cardiovascular risk. In patients with isolated systolic hypertension, antihypertensive therapy has been shown to reduce mortality and incidence of stroke, myocardial infarction, and heart failure. "Clearly, a shift needs to occur in clinical practice to focus more on the management of systolic rather than diastolic hypertension." The National Heart, Lung, and Blood Institute recommends that systolic BP should become the major end point for the detection, evaluation, and treatment of hypertension.

Therapy is not simple. Long-term adherence to a treatment program is a problem. About half of patients discontinue antihypertension drugs within a year. Problems with compliance include: patients' knowledge, attitudes, and beliefs; adverse effects; costs; availability of support systems; physician-patient relationship; and organization of the health care system.

Systolic hypertension in the elderly is usually due to age-related reduction in elasticity and compliance of large and medium-sized arteries. Elevated systolic BP and elevated pulse pressure increase risk of cardiovascular events. Although excessive lowering of BP can be a problem, particularly in frail elderly patients, most older patients with systolic hypertension tolerate reductions well. There is evidence that cognitive function is not impaired by antihypertension therapy, and may even be improved.

Although there is conclusive evidence to warrant treatment in those with systolic above 160, no large scale clinical trial has been performed to assess the value of therapy in those between 140 and 160.

Lifestyle modifications certainly can be advised without fear of adverse effects. This includes diet high in fruits, vegetables, grains, and low-fat dairy products, and low in salt.

When deciding on drug therapy for mild systolic hypertension, clinicians should evaluate the patient's entire cardiovascular risk pattern, and treat, not only the BP, but lipid abnormalities, smoking, blood glucose, weight, and physical inactivity.

NEJM August 16, 2001; 345: 534-35 Editorial by Aram V Chobanian, Boston University School of Medicine, Boston, Mass. www.nejm.org

Comment:

Drug treatment of systolic hypertension does not affect the cause of the hypertension (loss of elasticity and compliance of large vessels). Nevertheless reducing systolic BP does result in clinical benefit.

Elderly patients have difficulty in following a long-term treatment protocol for hypertension. Much of the difficulty is due to 3 factors: 1) adverse effects, 2) cost, and 3) complexity of the regimen.

Adverse effects of antihypertension drugs can be lessened by starting at low doses (lower than PDR-recommended starting doses) and very gradually titrating upward as needed. When a higher dose is required, adding a second or 3rd drug at low dose will lead to fewer adverse effects than would occur if the dose of a single drug is increased to maximum. Accepting an end-point somewhat higher than the suggested 140. Reducing systolic from 180 to 160 may result in more benefit than reducing it from 160 to 140.)

Cost can be minimized by using generic drugs (hydrochlorothiazide and beta-blocker) and by using a pill cutter. Using once-a-day dosage simplifies the regimen. RTJ

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A possible added benefit

8-3 HORMONE REPLACEMENT THERAPY AND LONGITUDINAL CHANGES IN BLOOD PRESSURE IN POSTMENOPAUSAL WOMEN

Systolic BP increases with advancing age in both sexes. After middle age, both systolic and diastolic BP become higher in women than in men. Is this increase in women related to estrogen deficiency?

This study hypothesized that hormone replacement therapy (**HRT**) would be associated with a lesser increase in BP in postmenopausal women as they age.

Conclusion: Women taking HRT had a smaller increase in systolic BP over time than those not taking HRT.

STUDY

1. "The Baltimore Longitudinal Study on Aging", an observational study, followed 226 postmenopausal women (mean age 64 at baseline). All were healthy.
2. Measured lifestyle variables, BP, and traditional cardiovascular risk factors at baseline and every 2 years thereafter.
3. Determined use of HRT.

RESULTS

1. Of the 226, 77 continuously used estrogen/progestin; 149 used neither.
2. At baseline, systolic BP was similar in both groups. (132 mm Hg vs 134)
3. Users who were age 55 at baseline experienced a systolic BP increase of 8 mm over 10 years vs

an increase of 19 mm Hg in non-users.

4. The difference was more evident in older ages. After 10 years of use, at age 65 the increase in systolic BP was 7 mm Hg in users vs 26 mm Hg in non-users.
5. Diastolic BPs did not differ.

DISCUSSION

1. Postmenopausal women have significantly higher systolic and diastolic BPs than premenopausal women.
2. The increase in systolic BP over time was significantly smaller in women taking HRT continuously.
3. The difference in systolic BP between users and non-users increased with age. These differences may not apply to older women with hypertension at baseline.
4. The investigators suggest several mechanisms: Arterial stiffness increases with aging. (Reflected by an increase in systolic BP.) Estrogen may reduce collagen accumulation, lessen loss of elastin and reduce smooth muscle proliferation in arterial walls.
5. HRT may increase production of endothelial-dependent nitric oxide (NO), with resultant vasodilation.
6. Diastolic BP is influenced primarily by peripheral vascular resistance, which represents the tone of small arteries. Although diastolic BP increases modestly up to middle age, it generally levels off and may even decrease in old age.

CONCLUSION

Postmenopausal women taking HRT had a smaller increase in systolic BP over time than non-users. The difference increased with age.

Annals Int Med August 21, 2001; 135: 229-38 Original investigation, first author Angelo Scuteri, National Institute of Aging, NIH and Johns Hopkins University, Baltimore, MD **www.annals.org**

Comment:

The biological basis for believing HRT is protective against atherosclerotic disease is strong. It benefits lipids and systolic BP, both strong predictors of cardiovascular disease. However, recent investigations report that estrogen is related to an *increase* in risk of cardiovascular disease, at least in the first year of use. This has been attributed to a possible estrogen-related increase in thrombogenic activity. Thereafter, risk seems to be lessened, and there may even be a benefit. Women who enter the menopause at high risk of cardiovascular disease should be cautious about starting HRT and, if they choose HRT, should take low doses of estrogen with prophylactic low-dose aspirin for at least a year.

For those of us who continue to believe in the protective benefits of HRT, this article adds another possible mechanism and gives encouragement to those who, with caution, prescribe HRT. RTJ

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Much Easier Now

8-4 HAND HYGIENE

A hand hygiene liaison group has been formed in the UK. Their purpose is to reduce transmission of infection. The group recognizes that washing with soap and water is *not* the only (or even the most effective) way of reducing transmission of organisms. They focused on some practical recommendations on easy ways of improving hand hygiene.

Hospital acquired infection is a serious and costly problem. It results in an increase in antimicrobial resistance. Methicillin resistant *Staphylococcus aureus* (MRSA), a surrogate marker for hospital acquired infection, is responsible for almost half of the cases of *S aureus* bacteremia and surgical wound infection. Proper hand hygiene could reduce the incidence.

Patient contact results in contamination of worker's hands. Dressing wounds resulted in an 80% chance of carrying MRSA on the hands for up to 3 hours. Forty percent of all patient-nurse interactions on an intensive care unit resulted in transmission of Klebsiella to the nurse's hands, even after minimal contact such as touching a patient's shoulder. The risk of transfer is proportional to the number of times a patient is touched. Hand washing removes the organisms.

What to do?

A. If there is soiling, formal hand washing with soap and water is required.

B. In no soiling, the group now recommends use of alcohol-glycerol hand rubs between patients.

They are quick to use (10 to 20 seconds) and can be used while walking or talking. This overcomes the objections to soap and water washing which takes time and requires presence of sinks.

A recent study reported that hand rubs cause less skin irritation than soap and water. Alcohol-based hand rubs may decontaminate hands more effectively than soap and water.

Hand hygiene is effective in reducing transmission. If "hand hygiene" were a new drug it would be accepted without question.

The issue is no longer whether hand hygiene is effective, but how to produce a sustained improvement in health care worker's compliance. We should adopt a standard that alcohol hand rub is available at every bedside.

BMJ August 25, 2001; 323: 411-12 Editorial, first author Louise Teare, Hand Hygiene Liaison Group, Chelmsford Public Health Laboratory, Chelmsford, UK **www.bmj.com/cgi/content/full/323/7310/411**

Comment:

Many clinicians pay lip-service to hand washing between patients. Washing at a sink with tap water is too disrupting and time-consuming.

If made available, I believe most primary care physicians would use alcohol-glycerin hand rubs between patients seen in the office and clinic. RTJ

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Bolus fibrinolytic agent + 7-day low-molecular weight heparin the best combination.

8-5 EFFICACY AND SAFETY OF TENECTEPLASE IN COMBINATION WITH ENOXAPARIN, ABCIXIMAB, OR UNFRACTIONATED HEPARIN: The ASSENT-3 Randomised Trial in Acute Myocardial Infarction

(*This remarkable trial was conducted in 575 hospitals and 26 countries. The participating investigators are listed in over a page of fine print.*)

Tenecteplase is a new genetically engineered variant of tissue plasminogen activator alteplase (*Activase*; tPA). It provides a new standard of fibrinolytic therapy by virtue of its equivalent efficacy with regard to 30-day mortality, its reduced propensity for bleeding complications, and its simple administration as a bolus.

Antithrombotic agents are also important components of pharmacological reperfusion therapy. At present, heparin and aspirin are given routinely to many patients with acute myocardial infarction (**MI**).

Current fibrinolytic therapies fail to achieve optimum reperfusion in many patients with acute MI. The combination of heparin with the new platelet inhibitors (glycoprotein IIb/IIIa inhibitors) improves reperfusion. Pilot studies with platelet glycoprotein IIb/IIIa inhibitors combined with reduced-dose fibrinolytic agents have also shown improved reperfusion.

This study of patients with acute MI, compared the efficacy and safety of 3 different therapeutic regimens using a new bolus thrombolytic.

Conclusion: Tenecteplase + enoxaparin, a low-molecular weight heparin, was considered the best combination.

STUDY

1. Followed over 6000 patients with acute ST-elevation MI. Assigned to one of 3 regimens, each of which contained the bolus fibrinolytic, tenecteplase. All were within 6 hours of onset.
2. Randomized to:
    1) Full dose tenecteplase + enoxaparin (*Lovenox* — a low-molecular weight heparin) for a maximum of 7 days (enoxaparin group)
    2) Half dose tenecteplase + 12-h infusion of abciximab (a glycoprotein IIb/IIIa platelet inhibitor) + weight-adjusted low-dose unfractionated heparin for 48 h (abciximab group)
    3) Full dose tenecteplase + weight adjusted unfractionated heparin for 48 h (unfractionated heparin group)
3. Enoxaparin was given as an intravenous bolus followed by a subcutaneous dose every 12 h. Abciximab was given as a bolus followed by an infusion for 12 h. Tenecteplase was given as a bolus over 5 seconds, dose according to body weight, after the bolus form of the other agents was given.
4. All received aspirin in addition.
5. Primary endpoints:
    1) Composite of 30 day mortality + in-hospital reinfarction or in-hospital refractory ischemia. (efficacy endpoint)
    2) Above composite + in-hospital intracranial hemorrhage or in-hospital major bleeding complications (efficacy + safety endpoint)

RESULTS

1. Efficacy endpoint: The enoxaparin and the abciximab groups were associated with more benefit than the unfractionated heparin group. (Unfavorable outcomes = 11.4%; 11.1%; and 15.4%)
2. Efficacy + safety endpoints: Also more benefit in the enoxaparin and in the abciximab groups than in the unfractionated heparin group. (Unfavorable outcomes = 13.7%; 14.2%; and 17.0%).

DISCUSSION

1. In patients with an acute MI, treatment with full dose tenecteplase + enoxaparin, as well as half dose tenecteplase + abciximab + unfractionated heparin reduced ischemic complications of acute MI when compared with full dose tenecteplase + unfractionated heparin.
2. Benefits appeared shortly after start of treatment.
3. In the tenecteplase + enoxaparin group there was no increase in intracranial hemorrhage, no excess thrombocytopenia, and only a non-significant increase (~ 3%) in major bleeding despite the 7-day length of treatment.
4. “In view of the present data and the ease of administration, enoxaparin might be regarded an attractive alternative anticoagulant given in combination with tenecteplase.”

5. However, what role the various pharmacological combinations will ultimately have in conjunction with early coronary interventions remains to be determined.
6. “Taking into account efficacy and safety, the combination of full-dose tenecteplase + enoxaparin emerged as the best treatment in this trial.” Because of ease of administration and the lack of monitoring of anticoagulation, this combination should be regarded as an attractive alternative pharmacological reperfusion strategy deserving further study.

CONCLUSION

The new fibrinolytic agent, tenecteplase, given as a bolus along with the low-molecular weight heparin, enoxaparin, given over 7 days, on the basis of efficacy and safety, was considered the best choice.
The ease of bolus administration is a benefit.

Lancet August 25, 2001; 358: 605-13 Original investigation by the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT-3) Investigators

Comment:

The advent of bolus fibrinolytic agents will place more burden on primary care clinicians and first responders to patients with an acute ST-elevation MI who do not have immediate access to emergency departments. Every minute counts.

The study did not compare the old fibrinolytic (alteplase; tPA; *Activase*) with the new bolus preparation tenecteplase. It cites a study "Single-Bolus Tenecteplase Compared with Front-Loaded Alteplase in Acute Myocardial Infarction" Lancet 1999; 354: 716-22. That study concluded that tenecteplase and alteplase were equivalent in 30 day mortality for treatment of acute MI.

The advantage of tenecteplase and other bolus fibrinolytics is in their convenience of administration and the opportunity to administer rapidly out-of-hospital. Activase is administered intravenously over 90 minutes in three different stages.

I did not abstract this article as a definite answer to fibrinolysis and reperfusion. I abstracted it to emphasize the coming-out of the new bolus fibrinolytic agents. There are now 3 "teplase" drugs under review. RTJ

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Long-Term Benefits of A Newer Antiplatelet Agent. (Plavix)

8-6 EFFECTS OF CLOPIDOGREL IN ADDITION TO ASPIRIN IN PATIENTS WITH ACUTE CORONARY SYNDROMES WITHOUT ST-SEGMENT ELEVATION

Acute coronary syndromes *without* ST elevation (unstable angina and non-ST segment elevation MI) are caused by thrombus formation on a ruptured or eroded atherosclerotic plaque. In these patients, aspirin and heparin reduce risk of death from new cardiovascular causes, new myocardial infarction (**MI**), and recurrent ischemia. But, substantial risk in both short and long-term remains despite current treatments.

This study assessed the efficacy and safety of the antiplatelet agent clopidogrel (*Plavix*) given in addition to aspirin in these patients. Clopidogrel and aspirin decrease platelet aggregation through different pharmacological effects. They may act synergistically.

Conclusion: Long-term clopidogrel in addition to aspirin provided more benefit than aspirin alone.
Risk of bleeding increased.

STUDY

1. Randomized over 12 500 patients (mean age 64) with acute non-ST elevation coronary syndromes.

All presented within 24 hours of onset. All had ECG changes and/or elevated cardiac enzymes at entry.

2. Randomized to: 1) clopidogrel 300 mg orally immediately followed by 75 mg once daily for up to 12 months. or 2) placebo.
3. All received daily aspirin and other drugs as indicated.
4. Follow-up = mean of 9 months

RESULTS

1. The first primary outcome — a composite of death from cardiovascular causes, nonfatal MI, or stroke — occurred in 9.3% of clopidogrel group vs 11.4% in placebo group. [NNT(benefit 1 patient over 9 months) = 48]
2. Second primary outcome — the first primary outcome or refractory ischemia— occurred in 16.5% of the clopidogrel group vs 18.8% of the placebo group. [NNT = 43]
3. The percentages of patients with in-hospital refractory or severe ischemia, heart failure, and revascularization were significantly lower in the clopidogrel group. (*By my calculation, the NNT varied between 100 and 143. RTJ*)
4. Benefits were evident within 24 hours.
5. Adverse effects: Major bleeding occurred significantly more often in the clopidogrel group (3.7% vs 2.7%; NNT (harm one patient over 9 months) = 100). No increase in rate of hemorrhagic stroke.

DISCUSSION

1. In patients with acute coronary syndromes without ST elevation, clopidogrel was beneficial when added to aspirin and other medications (heparin, statins, ACE inhibitors, beta-blockers).The risk of MI and refractory ischemia was reduced. There was also a trend toward lower rates of ischemic stroke and death from cardiovascular causes.
2. Benefits of clopidogrel (which blocks adenosine diphosphate-induced platelet aggregation) were in addition to aspirin (which acetylates platelets).

CONCLUSION

When added to aspirin, the anti-platelet agent clopidogrel, had significant benefits in patients with acute coronary syndromes without ST elevation. The risk of major bleeding was increased.

NEJM August 16, 2002; 345: 494-502 Original investigation, by the Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators (CURE) **www.nejm.org**

Comment:

Clopidogrel is expensive — well over $100 a month. Its advantage is that it may be given by mouth over months with continuing benefits.

The glycoprotein IIb/IIIa platelet inhibitors reduce incidence of early events, but long term oral therapy is not beneficial.

Primary care clinicians and their patients (after being fully informed) must consider benefits, harms, and costs. When considering the clinical application of a given benefit/harm-cost ratio we must judge the magnitude of both benefits and harms. The NNT (benefit) of nine months of clopidogrel therapy is 48. I believe most patients would consider prevention of

death, recurrent MI, and stroke to be a great benefit. Thus, in these circumstances, a patient might opt to take one chance in 48 in order to avoid these endpoints while accepting the one chance in 100 of a major bleed. If the benefits were less clinically significant, the patient might not consider the expense worthwhile.

Newer treatments for ischemic heart disease are coming rapidly. They include improved CABG, new stents for use with PTCA, new bolus thrombolytics, new anti-platelet drugs, and their combinations. Finding the best program will require much more experience. I suspect, as usual, there will be individual preferences which require primary care clinicians to inform individual patients and negotiate long-term care.

This same group reported similar long-term benefit of oral clopidogrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention. (Lancet August 18, 2001; 358: 527-33

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Not as safe as hoped

8-7 RISK OF CARDIOVASCULAR EVENTS ASSOCIATED WITH SELECTIVE COX-2 INHIBITORS

Cyclo-oxygenase enzymes occur in 2 isoforms:

Cyclo-oxygenase-1 (**COX-1**) is an enzyme present normally at all times in many cells, including the stomach and platelets. One action of COX-1 in platelets is to produce thromboxane, a platelet activator and aggregator. Thus, *COX-1 is pro-thrombotic.*

Cyclo-oxygense-2 (**COX-2**) is not present normally. It is induced by inflammation and produces prostaglandins related to pain and fever. Another action is on platelets to produce prostacyclin, a vasodilator and inhibitor of platelet aggregation. Thus, *COX-2 is anti-thrombotic*.

Aspirin and non-selective NSAIDs (eg, naproxin) inhibit both COX-1 and COX-2. The new selective COX-2 inhibitors inhibit COX-2 and spare COX-1. (The protective action of COX-1 on the stomach is preserved.)

Aspirin binds covalently and irreversibly to both COX-1 and COX-2 in platelets. It action is prolonged — the entire life of each platelet, ~ 10 days. It inhibits both the pro-thrombotic action of COX-1 and the anti-thrombotic action of COX-2. On balance, its action on impeding the pro-thrombotic action of COX-1 is greater than its action in impeding the anti-thrombotic action of COX-2. As a result platelet aggregation and activation is impeded.

In situations where COX-2 has not been induced, aspirin acts only on COX-1, producing a greater anti-platelet, anti-thrombotic effect. *Aspirin is anti-thrombotic.*

Non-selective NSAIDs (eg naproxin) also inhibit both COX-1 and COX-2. They also have significant anti-thrombotic effects since, like aspirin, they impede action of COX-1 more than COX-2. But, the duration of their effect is much shorter than aspirin. They bind reversibly and transiently to platelets. *Non-selective NSAIDs are anti-thrombotic* albeit less so than aspirin.

The new selective COX-2 inhibitors — COX-1 sparers (rofecoxib [*Vioxx*] and celecoxib [*Celebrex*]) inhibit the anti-thrombotic effect of COX-2 and do not have any effect on COX-1. They do not impede the pro-thrombotic effect of COX-1. *Selective COX-2 inhibitors are pro-thrombotic*.

The present study hypothesized that the pro-thrombotic action of selective COX-2 inhibitors would increase risk of cardiovascular events (eg, myocardial infarction, ischemic stroke, and sudden death)

Their meta-analysis indicated the selective COX-2 inhibitors are indeed associated with an increased risk of cardiovascular events compared with naproxin and placebo. In a comparison of annualized myocardial infarction rates of a large group of patients taking placebo vs groups of patients taking rofecoxib or celecoxib incidence was higher in both COX-2 inhibitor groups (0.52%. vs 0.74% vs 0.80%).

The authors concluded that the selective COX-2 inhibitors are associated with an increased risk of cardiovascular events. This raises a cautionary flag about use of selective COX-2 inhibitors. Further study is required.

JAMA August 22/29, 2001; 286: 954-59 "Special Communication" analysis, first author Debabrata Jukherjee, Cleveland Clinic Foundation, Cleveland, Ohio. **www.jama.com**

Comment:

Patients at increased risk of cardiovascular events (eg, established coronary atherosclerosis, dyslipidemia, hypertension, diabetes) would be more at risk of cardiovascular events induced by the selective COX-2 inhibitors. These patients would likely be taking aspirin. The authors present data which indicate addition of low-dose aspirin to COX-2 inhibitors protects against the pro-thrombotic effects of selective COX-2 inhibitors. This of course negates the stomach-protecting reason for prescribing COX-2 inhibitors in the first place.

The likelihood of prothrombotic effects of COX-2 inhibitors is also increased in individuals with underlying thrombotic tendencies (eg, lupus anticoagulant, factor V Leiden).

The likelihood of gastrointestinal complications in patients taking aspirin and non-selective NSAIDs depends on preexisting risk factors — age, history of peptic ulcer, history of gi bleeding.

Thus there are complex pros and cons about use of non-selective COX-2 inhibitors. Primary care clinicians will have a puzzle to solve when advising individual patients.

For a more detailed discussion about COX-2 inhibitors see "The COXIBs, Selective Inhibitors of Cycloxygenase-2" "Drug Therapy" NEJM August 9, 2001; 345: 433-42

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If true, a remarkable benefit

8-8 RISK OF MACULAR DEGENERATION IN USERS OF STATINS

Macular degeneration (**MD**) is the main cause of blindness in the Western world.

Atherosclerosis and lipid abnormalities are associated with an increased risk of MD.

Statin drugs modify lipid profiles and lower risk of coronary heart disease. They also prevent stroke and possibly, Alzheimer's disease.

This study asked – do statins reduce risk of MD as well?

Conclusion: Risk was much lower in those taking statins.

STUDY

1. Followed 379 persons (age 66-75) regarding use of medications, including statins, currently and in the past 5 years.
2. Took stereoscopic photos of the fundi and graded them by the Wisconsin age-related maculopathy grading system.
3. Correlated statin use with risk of MD.

RESULTS

1. Of the 379, 77 (20%) had some evidence of MD.
2. Twenty seven (7%) of the 77 reported taking statins.
3. MD was less common in those taking statins:

Of the 27 taking statins, only 1 of 27 (4%) showed signs of MD

Of the 352 not taking statins, 79 (22%) showed signs of MD.

(Odds ratio for MD among takers vs non-takers = 0.14) [Confidence interval = 0.02 to 0.83]

4. In a model adjusting for age, sex, smoking, and history of coronary angioplasty or bypass grafting, the odds ratio for MD among those taking statins, compared with those not taking statins, was 0.09.

DISCUSSION

1. In this study, older patients taking statins had about 1/10 the risk of age related MD compared with those not taking statins. However, the confidence intervals were wide, giving an imprecise estimate of the risk reduction.

2. The investigators suggest several mechanisms for this association:

Statins might prevent the accumulation of the basal linear deposit in Bruch's membrane.

(This occurs with higher concentrations of plasma cholesterol.)

Antioxidant properties of statins might protect the outer retina from oxidative damage.

Simvastatin inhibits endothelial cell apoptosis and preserves ischemic vasculature. This may help to maintain a competent vascular supply to the macula.

CONCLUSION

Risk of macular degeneration was considerably less in elderly persons taking statin drugs.

BMJ August 18, 2001; 323: 375-76 Original investigation, first author Nigel F Hall, University of Southampton, UK. www.bmj.com

Comment:

This possibly fits the "too good to be true" category. If confirmed, many more elders would start taking statins. Until I moved to a retirement complex, I had no idea of how common and devastating MD is.

This study would be easy to confirm, given the widespread use of statins and the frequency of occurrence of MD in the elderly. RTJ

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Not a good idea. Colonoscopy is better

8-9 ONE-TIME SCREENING FOR COLORECTAL CANCER WITH COMBINED FECAL OCCULT-BLOOD TESTING AND EXAMINATION OF THE DISTAL COLON

Both FBOT and sigmoidoscopy have been recommended for screening for colorectal adenomas and cancer. What is the sensitivity of detection when both tests are combined?

This study assessed the sensitivity of FBOT + examination of the distal colon vs examination of the entire colon.

Conclusion: FBOT + sigmoidoscopy missed many neoplasms.

STUDY

1. Entered 2885 subjects age 50 to 75. (Mean = 60) All were asymptomatic.

2. All submitted cards from 3 days for rehydrated FBOT testing. (Rehydration increases sensitivity.)

All underwent complete colonoscopy.

3. Defined sigmoidoscopy as examination of the rectum and sigmoid colon up to the sigmoid flexure

during the colonoscopy.

4. Defined advanced neoplasia as: adenomas 10 mm or more; villous adenomas; adenoma with advanced dysplasia; or invasive cancer.

RESULTS

1. Of the 2885: Advanced neoplasia in the entire colon was present in 11%.
2. FBOT:

Overall, positive in 239 (8%). False positive rate = 6%; true positive rate = 2%

Advanced neoplasia in the entire colon was detected in 306 subjects. 182 distal; 150 proximal.

Some were present in both.

Of the 306, 24% had a positive FBOT.

(Sensitivity of FBOT in detecting advanced neoplasia was low.)

3. Sigmoidoscopy:

Detected 70% of all subjects with advanced neoplasia; missed in 30%.

4. Combined sigmoidoscopy + FBOT detected 76% of advanced neoplasia.

(*Note that when a positive FBOT test was present, or when a positive sigmoidoscopy was present, these calculations were based on the assumption that colonoscopy would be performed. Colonoscopy was considered to diagnose 100% of advanced neoplasia*.)

DISCUSSION

1. FBOT is *not* useful in detecting small tubular adenomas.
2. FBOT identified only about 1/4 of advanced neoplasia.
3. Colonoscopy must follow a positive FBOT or a positive sigmoidoscopy to complete the screening process. Colonoscopy will include removal of most lesions.
4. In older persons, advanced neoplasia is more likely to occur in the proximal colon.
5. Sigmoidoscopy may fail to reach the splenic flexure. It would then be less sensitive in detecting advanced neoplasia than this study suggests.

CONCLUSION

One-time screening of asymptomatic subjects with FBOT plus sigmoidoscopy failed to identify about 1 of every 4 subjects with advanced neoplasia.

NEJM August 23, 2001; 345: 555-60 Original investigation by the Veterans Affairs Cooperative Study Group, first author David A Lieberman, Oregon Health Sciences University, Portland. **www.nejm.org**

Comment:

The main purpose of screening is not to detect cancer, but to detect precancerous lesions which can be removed. A positive FBOT, a positive sigmoidoscopy, or a positive colonoscopy by themselves will not reduce risk of colorectal cancer. A removal procedure must follow.

Some, I suspect many, sigmoidoscopies will miss the sigmoid flexure.

This study concludes what many have believed was self-evident. It is cost effective to screen with complete colonoscopy and omit the sigmoidoscopy and FBOT. Screening thus will be much more rewarding because:

More precancerous lesions will be discovered. Colonoscopy will detect precancerous lesions at an earlier stage. Most can be removed concurrently. (Ie, combined screening and treatment)

Colonoscopy will have to be done anyway:

In those with a positive sigmoidoscopy.

In those with a positive FBOT.

Over time, with yearly FBOT screens, more false positives will occur. The cumulative requirement for colonoscopy will rise.

Why not proceed directly to colonoscopy for screening every 10 years? We should at least advise patients over age 50 of the advantages and allow them to choose.

The problem – can we afford it? Medicare has added coverage.

What is the downside of colonoscopy? Preparation is not pleasant. Anesthesia is required. Serious bleeding and perforation occurs in about 1 of 1000. Cost is high.

I believe most primary care clinicians now advise periodic screening colonoscopy.

In time, paramedical personnel will likely be enlisted to become very proficient, and perform colonoscopy at a reduced cost. RTJ

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REVIEW ARTICLE

8-10 MANAGEMENT OF NODULAR THYROID DISEASE

Thyroid nodules are commonly found in middle aged persons, especially women. Nodules raise concerns about thyroid cancer, but it is rare. The main aim of management is to identify the small proportion of patients with cancer who require treatment while avoiding unnecessary testing and treatment for the majority.

Markers of cancer associated with nodules include: males over age 70; history of head or neck irradiation; rapid growth of the nodule; and family history of thyroid cancer. Physical signs include firm, non-tender nodules; local lymphadenopathy; and recurrent laryngeal nerve palsy. But most patients with thyroid cancer do not have any of these features.

Clinically, solitary nodules are more common than multinodular goiters. Solitary nodules used to be considered more likely to harbor malignant disease. This view is questionable. Half of patients with apparent solitary nodules turn out to have multinodular goiter at surgery. The incidence of cancer in multinodular thyroids and single nodules is similar.

What biochemical tests should be done? The only tests usually performed are thyroid function tests. Most patients are euthyroid. “Overt thyroid dysfunction effectively rules out malignancy.”

Calcitonin is measured when screening family members for medullary cell carcinoma. But, further studies are needed before routine calcitonin measurement is accepted in evaluation of nodules.

What about radionuclide scanning? A malignant nodule should appear as a “cold”, nonfunctioning area; a benign nodule as “warm” or “hot”. Since most nodules are cold and generally benign, and warm nodules can be malignant, many centers have abandoned radionuclide scanning.

What about ultrasound? Ultrasound classifies nodules as solid or cystic. But, most “cystic” nodules are partly solid. Purely cystic nodules are rare. The risk of cancer is in fact similar, or higher in cystic nodules. Ultrasound does not reliably distinguish benign from malignant.

What about trials of thyroid stimulating hormone (TSH) suppression by exogenous thyroxine? This test is based on the assumption that dependency of benign and malignant nodules on TSH differs. Benign nodules might shrink; malignant nodules do not. Natural history studies show that most benign nodules remain the same, shrink, or spontaneously disappear over 10

years. Thyroxine administration to suppress TSH may lead to hyperthyroidism and reduced bone density and is a risk factor for atrial fibrillation. “Trials of thyroxine suppression do not seem to be indicated.”

What should we do? Fine needle aspiration cytology is safe, simple, and quick. Each nodule should be aspirated as there is a significant risk of malignancy in non-dominant nodules. Most aspirates turn out to be benign. About 4% are malignant. There are qualifications to aspiration: Samples are often not satisfactory and may require repetition. Large bore needle is no more accurate than small bore, and is associated with more side effects. Cystic lesions often yield insufficient cells for diagnosis. Neither the size of the cyst nor the color of the aspirate is discriminatory. The cyst should be aspirated to dryness, but generally recurs. Surgery should then be considered.

Follicular adenomas cannot be distinguished from carcinomas; 15% will be malignant. They should be regarded as suspicious. Age, clinical features, and discussions with the patient will influence the decision about surgery. Many centers suggest surgical excision of all indeterminate follicular lesions.

Although the optimum diagnostic strategy for euthyroid patients with nodular thyroid disease is still a matter of debate, there is agreement that fine needle aspiration cytology and tests of thyroid function are cornerstones of investigation.

The challenge remains identifying which palpable nodules are malignant.

BMJ August 11, 2001; 323: Editorial by M Keston Jones, Singleton Hospital, Swansea, UK

Comment:

The advice regarding investigation of nodules to detect cancer differs from the old tradition in several ways:

1. Radionuclide scanning and ultrasound may not be helpful
2. TSH suppression with thyroxine is not indicated.
3. Differentiating single and multinodular goiters is not helpful in assessing risk.
4. Overt thyroid dysfunction effectively rules out malignancy

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Never too late to start?

8-11 BONE MINERAL DENSITY RESPONSE TO ESTROGEN REPLACEMENT IN FRAIL ELDERLY WOMEN

Bone mineral density (**BMD**) declines with age. Bone loss may accelerate as age increases.

Although estrogen-based hormone replacement therapy (**HRT**) is the foundation of osteoporosis prevention, it is rarely initiated in elderly women.

This study asks – does HRT initiated in elderly women increase BMD?

Conclusion: It does.

STUDY

1. Randomized, double-blind placebo-controlled trial followed 67 women over age 75. (Mean age = 82)
   All were considered to be mild-to-moderately frail. None had been taking estrogens.
2. Randomized to: 1) conjugated estrogens (0.625 mg/d continuously) + medroxyprogesterone 5 mg/d for 13 days every 3rd month or 2) placebos.
3. All received supplemental calcium and vitamin D, adjusted to daily intake of 1200 mg and 800 U.
4. Determined 9-month change in BMD of the lumbar spine and hip.

RESULTS

1. Compared with placebo, HRT resulted in significantly larger increase in BMD in the lumbar spine

(+4% vs +0.4%); and hip (+2% vs –0.1%).

2. Total body, femoral neck, and trochanter BMD also increased.
3. HRT also was associated with significant decreases in markers of bone turnover.
4. Adverse effects: Some intolerance developed early, but symptoms substantially decreased when dose was temporarily lowered. Only four of 45 withdrew because of adverse events — breast discomfort, bloating, vaginal bleeding, and perceived decline in well-being. Seven withdrew for other reasons.

DISCUSSION

1. In these frail elderly women over age 75, HRT resulted in significant increases in BMD.
2. The increase in lumbar spine BMD after 9 months was similar to the increases reported in younger women taking HRT.
3. Lower initial BMD and older age were associated with greater BMD response.
4. It was once commonly believed that bone turnover remained elevated for only a few years after menopause and that bone loss subsequently slowed or ceased. Recent studies provide evidence that bone turnover remains elevated into old age and that bone loss may accelerate rather than slow in the elderly. (Subjects in this study had high rates of bone turnover as indicated by serum and urine markers.)
5. Another study (Annals Internal Medicine 1999; 130: 897-904) reported a lower dose of conjugated estrogen (0.3 mg) coupled with calcium and vitamin D increased BMD in women over age 65.
6. Traditional thought has been that the estrogen-dependent compartment of bone becomes depleted approximately 15 years after menopause. This concept has been challenged by those who believe that estrogen deficiency is also responsible for the continuing decline in BMD that previously had been attributed to aging.

CONCLUSION

In physically frail women over age 75, 9 months of HRT significantly increased BMD.

JAMA August 15, 2001; 286: 815-20 Original investigation, first author Dennis T Villareal, Washington University School of Medicine, St. Louis, MO.

Comment:

Almost 300 eligible women were screened initially. 131 were excluded by patient choice. Only 67 were finally randomized. Of these 11 withdrew. This indicates how difficult it will be to start and continue HRT in elderly women.

It would seem reasonable to judge that fracture rate would decrease with an increase in BMD. The study did not address this point. Risk of falling must be addressed along with BMD.

I believe estrogens do indeed continue to prevent bone loss and increase bone density in women well past the menopause. Women in their 70s and 80s who are beginning to show continuing bone loss should be made aware of the possible benefits of estrogen as well as of bisphosphonates. It is not too late for many to obtain benefit. We should tell them of these benefits and allow them to make an informed choice. Which is better, estrogen or bisphosphonates? I believe choice is a matter of acceptability with adverse effects. Continued compliance over years will be difficult to achieve.

All women should receive adequate calcium and vitamin D throughout life.

Osteoporosis is inevitable as individuals age. Prevalence in old age could be considered to be 100%. For a disease with 100% chance of development would not universal preventive measures, including drug treatment, be reasonable? RTJ

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This study will please old-time clinicians.

8-12 PROGNOSTIC IMPORTANCE OF ELEVATED JUGULAR VENOUS PRESSURE AND A THIRD HEART SOUND IN PATIENTS WITH HEART FAILURE.

This study asks — does examination of the jugular venous pulse and auscultation of the heart add any important clinical information? In the light of modern technology, is the old-time clinician's reliance on the physical examination of any value?

Conclusion: In patients with heart failure (**HF**), the physical examination does add clinically meaningful information.

STUDY

1. Entered a total of 2569 patients (mean age 62) with symptomatic congestive HF or a history of HF and an ejection fraction < 0.35
2. At baseline, recorded presence or absence of a 3rd heart sound and elevated jugular venous pressure. Although the physical examination was not standardized, it probably was representative of usual clinical practice.
3. Determined risks of hospitalization for HF and progression of HF, defined as death from pump failure and the composite of death + hospitalization for HF.
4. Followed a mean of 32 months to assess prognostic importance of the physical examination.

RESULTS

1. Elevated jugular venous pressure was present in 11%; third heart sound in 23%.
2. Elevated jugular venous pressure was associated with an increased risk of hospitalization for HF (RR = 1.3 compared with those without elevation) and death or hospitalization due to HF (RR = 1.3).
3. Presence of a third heart sound was associated with similar increased risks.

DISCUSSION

1. Finding elevated jugular venous pressure or a third heart sound on physical examination conveys important information in patients with symptomatic heart failure.
2. Elevated jugular venous pressure reflects increased right atrial pressure, which itself correlates with elevated left-sided filling pressure.
3. In one study of 50 patients with advanced HF, 96% had a third heart sound, but agreement between observers was moderate or low. Patients with HF may have a third heart sound as a result of low ventricular compliance, increased filling pressures, or increased early diastolic filling rates.

CONCLUSION

Detection of elevated jugular venous pressure or a third heart sound in patients with HF was associated with adverse outcomes including progression of HF.

NEJM August 23, 2001; 345: 574-81 Original investigation, first author Mark H Drazner, University of Texas Southwestern Medical Center, Dallas. This was a subset of the Studies of Left Ventricular Dysfunction [SOLVID] trial which reported benefit from the ACE inhibitor enalapril in HF. NEJM 1991; 325: 293-302

Comment:

Our younger colleagues may counter – what does this prognostic information add to the care and treatment of the patient? We already know the prognosis is poor. Would the presence of an elevated jugular venous pulse or a third heart sound change treatment of a patient with HF? I believe it would. It identifies a subset of patients with a poor prognosis who would benefit from heightened therapeutic interventions. RTJ

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Amazing Perception 100 Years Ago

8-13 THE JUGULAR VENOUS PULSE AND THIRD HEART SOUND IN PATIENTS WITH HEART FAILURE

In 1902, Mackenzie provided nomenclature that is still in use. He called the two wave crests A and V:

> There are two rises in the auricular pressure curve, a large and a small one, with of course two falls. The first rise in pressure immediately precedes the rise in ventricular pressure. It can only be due to the systole of the auricle. Immediately after the auricle ceases to contract, there is a great fall (x) in the pressure due to the diastole of the auricle. The auriculo-ventricular valves being closed, the blood pouring into the auricles from the veins, the pressure gradually rises, producing the second small wave in the curve. This wave is terminated by the opening of the auricular-ventricular valves at the beginning of ventricular diastole. When the pressure becomes lower in the ventricles than in the auricles, the valves open and the contained blood passes through, reducing the auricular pressure, and causing the second fall (y). After this, the pressure slowly rises by the accumulation of blood in both chambers, until it is suddenly increased by the next auricular systole.

Proper examination of the jugular venous pulse requires an examining table that permits controlled adjustment of the patient's trunk above the horizontal plane. This should begin at about a 30-degree angle of elevation with subsequent adjustment of the trunk that achieves the maximal visible oscillations of the right internal jugular vein. Attention should be focused on the nonpulsatile external jugular vein for the mean right atrial pressure, and then on the heights of the internal jugular A and V waves, in centimeters above the sternal angle.

The third heart sound is due to the sudden cessation of distention of the ventricle in early diastole. It is a soft, dull, low frequency sound that requires meticulous auscultatory technique for detection. It is best detected when the bell of the stethoscope is applied with just enough pressure to form a skin seal. It is heard over the left ventricular impulse, best when the patient is placed in the partial left lateral decubitus position.

Sophisticated laboratory methods provide contemporary clinicians with unprecedented diagnostic information. Reliance on these methods has overshadowed the bedside examination on which previous generations of physicians depended. "The stethoscope is the oldest diagnostic instrument in continuous clinical use. It is the logo of modern medicine and has become more visible than ever, worn draped across the neck or over the shoulder instead of resting in the pocket of a laboratory coat. The skill with which it is used tends to vary inversely with the prominence of its display."

NEJM August 23, 2001; 345: 612-13 Editorial by Joseph K Perloff, UCLA School of Medicine, Los Angeles. CA

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Common, disabling, and treatable

8-14 RECOGNITION AND TREATMENT OF POSTTRAUMATIC STRESS DISORDER.

This editorial comments on 3 reports about posttraumatic stress disorder (**PTSD**) appearing in this issue of JAMA. Lifetime prevalence in the US is estimated to be about 8%. Women are affected twice as often as men.

The articles draw attention to 3 important facts:

PTSD is a worldwide problem which is reaching alarming proportions.

It is associated with persistent disability and comorbidity.

Treatment can produce a meaningful reduction in distress.

PTSD often presents in medical disguise. It is largely unrecognized by medical professionals. Primary care clinicians should be aware. The essential features of PTSD are:

One or more traumatic events give rise to 4 symptom clusters

Recurrent and painful re-experiencing of the event.

Phobic avoidance of trauma-related situations and memories.

Emotional numbing and withdrawal

Hyperarousal.

On average, a patients with PTSD will endure 20 years of active symptoms, and experience almost one day a week of work impairment. Rates of suicide are high. Co-morbidities include: depression; anxiety; alcohol and substance abuse; smoking; and obesity. Gastrointestinal, cardiovascular, musculoskeletal, endocrine, respiratory, and infectious diseases appear more commonly for up to 20 years after the traumatic experience.

The cost of PTSD exceeds that of all other anxiety disorders.

People with PTSD might be expected to seek mental health treatment. Evidence suggests that they often do not.

How can PTSD be recognized? Tip offs include: Marked and persistent somatization. A large variety of symptoms. High rate of attendance at primary care offices and clinics. Hypervigilance to symptoms. Poor pain-coping mechanisms. High prevalence of smoking.

PTSD can be established only if the existence of a traumatic event has been established. "However, clinical suspicion may be warranted based on symptoms or behaviors even if no such event has yet been established."

To elicit information about PTSD, clinicians must establish trust and confidence. It may require physician's unwillingness to accept an initial denial as being the final answer. (Eg, initially, domestic violence may be denied.)

Treatment approaches:

PTSD requires that clinicians give patients adequate time to disclose their stories. "Brief treatment does not mean rushed treatment." Primary care clinicians are ideally placed to provide front-line support. Education involves an explanation about the nature of PTSD and responses to stress. It involves encouraging patients to speak about their traumatic experiences in a non-pressured way.

Pharmacotherapy:

Selective serotonin reuptake inhibitors (SSRIs; fluoxetine (*Prozac*); and sertraline (*Zoloft*)) can have substantial benefit. SSRIs can improve quality of life and reduce disability. They can modulate affect, memories, and impulses. They often act rapidly, within weeks. One study reported that 40% of traumatized women reached clinical remission at 12 weeks. How long to continue? The long duration of PTSD is likely to require maintenance therapy -- up to 12 months. Four months of therapy may not be an adequate trial. However, if there is no improvement in 4 weeks on an adequate dose, continued treatment is unlikely to benefit.

Since symptoms may peak within 2 weeks of the trauma, vigorous attempts to treat PTSD early on are warranted. Initial temporary use of a hypnotic agent followed within 3 weeks with a SSRI has been recommended for acute symptoms.

Psychosocial therapy:

In addition to drug therapy, psychosocial (cognitive-behavior) treatment is effective. (If referral to a psychotherapist is available.) Unfortunately psychosocial therapy is unlikely to be adopted in primary care unless treatment is considerably

modified and simplified. One technique that might deserve further study is encouraging patients to write about their traumatic experiences. (*Certainly primary care clinicians can elicit patient's experiences and feelings and listen empathetically*.)

Conclusion:

There are many gaps in our understanding. The cross-cultural application of treatments deserves more study. PTSD is a world-wide health problem. It must be recognized. Clinicians must be alert to the its presence and presentation. There is no reason it cannot be treated effectively in primary care.

JAMA August 1, 2001; 286 : 584-88 Commentary by Jonathan R T Davidson, Duke University Medical Center, Durham NC

Comment:

I expect the prevalence of PTSD will increase in our troubled world. Primary care clinicians may be seeing displaced persons who are ill, have undergone trauma, have little family support, no funds, and are unable to understand and speak the English language. Can we imagine how stressed we would feel if we were exposed to these conditions in a foreign country?

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REVIEW ARTICLE

8-15 SUBCLINICAL HYPERTHYROIDISM

"Subclinical Hyper-thyroidism". (**SCHyperT**) is defined as — the combination of an *undetectable* serum thyrotropin concentration (**TSH**), as measured by an assay with a threshold of detection that is 0.1mU per liter or less, and *normal* serum thyroxine and triiodothyronine concentrations (usually at the upper end of the normal range). Since screening for thyroid function is commonly done, more SCHyperT patients will be identified.

Before clinical features of thyrotoxicosis are evident, the hypothalamic-pituitary axis responds to minor increases in thyroid hormone concentrations (which may remain within the normal range) by switching off the production of TSH. Although absence of symptoms was once part of the definition of SCHyperT, we now know that subtle symptoms or signs of thyrotoxicosis may be present.

SCHyperT may be *endogenous* (associated with thyroid hormone production by nodular goiter or underlying Graves' disease) or *exogenous* (due to treatment with thyroxine).

There are other causes of a low or undetectable TSH and normal free T4 and free T3:

A. Nonthyroidal illnesses

B. Certain drugs (eg, corticosteroids)

C. During hyperthyroid state of subacute, silent, or postpartum thyroiditis.

The presence of thyrotropin (TSH) receptor antibodies is diagnostic of Graves' disease, irrespective of the clinical findings. But they may be absent in up to 20% of cases, and more often are absent in Graves'-associated subclinical hyperthyroidism.

What are likely complications of SCHyperT?

Atrial fibrillation: Risk relative to those without SCHyperT = 3.

Osteoporosis: Effects of SCHyperT on bone are less well defined than the effects of overt hyperthyroidism. Studies do indicate that in those with multinodular goiter, osteoporosis is more common. The bone loss can be reversed by treatment that restores TSH to normal.

In spite of these observations, the author states — "The natural history of SCHyperT remains unclear."

The evidence that SCHyperT is a risk factor for osteoporosis and atrial fibrillation is not definitive. "However, it would be surprising if the complications of overt hyperthyroidism were not seen, albeit at a reduced frequency, in a condition that is effectively the mildest form of thyrotoxicosis." Complications are more likely to occur in patients with multinodular goiter since the biochemical abnormalities are persistent and the older age of affected patients puts them at increased risk for bone loss and ischemic or structural heart disease. The so called simple, diffuse goiter observed in patients in their late teens tends to progress to a more obvious, multinodular goiter around age 40. As the autonomous nodules become larger and more numerous, subclinical or overt hyperthyroidism is increasingly present. Each year, about 5% of patients with multinodular goiter will progress to overt hyperthyroidism.

What to do for a patient with SCHyperT?

Obviously, for patients with exogenous SCHyperT the dose of the treatment thyroxine should be reduced to return the TSH to normal.

For endogenous SCHyperT, opinions vary. The American Association of Clinical Endocrinologists concludes that endogenous SCHyperT associated with multinodular goiter should be treated.

Even after additional investigations such as isotope uptake and imaging, and measurement of TSH-receptor antibody, it may de difficult to decide whether the pattern is a consequence of non-thyroidal illness, concomitant medication, underlying autonomous thyroid function, or the initial phase of thyroiditis. Thyroid function tests should be repeated in 8 weeks. A normal or elevated TSH at this time suggests recovery from a non-thyroidal illness or recovery from the initial phase of thyroiditis. If the low TSH pattern persists, the choice should be made between 1) a trial of antithyroid drugs and 2) close clinical follow-up.

For the many with endogenous SCHyperT who do not have multinodular goiter, and no complications from excess endogenous thyroxine production, treatment is not necessary. Thyroid function tests should be done every 6 months. Recognize that serum T3 may become elevated before T4.

Treatment of patients with SCHyperT due to nodular goiter is more routinely justified given the expected progression to overt hyperthyroidism.

NEJM August 16, 2001; 345: 512-16 "Clinical Practice" review article by Anthony D Toft, Royal Infirmary of Edinburgh, Scotland.

Comment:

SCHyperT is commonly due to excess thryoxine medication (exogenous). Treatment is simple, but important.

For patients with suspected endogenous SCHyperT, I believe most primary care clinicians would opt for careful follow-up. Once persistent hyperthyroidism is evident, the patient can be referred to a specialist who then has the decision to observe, or treat with anti-thyroid drugs, or I^{131}.

Those with multinodular goiter would be referred sooner.

Since osteoporosis is a complication of SCHyperT, drug treatment to preserve bone should be started at any age at which the SCHyperT is diagnosed.

Treatment decisions are more difficult than for subclinical hypo-thyroidism. RTJ

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HIGHLIGHTS AUGUST 2001

8-1 CHARACTERISTICS OF PATIENTS WITH UNCONTROLLED HYPERTENSION IN THE UNITED STATES

Most cases of uncontrolled hypertension consist of isolated systolic hypertension in older adults, most of whom have access to health care.

Practical point: Primary care clinicians have the opportunity and responsibility of diagnosing and treating systolic hypertension in their elderly patients. I believe treatment should begin low and continue slow. There is no urgency. It is most important to avoid adverse effects lest the patient become discouraged and discontinue treatment.

I do *not* believe there is magic in the under-140 cut point. We may be satisfied with a reduction to below 160 in order to avoid adverse effects.

Treatment of systolic hypertension does not remove the cause. (Ie, does not improve compliance of large vessels.) This risk factor remains. Nevertheless, reducing the systolic load probably slows progression of the stiffening, and lowers risk of endothelial rupture and arterial thrombosis.

8-2 CONTROL OF HYPERTENSION — AN IMPORTANT NATIONAL PRIORITY

Epidemiologic data indicate that systolic BP is more important than diastolic as a determinant of cardiovascular risk. In patients with isolated systolic BP, antihypertensive therapy has been shown to reduce mortality and the incidence of stroke, myocardial infarction, and heart failure. "Clearly, a shift needs to occur in clinical practice to focus more in the management of systolic rather than diastolic hypertension." The National Heart, Lung, and Blood Institute recommends that systolic BP become the major end point for the detection, evaluation, and treatment of hypertension.

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8-3 HORMONE REPLACEMENT THERAPY AND LONGITUDINAL CHANGES IN BLOOD PRESSURE IN POSTMENOPAUSAL WOMEN

Postmenopausal women taking HRT had a smaller increase in systolic BP over time than non-users. The difference increased with age.

Practical point: Primary care clinicians may consider this another mechanism for the protective effect of HRT. For those clinicians who believe the benefits of HRT outweigh the harms, another reason to prescribe it.

8-4 HAND HYGIENE

Proper hand hygiene could reduce the incidence of transmission of infection. Washing with soap and water is not the only (or even the most effective) way of reducing transmission of organisms.

The Hand Hygiene group now recommends use of a alcohol-glycerol hand rubs between patients. They are quick to use (10 to 20 seconds) and can be used while walking or talking. This overcomes the objections to soap and water washing which takes time and requires presence of sinks.

8-5 EFFICACY AND SAFETY OF TENECTEPLASE IN COMBINATION WITH ENOXAPARIN, ABCIXIMAB, OR UNFRACTIONATED HEPARIN: The ASSENT-3 Randomised Trial in Acute Myocardial Infarction

Tenecteplase is a new genetically engineered variant of alteplase (tPA; tissue plasminogen activator). It provides a new standard of fibrinolytic therapy by virtue of its equivalent efficacy with regard to 30-day mortality, its reduced propensity for bleeding complications, and its simple administration as a bolus.

“In view of the present data and the ease of administration, enoxaparin might be regarded an attractive alternative anticoagulant given in combination with tenecteplase.”

Taking into account efficacy and safety, the combination of full-dose bolus tenecteplase + enoxaparin for 7 days emerged as the best treatment in this trial. Because of ease of administration and the lack of monitoring of anticoagulation, this combination should be regarded as an attractive alternative pharmacological reperfusion strategy deserving further study.

8-6 EFFECTS OF CLOPIDROGREL IN ADDITION TO ASPIRIN IN PATIENTS WITH ACUTE CORONARY SYNDROMES WITHOUT ST-SEGMENT ELEVATION

The anti-platelet agent clopidogrel, given in addition to aspirin, had significant benefits in patients with acute coronary syndromes without ST elevation. The risk of major bleeding was increased.

8-7 RISK OF CARDIOVASCULAR EVENTS ASSOCIATED WITH SELECTIVE COX-2 INHIBITORS.

The new selective COX2 inhibitors (rofecoxib; celecoxib) are pro-thrombotic. Meta-analyses thus far indicate an association with increased incidence of cardiovascular events compared with non-selective NSAIDs as well as placebo.

8-8 RISK OF MACULAR DEGENERATION IN USERS OF STATINS

An exciting, but preliminary report of considerable lowering of risk of macular degeneration in older persons taking statin drugs.

8-9 ONE-TIME SCREENING FOR COLORECTAL CANCER WITH COMBINED FECAL OCCULT-BLOOD TESTING AND EXAMINATION OF THE DISTAL COLON

One-time screening of asymptomatic subjects with FBOT plus sigmoidoscopy failed to identify about 1 of every 4 subjects with advanced neoplasia.

8-10 MANAGEMENT OF NODULAR THYROID DISEASE

Although the optimum diagnostic strategy for euthyroid patients with nodular thyroid disease is still a matter of debate, there is agreement that fine needle aspiration cytology and tests of thyroid function are cornerstones of investigation.

The challenge remains identifying which palpable nodules are malignant.

The advice regarding investigation of nodules to detect cancer differs from the old tradition in several ways:

1. Radionuclide scanning and ultrasound may not be helpful
2. TSH suppression with thyroxine is not indicated.
3. Differentiating single and multinodular goiters is not helpful in assessing risk.
4. Overt thyroid dysfunction effectively rules out malignancy

8-11 BONE MINERAL DENSITY RESPONSE TO ESTROGEN REPLACEMENT IN FRAIL ELDERLY WOMEN

In physically frail women, mean age 82, 9 months of HRT significantly increased BMD.

Traditional thought has been that the estrogen-dependent compartment of bone becomes depleted approximately 15 years after menopause. This concept has been challenged by those who believe that estrogen deficiency is also primarily responsible for the continuing decline in BMD that previously had been attributed to aging.

It was once commonly believed that bone turnover remained elevated for only a few years after menopause and that bone loss subsequently slowed or ceased in older women. Recent studies provide evidence that bone turnover remains elevated into old age and that bone loss may accelerate rather than slow in the elderly. (Subjects in this study had high rates of bone turnover as indicated by serum and urine markers.)

Practical point; Primary care clinicians should inform their elderly female patients of the possibility that bone sparing therapy is effective regardless of age, and allow them to make an informed choice to accept or reject.

8-12 PROGNOSTIC IMPORTANCE OF ELEVATED JUGULAR VENOUS PRESSURE AND A THIRD HEART SOUND IN PATIENTS WITH HEART FAILURE.

Detection of elevated jugular venous pressure or a third heart sound in patients with HF was associated with adverse outcomes including progression of HF.

Practical point: The physical examination identifies a subset of patients with a poor prognosis who would benefit from heightened therapeutic interventions

8-13 THE JUGULAR VENOUS PULSE AND THIRD HEART SOUND IN PATIENTS WITH HEART FAILURE

Read the description of the jugular venous pulse described by Mackenzie in 1903.

8-14 RECOGNITION AND TREATMENT OF POSTTRAUMATIC STRESS DISORDER.

PTSD is a worldwide problem which is reaching alarming proportions. It is associated with persistent disability and comorbidity. Treatment can produce a meaningful reduction in distress. The condition must first be recognized.

Practical point: Primary care clinicians will be seeing more patients with PTSD. Certainly they can elicit patient's experiences and feelings and listen empathetically. Compassionate understanding and treatment with selective serotonin reuptake inhibitors will benefit. There is no reason PTSD cannot be treated effectively in primary care.

8-15 SUBCLINICAL HYPERTHYROIDISM

"Subclinical hyper-thyroidism". (**SCHyperT**) is defined as — the combination of an *undetectable* serum thyrotropin concentration (**TSH**), as measured by an assay with a threshold of detection that is 0.1mU per liter or less, and *normal* serum thyroxine and triiodothyronine concentrations (usually at the upper end of the normal range).

For the many with endogenous SCHyperT who do not have multinodular goiter, and no complications from excess endogenous thyroxine production, treatment is not necessary. Thyroid function tests should be done every 6 months. Recognize that serum T3 may become elevated before T4.

Treatment of patients with SCHyperT due to nodular goiter is more routinely justified given the expected progression to overt hyperthyroidism.

. "It would be surprising if the complications of overt hyperthyroidism were not seen, albeit at a reduced frequency, in a condition that is effectively the mildest form of thyrotoxicosis."