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10-1 RISK OF CERVICAL CANCER ASSOCIATED WITH EXTENDING THE INTERVAL BETWEEN CERVICAL-CANCER SCREENINGS

Compared with annual screening, screening performed once three years after the last negative test in women who previously had 3 or more consecutive negative PAP tests, is associated with an average excess risk of cervical cancer of approximately 3 in 100 000. If continued, screening annually after 3 negative tests, would result in thousands and thousands of additional PAP tests and colposcopic examinations to detect only one additional case of cervical cancer.

The US Preventive Services Task Force recently recommended screening be performed "at least every 3 years" rather than every year. The American Cancer Society suggests lengthening the intervals between screenings to as long as 3 years among women age 30 and over who previously have had negative results on three or more consecutive cervical cancer tests.

Given that half of all cases of cervical cancer occur in women who have never been screened, screening all women at least once would be expected to contribute more to decreasing mortality than the continued annual testing. The focus should be on screening women who have rarely or never undergone screening.

10-2 TREATING THROMBOSIS IN THE 21ST CENTURY

Now, a minimal anti-thrombin-binding unit of heparin, a pentasaccharide called fondaparinux, has been synthesized and is undergoing clinical trials. Fondaparinux enhances anti-thrombin activity. It is a specific inhibitor of activated factor X (Xa). It requires subcutaneous administration. It can be given once a day on a weight basis. It does not require laboratory monitoring.

A second new anticoagulant (melagatran) took its cue from the leach which produces a direct thrombin inhibitor (hirudin). Hirudin acts independently of anti-thrombin and other plasma proteins. The discovery of hirudin led to other direct thrombin inhibitors, one of which is melagatran. Melagatran can also neutralize clot-bound thrombin. Chemical modification (to "ximelagatran") allows better oral absorption. It is the first new oral anticoagulant since warfarin. Like fondaparinux, it does not require laboratory monitoring.

10-3 SUBCUTANEOUS FONDAPARINUX VERSUS INTRAVENOUS UNFRACTIONATED HEPARIN IN THE INITIAL TREATMENT OF PULMONARY EMBOLISM.

Once-daily fondaparinux without monitoring is at least as effective and safe as adjusted-dose IV unfractionated heparin in the initial treatment of hemodynamically stable patients with pulmonary embolism.

"Because of its simplicity, once-daily subcutaneous fondaparinux without anticoagulation monitoring could replace intravenous administration of unfractionated heparin in most patients."

10-4 COMPARISON OF XIMELAGATRAN WITH WARFARIN FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM AFTER TOTAL KNEE REPLACEMENT

Fixed dose ximelagatran 36 mg bid, administered without coagulation monitoring, was significantly more effective than warfarin in prevention of thromboembolism after knee replacement. Safety was similar "It could therefore be considered an alternative to other thromboprophylactic agents."

10-5 SECONDARY PREVENTION OF VENOUS THROMBOEMBOLISM WITH ORAL DIRECT THROMBIN INHIBITOR XIMELAGATRAN

Ximelagatran is a direct thrombin inhibitor undergoing active investigation as an anticoagulant. It is given in a fixed dose daily, and needs no monitoring.

Beginning and continuing extended secondary prevention of VTE with ximelagatran 24 mg bid for an additional 18 months after 6 months of standard anticoagulation effectively prevented recurrences. [NNT = 10]

The incidence of major hemorrhage was low and similar to placebo. Ximelagatran was equally effective in subgroups that had risk factors for recurrence—previous VTE, proximal deep VTE, and pulmonary embolism.

The fixed-dose ximelagatran was well tolerated without monitoring measures of coagulation.

10-6 SUSTAINED EFFECT OF INTENSIVE TREATMENT OF TYPE 1 DIABETES MELLITUS ON DEVELOPMENT OF PROGRESSION OF DIABETIC NEPHROPATHY

The development of decreasing glomerular filtration rate and end-stage renal disease is a long pathological process presumably reflecting the effects of hyperglycemia on renal cells.

The Diabetes Control and Complications Trial (DCCT; 1993) demonstrated the benefits of intensive treatment of diabetes over 6.5 years in reducing glycemic levels and slowing the progression of diabetic nephropathy. The present study followed the DCCT cohort for an additional 8 years to determine if the benefits of intensive vs conventional treatments on kidney function would persist.

Benefits were persistent, reducing incidence of hypertension and albuminuria for 8 years after the end of the original study despite deteriorating glucose control.

In addition, there were clear residual benefits of intensive treatment on future development of hypertension over the ensuing 8 years.

The intensively treated participants had few manifestations of nephropathy during the DCCT due to their relatively low level of HbA1c. The near normal hyperglycemic control for 6.5 years may have simply delayed the development of indicators of diabetic nephropathy during the 8 more years of follow-up.

I believe primary care clinicians will have little difficulty extrapolating these benefits to patients with type 2 diabetes. The greater the number of days with normal glucose levels, the longer the delay in development of microvascular complications.

10-7 SHOULD DOCTORS PRESCRIBE ALCOHOL TO ADULTS ?

"There is no more emblematic standard of good health in the United States than the food guide pyramid. It is widely recognized if not well followed. The pyramid advises Americans to eat lots of grains and fruits and vegetables, some meat and dairy, and a small amount of fat and sugars."

"One day soon, it (*the food pyramid*) may advise adult Americans to have a drink of beer, wine, or spirits every day as well. The idea is not as radical as it seems. "

Epidemiological evidence from more than 100 observational studies over the past 3 decades has shown than moderate alcohol consumption helps prevent heart disease. Other health benefits include reduced risk for ischemic stroke, peripheral vascular disease, and diabetes. Risk of heart disease among moderate drinkers is 35% or so lower than in non-drinkers. "Alcohol clearly has a sizable effect, and it's not so easy to ignore that."

The policy makers at the U.S. Department of Health and Human Services are reconsidering their stance on alcohol—which in the past has consisted of mentioning the health benefits of alcohol while emphasizing the adverse effects—as they update the U.S. dietary guidelines. With the policy experts talking ever more seriously about endorsing moderate drinking, is it time for physicians to consider selective prescription of alcohol for patients?

"For appropriate patients who do not drink, or do so only occasionally, and who wish to do so, encouraging a glass of wine or other alcoholic beverage with dinner every night may be the best advice you can give them."

Some authorities urge caution. Most current guidelines recommend moderate drinking only for people who already drink, and urge abstainers *not* to start drinking for their health. Some physicians now believe clinicians should discuss alcohol consumption with all patients and inform those without contraindications of the benefit of regular moderate consumption.

10-8 TAKING SIMVASTATIN IN THE MORNING COMPARED WITH EVENING

The statin drug, simvastatin, taken in the evening produced lower cholesterol levels. Lowering LDL-c by 10 mg/dL is clinically significant. This is achieved with no additional cost or inconvenience

10-9 INHALED INSULIN PROVIDES IMPROVED GLYCEMIC CONTROL IN PATIENTS WITH TYPE 2 DIABETES MELLITUS INADEQUATELY CONTROLLED WITH ORAL AGENTS.

Recently, a dry powder inhaled insulin **(IN-I)** system has been developed. It provides a new method of treatment. The pulmonary route exploits the large vascular bed and permeability of the alveoli to deliver insulin directly into the blood stream. IN-I has a rapid onset of action, actually faster than injected regular insulin and insulin lispro. Its duration of action is about 6 hours.

Pre-meal inhaled powdered insulin **(IN-I)** added to oral agents produced a significantly greater reduction in HbA1c than oral agents alone (metformin or sulfonylurea, or both)—a mean reduction in HbA1c of 2.3 %. HbA1c remained stable in the control group—about 10%

One third of the IN-I + oral agents group achieved a HbA1c less than 7% vs none in the oral agents alone group. (Mean HbA1c dropped from about 10% to 7.5% in the IN-I group.)

Fasting plasma glucose improved significantly.

This means of administration will eliminate the fear of injections. Patient satisfaction was high--97% opted to continue in a 1-year extension of the therapy.

This is an early proof of concept study. Primary care clinicians will watch for developments with great interest. Cost is to be determined.

10-10 COMBINATION ESTROGEN-PROGESTIN ORAL CONTRACEPTIVES.

The substantial benefits of O-Cs include avoidance of the dangers of pregnancy as well as a reduction in risk of ovarian cancer, acne, dysfunctional uterine bleeding, and possibly endometrial cancer.

Risks include venous thromboembolism and arterial vascular disease (myocardial infarction and stroke). The challenge for clinicians is to identify women in whom the risks outweigh the benefits. Both the American College of Obstetricians and Gynecologists and the WHO have published guidelines which differ only slightly. (*See abstract*)

At present, the doses of estrogen contained in O-Cs are 2 to 5 times less and the progestin content is 5 to 10 times less than originally formulated. This reduces the risk of venous thrombosis without any loss of effectiveness.

“Even when the health risks are taken into account, the net health benefit of oral-contraceptive use is great, especially given the effect on risk of ovarian cancer and effectiveness in preventing pregnancy.”

Hypertension and smoking are the most common contraindications to be considered.

10-11 CURRENT SMOKING, SMOKING CESSATION, AND THE RISK OF SUDDEN CARDIAC DEATH IN PATIENTS WITH CORONARY ARTERY DISEASE.

In smokers with CAD who quit, risk of sudden cardiac death **(SCD)** is significantly reduced and compares with the risk of those who never smoked. The decline in risk associated with cessation is immediate and not time dependent. This supports the view that the risk is due to direct toxic effects. The risk in smokers is not related to the amount of smoking.

In absolute terms, smoking cessation and never smoking resulted in a 3.5% lower risk of SCD over 8 years compared with those who continued to smoke. [NNT(8 years to prevent one SCD) = 30]. And a 11% reduction in all-cause death. [NNT = 10].

The risk of continuing smoking on SCD is even more pronounced than other risk factors—age, sex, New York Heart Association functional class, BP, and dyslipidemia.

Cessation is certainly one of the most effective preventive measures. Despite being informed of the risks, many patients continue to smoke. Primary care clinicians who succeed in getting recalcitrant smokers to stop achieve a major therapeutic intervention. Would asking them to read a copy of this article help? RTJ

10-12 RESTLESS LEG SYNDROME SYMPTOMS IN PRIMARY CARE.

Restless leg syndrome **(RLS)** is a sleep disorder that accounts for a significant proportion of patients with sleep complaints.

Currently, to be considered positive for RLS, four criteria must be met:

1. Urge to move the legs, usually accompanied by an unpleasant sensation in the legs.
2. Symptoms must be aggravated by rest.
3. Symptoms must be alleviated by movement, in particular, walking.
4. Must be worse in the evening or at night either currently or in the past when the condition first started.

In this study, twenty four percent of patients were positive for all 4 of the essential symptoms.; 15% reported the symptoms at least weekly. A large number of RLS patients may be seen by primary care clinicians.

A variety of drugs has been recommended for treatment: dopamine precursors (eg, levodopa; *Laradopa*), dopamine agonists (eg bromocriptine; *Parlodel*), anticonvulsants, benzodiazepines, and even opioids. The variety of drugs recommended for treatment speaks for the lack of studies to determine preference. Drug therapy in practice would likely be based on trial and error. The FDA has not reviewed them for specific use in RLS.

10-13 GOUT

Hyperuricemia is central to gout, but does not inevitably cause disease. Indeed, urate levels are frequently normal during attacks. Factors other than serum urate contribute to clinical gout in an additive manner—hypertension, thiazide and loop diuretics, obesity, and high alcohol intake. Gout is also associated with insulin resistance.

Lifestyle changes sometimes return uric acid levels to normal--stop drinking alcohol, switch from thiazides, or, if obese, lose weight. Conventional low purine diets are unpalatable and typically are only moderately effective.

Treatment of acute attacks include NSAIDs, corticosteroids, and colchicine.

Long term prophylactic treatment includes NSAIDs, colchicine, and allopurinol.

Although most patients have substantially reduced renal urate clearance (probenecid may used for these patients). . . “It is common and acceptable practice to use the xanthine oxidase inhibitor allopurinol (*Generic; Zyloprim*), which inhibits uric acid synthesis whether or not the patient overproduces urate.” “Irrespective of the cause of hyperuricemia, allopurinol is the most frequently used anti-hyperuricemic agent.” Its once-daily administration is convenient and effective regardless of the cause of the hyperuricemic.

10-14 EXERCISE PLUS BEHAVIORAL MANAGEMENT IN PATIENTS WITH ALZHEIMER DISEASE.

Improving physical conditioning in patients with AD may extend their independent mobility and enhance their quality of life despite progression of the disease. Even the oldest adults can improve cardiovascular function and increase flexibility, balance, and strength.

A number of studies link AD with physical deterioration. When compared with age-matched controls, AD patients show more signs of undernutrition, higher risk of falls and fractures, and a more rapid decline in mobility. Reduced muscle mass has been associated with loss of independence.

In this study exercise training improved physical health and lessened depression in patients with AD,

10-15 PROGNOSTIC IMPORTANCE OF PHYSICAL EXAMINATION FOR HEART FAILURE IN NON-ST-ELEVATION ACUTE CORONARY SYNDROMES: *The Enduring value of Killip Classification*

The Killip classification first proposed in 1967:

Killip I—no evidence of HF

Killip II—mild HF, with rales involving 1/3 or less of the posterior lung fields and a systolic BP 90 mm or higher.

Killip III—pulmonary edema with rales involving more than 1/3 of the posterior lung fields, and systolic BP of 90 or more.

Killip IV—cardiogenic shock with any rales and systolic BP under 90.

Killip classification is a powerful independent predictor of all-cause mortality in patients with *non*-ST –elevation acute coronary syndromes as well as in ST-elevation myocardial infarction.

Age, Killip class, heart rate, systolic BP and ST depression should receive particular attention in the initial assessment of *non*-ST –elevation acute coronary syndromes.

Cardiogenic shock tends to develop during hospitalization, often secondary to recurrent ischemia or infarction. Once it develops, it is associated with an extremely high mortality rate. This delay in presentation of shock in *non*-ST-elevation acute coronary syndromes creates a fortuitous window, during which early revascularization may prevent shock.

10-16 PROGNOSTIC VALUE OF MYELOPEROXIDASE IN PATIENTS WITH CHEST PAIN

Clinical criteria, ECG criteria, and conventional laboratory tests, including troponin T, often do not adequately predict the risk of cardiovascular events in patients presenting with acute coronary syndromes.

C-reactive protein and other markers have been advocated as a more accurate means of gauging risk, but additional tools are needed to predict vulnerability of coronary arteries to major events in the near term. Myeloperoxidase is an excellent candidate. It predicts cardiovascular risks independently of C-reactive protein and other markers of inflammation.

“Our findings suggest that myeloperoxidase serves as a marker of the vulnerable plaque and one that can be used to identify patients at *imminent* risk for major adverse cardiac events, independently of evidence of myocardial necrosis.”

A single measurement of myeloperoxidase independently predicted early risk of myocardial infarction, as well as the risk of major adverse cardiac events in the ensuing 30 days and 6 months. It identified patients at risk in the absence of myocardial necrosis.

This is a preliminary report. Watch for developments.

10-17 THE GREATEST THREAT TO WOMEN'S HEALTH

Heart attacks and stroke kill twice as many women as all cancers combined. Moreover, contrary to conventional wisdom, women are more likely to die from cardiovascular disease than men.

Getting women to stop smoking, eat healthily, drink alcohol only in moderation, lose weight if appropriate, and take regular exercise involves changing behaviors that are often ingrained from childhood.

More than half of all deaths and disability from heart disease and stroke can be prevented.

"Advising women, as well as men, about their risks of cardiovascular disease should, we urge, be mandatory for all primary care practitioners."

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10-1 RISK OF CERVICAL CANCER ASSOCIATED WITH EXTENDING THE INTERVAL BETWEEN CERVICAL-CANCER SCREENINGS

What is the excess risk of cervical cancer associated with less than annual screenings?The US Preventive Services Task Force recently recommended screening be performed "at least every 3 years" rather than every year. The American Cancer Society suggests lengthening the intervals between screenings to as long as 3 years among women age 30 and over who previously have had negative results on three or more consecutive cervical cancer tests.

Many clinicians perform screening annually. Resistance to less frequent screening may be due to a perception that there is an unacceptably high risk of cervical cancer.

This study, using data on large national publicly funded program of cervical-cancer screening (CCS), estimated the excess risk of cancer associated with extended intervals between screenings among women with documentation of negative results on previous consecutive conventional PAP tests.

Conclusion: Screening once 3 years after the last negative test in women age 30-64 who had 3 or more consecutive negative PAP tests was associated with an average excess risk of 3 in 100 000. "It is important to screening strategies that women with previous negative tests and their clinicians accept less frequent screening."

STUDY

1. Analyzed data from the National Breast and Cervical Cancer Detection Program which provided screening to low-income, underinsured women throughout the USA.
2. Most PAP tests were conventional, rather than liquid-based.
3. Grouped women into 4 screening categories:

    Only one PAP

    Initial negative PAP followed by a second.

    Two negative PAPs followed by a third

    Three or more negative PAPs followed by another PAP test.

(All had the PAP tests performed within 36 months of each other.)

4. Used a model of the natural history of cervical cancer to estimate the risk of newly diagnosed cancer that would be predicted to occur on the basis of a given prevalence of dysplasia. (In many women, dysplasia regresses to no dysplasia over time; and some progress.)
5. Estimated the average risk of cancer within 3 years in a hypothetical cohort 100 000 women who were screened once three years after the last negative PAP test rather than annually.
6. Estimated the number of additional PAP smears and colposcopic examinations that would be required to avert one case of cancer, given a particular interval between screenings.

RESULTS

1. On follow-up with a 4th test, among over 31 000 women age 30-64 who had 3 or more consecutive negative tests, the prevalence of biopsy-proven grade 2 cervical intraepithelial neoplasia was 3 per 10 000; and the prevalence of grade 3 neoplasia was 2 per 10 000. None had invasive cervical cancer.
2. According to the model, the estimated risk of cancer associated with PAP tests done every year for three years was 2 in 100 000 among women age 30-44; 1 in 100 000 in women among women age 45-59; and 1 in 100 000 among women age 60-64.
3. If screening were performed once 3 years after the last negative test, risk of cancer would be 5 in 100 000 among women age 30-44; 2 in 100 000 in women age 45-59; and 1 in 100 000 in women age 60-64
4. Screening women annually for three years after the last negative test, rather than once at three years, would add thousands of PAP tests and colposcopic examinations to detect one additional case of cervical cancer.

DISCUSSION

1. Women age 30-64 with 3 or more consecutive negative PAP tests who are screened 3 years after the last negative test, rather than annually, have an excess risk of cancer of no more than 3 in 100 000.
2. "The fact that the difference in the risk of cancer is small highlights the importance of attention to the costs and the harms associated with over-screening."
3. Lower socio-economic status is a risk factor for cervical neoplasia. Patients in this cohort were underinsured and had low income. The study reflects outcomes among women at higher-than-average risk.
4. In part because of the current findings, the CDC changed its screening policy, increassing the interval between screenings to 3 years after 3 consecutive negative tests.
5. The focus should be on screening women who have rarely or never undergone screening. These women account for more than half of all cases of cervical cancer in the USA each year.
6. What about testing for human papilloma virus (HPV)? The low prevalence of dysplasia and cancer in this and other populations indicates the need for caution in adopting more sensitive but less specific tests for use in women with previous negative tests. Testing for HPV would increase costs, increase number of interventions, and reduce quality of life associated with positive results.

CONCLUSION

As compared with annual screening, screening performed once three years after the last negative test in women who previously had 3 or more consecutive negative PAP tests is associated with an average excess risk of cervical cancer of approximately 3 in 100 000.

NEJM October 16, 2003; 349: 1501-09 Original investigation, first author George F Sawaya, University of California, San Francisco.

An editorial in this issue (pp 1495-96 by Sarah Feldman, Brigham and Women's Hospital, Boston Mass, comments:

The mortality from cervical cancer has declined dramatically over the past 60 years. The PAP teat has enabled detection of intraepithelial neoplasia before it progresses to cancer, and to deteect cancer at an early stage. When detected early, the 5-year survival is more than 90%.

The PAP test is the most widely used screening tool in the USA, exceeding screening for colon cancer by far.

The preceding study calculated that in women with 3 negative PAP tests, if continued, screening annually would result in thousands and thousands of additional PAP tests and colposcopic examinations to detect only one additional case of cervical cancer.

Ensuring that women are tested at least every 3 years is important since 10% of cancers occur in women who have had a PAP test but who have not been screened within 5 years. As women move away from annual screening, it is important not to discontinue screening entirely.

Given that half of all cases occur in women who have never been screened, screening all women at least once would be expected to contribute more to decreasing mortality due to cervical cancer than the continued annual testing.

Comment:

First focus on women who have never had a PAP test.

Extending the period between the 3rd and 4th PAP tests will save time, inconvenience, and cost. Women who are accustomed to annual screening need to be reassured that the longer interval is safe.

10-2 TREATING THROMBOSIS IN THE 21ST CENTURY

For nearly 50 years the mainstays of antithrombotic therapy have been warfarin and heparin.

Heparin exerts its anticoagulant activity indirectly by activating anti-thrombin, enhancing the ability of anti-thrombin to inhibit factor Xa and thrombin.

Warfarin inhibits the vitamin-K dependent factors (prothrombin, Factors VII, IX, and X)

Both heparin and warfarin have well known drawbacks.

Now, a minimal anti-thrombin-binding unit of heparin, a pentasaccharide called fondaparinux, has been synthesized and is undergoing clinical trials. Fondaparinux also activates anti-thrombin and is a specific inhibitor of activated factor X (Xa). It requires subcutaneous administration. It can be given once a day on a weight basis. It does not require laboratory monitoring.

A second new anticoagulant (melagatran) took its cue from the leach which produces a direct thrombin inhibitor (hirudin). It acts independently of anti-thrombin and other plasma proteins. The discovery of hirudin led to other direct thrombin inhibitors, one of which is melagatran. Melagatran can also neutralize clot-bound

thrombin. Chemical modification (to "ximelagatran") allows better oral absorption. It is the first new oral anticoagulant since warfarin. Like fondaparinux, it does not require laboratory monitoring.

Three studies reported in this issue of NEJM describe some of the clinical effects of these new anticoagulants. See the following abstracts.

NEJM October 30, 2003; 349: 1762-64 Editorial by Sandor S Shapiro, Jefferson Medical College, Philadelphia, PA

Dr. Shapiro begins the editorial by presenting a fascinating capsule history of our understanding of clotting and the progress of anti-thrombotic therapy. This must be one of the greatest therapeutic advances in medicine in the past century and a half.

1832 Johannes Muller identified the insoluble clot substance "fibrin". Virchow named its hypothetical soluble precursor "fibrinogen".

1856 Denis isolated fibrinogen. Schmidt demonstrated that the transformation of fibrinogen to fibrin was an enzymatic process.

1882 Bizzozero first described convincingly that platelets are a necessary element in blood coagulation.

1890 Arthus discovered the anti-coagulant effect of citrate and oxalate and demonstrated the absolute requirement of calcium ions in coagulation.

1905 Morawitz synthesized these observations into the first formulation of the biochemistry of coagulation. Prothrombin is converted to thrombin by "thrombokinase" (tissue factor) in the presence of calcium. Thrombin converts fibrinogen to fibrin.

1920s Dam, in Denmark, discovered vitamin K (Koagulation) the absence of which caused a hemorrhagic disease in chicks. The diseased chicks were deficient in prothrombin, and, as subsequently shown, were also deficient in other vitamin K-dependent factors (VII, IX, and X)

1930s Quick developed the "prothrombin time", the basis of monitoring the effects of warfarin. This led to the discovery of factors V, VII, and X. Other tests developed during this period led to the recognition that the enzyme, factor Xa, is the direct proteolytic activator of prothrombin.

First half of 20th century McLean, Holt, and Howell isolated an anticoagulant from the liver (hepar) and named it "heparin".

1936 Best (of insulin fame) and colleagues produced relatively large amounts of heparin which was subsequently used by Murray to treat post-surgical thrombosis.

Early 1930s Link at the University of Wisconsin identified dicumarol as the component of spoiled sweet clover, the ingestion of which caused a bleeding disease in cattle described earlier by Shofield and Roderick.

1939 Link, searching for a better rat poison, synthesized dicumarol and a series of congeners. He assigned the patents to the Wisconsin Alumni Research Foundation. He named the most potent congener "warfarin" for the Wisconsin Alumni Research Foundation.

1955 The rat poison had been considered too toxic for humans until an unsuccessful suicide attempt suggested the relative lack of toxicity in humans.

1999 Warfarin was the 11th most frequently prescribed drug in the USA.

Truly, we do stand on the shoulders of giants, most of whom we have never known or heard of before. RTJ

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10-3 SUBCUTANEOUS FONDAPARINUX VERSUS INTRAVENOUS UNFRACTIONATED HEPARIN IN THE INITIAL TREATMENT OF PULMONARY EMBOLISM.

The standard treatment of hemodynamically stable patients with pulmonary embolism **(PE)** is intravenous unfractionated heparin. This requires laboratory monitoring and hospitalization.

This trial included over 2200 patients with acute symptomatic PE. It compared efficacy and safety of fondaparinux (*Atixtra*) with unfractionated heparin. Is fondaparinux better, as effective as, or not as effective as unfractionated heparin?

Patients were randomized to 1) fondaparinux [one daily SC dose based on patient weight], or 2) continuous IV unfractionated heparin aimed at activated partial-thromboplastin time 1.5 to 2.5 times control.

Both were given for at least 5 days and until the concomitantly given warfarin resulted in an INR above 2.0. Warfarin was continued for 3 months.

Some patients in the fondaparinux group received the drug for part of the time as outpatients.

Follow-up = 3 months.

Results:	Fondaparinux	Heparin	Absolute difference
Recurrent thromboembolic events	3.8%	5.0%	1.2% favoring fondaparinux.
Major bleeding	1.3%	1.1%	
Mortality rates were similar.			

Conclusion:

Once-daily fondaparinux without monitoring is at least as effective and safe as adjusted-dose IV unfractionated heparin in the initial treatment of hemodynamically stable patients with pulmonary embolism.

“Because of its simplicity, once-daily subcutaneous fondaparinux without anticoagulation monitoring could replace intravenous administration of unfractionated heparin in most patients.”

NEJM October 30, 2003; 349: Original investigation by the Matisse Investigators, reported from the Academic Medical Center, Amsterdam, Netherlands.

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10-4 COMPARISON OF XIMELAGATRAN WITH WARFARIN FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM AFTER TOTAL KNEE REPLACEMENT

Venous thromboembolism **(VTE)** occurs very commonly in patients undergoing knee replacement. In up to 20% the VTE is proximal, and up to 7% have a pulmonary embolus (0.2 to 0.7% fatal). Many patients have VTE even when treated with warfarin or low molecular weight heparin. .

A previous study reported that the efficacy of 24 mg ximelagatran (*Exanta*) twice daily after knee replacement was *similar* to warfarin in prevention of VTE.

This study asked if a higher dose of ximelagatran is *superior* to warfarin in preventing VTE after knee replacement.

Study: Randomized double-blind trial of over 1850 patients (mean age 68) compared regimens of ximelagatran at doses of 24 mg bid, 36 mg bid, and warfarin aimed at INR of 2.5.. Ximelagatran was started the morning after surgery; warfarin was started the evening of the day of surgery. Drug therapy continued for 7 to 10 days. Composite primary end point = VTE, death from all causes, and incidence of bleeding. Composite secondary end point = proximal deep vein VTE, pulmonary embolism and death.

Results: The 36 mg dose was superior to warfarin:

	Primary end point	Secondary end point	Major bleeding
Warfarin	27.6%	4.1%	0.7%
Ximelagatran 36 mg	20.3%	2.7 %	0. 8%
Ximelagatran 24 mg	24.9%	2.5%	

Absolute difference of 36 mg vs warfarin in primary endpoint = 7.3% (NNT = 14)

Adverse effects: Wound bleeding and appearance of the wound—no significant difference. At 4 to 6 weeks, alanine amino transferase was more than three times upper normal in 4 patients in the 36 mg group.

Conclusion: Fixed dose ximelagatran 36 mg bid, administered without coagulation monitoring, was significantly more effective in prevention of thromboembolism after knee replacement than warfarin, and had similar safety. “It could therefore be considered an alternative to other thromboprophylactic agents.”

NEJM October 30, 2003; 349: 1703-12 Original investigation by the Exanta Used to Lessen Thrombosis (EXULT) Study Group, first author Charles W Francis, University of Rochester, New Yor

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A New Exciting Anti-Coagulant

10-5 SECONDARY PREVENTION OF VENOUS THROMBOEMBOLISM WITH ORAL DIRECT THROMBIN INHIBITOR XIMELAGATRAN

For many patients with VTE, secondary prevention with warfarin is not extended beyond 6 months. After this time the risk of bleeding may outweigh benefits of warfarin. Treatment for longer than 6 months with lower-intensity warfarin may reduce risk of bleeding, but this is controversial. “There is currently no general recommendation that therapy be continued beyond 6 months in patients who have had a first event and have no major risk factors for recurrent venous thromboembolism”

This study evaluated the long-term efficacy and safety of fixed dose oral ximelagatran initiated 6 months after standard anticoagulant therapy for VTE.

STUDY:

1. Double-blind randomized trial entered over 1200 patients with VTE. All had undergone 6 months of standard anticoagulant therapy. After the 6 months therapy, patients were randomized to receive 24 mg ximelagatran bid or placebo for an additional 18 months. Coagulation was not monitored.

RESULTS:

1.	Ximelagatran (n = 612)	Placebo (n = 611)	NNT*
Symptomatic recurrent VTE	12 patients	71 patients	10
Death from any cause	6 patients	7 patients	
Bleeding	134	111	
Major hemorrhage	6	5 (None fatal)	

(* Number needed to treat for an additional 18 months to prevent one recurrence .)

2. Cumulative risk of transient elevation of alanine aminotransferase to more than 3 times upper limits was 6.4% as compared with1.2% of the placebo group. The increase in ALT was transient and restricted to the first 4 months of therapy. No progressive hepatic dysfunction occurred. ALT levels spontaneously decreased after 4 months despite continued ximelagatran.

CONCLUSION:

Beginning and continuing extended secondary prevention of VTE with ximelagatran 24 mg bid for an additional 18 months after 6 months of standard anticoagulation effectively prevented recurrences. The incidence of major hemorrhage was low and similar to placebo. Ximelagatran was equally effective in subgroups that had risk factors for recurrence—previous VTE, proximal deep VTE, and pulmonary embolism.

The fixed-dose ximelagatran was well tolerated without monitoring measures of coagulation.

NEJM October 30, 2003; 349: 1713-21 Original investigation, by the THRIVE investigators (Thrombin Inhibitor in Venous Thromboembolism), first author Sam Schulman, Karolinska Hospital, Stockholm, Sweden.

Comment:

Looks like ximelagatran will be the next great therapeutic advance for treating and preventing VTE.

Anticoagulant therapy beyond 6 months will prevent some recurrences. This is especially relevant to those with pro-thrombotic factors.

No matter how long anticoagulation is continued, when it is discontinued, VTE may recur. The protocol for secondary prevention is not settled—how long and what drug to use? Aspirin, regular dose warfarin, low-dose warfarin, and now ximelagatran, are options. Clinical judgment for the individual patient and patient preference continue to decide the choice. RTJ

The Longer Glycemia Is Controlled, The More Delayed Microvascular Complications

10-6 SUSTAINED EFFECT OF INTENSIVE TREATMENT OF TYPE 1 DIABETES MELLITUS ON DEVELOPMENT OF PROGRESSION OF DIABETIC NEPHROPATHY

The Epidemiology of Diabetes Interventions and Complications (EDIC) Study

The development of decreasing glomerular filtration rate and end-stage renal disease is a long pathological process presumably reflecting the effects of hyperglycemia on renal cells.

The Diabetes Control and Complications Trial (DCCT; 1993) demonstrated the benefits of intensive treatment of diabetes over 6.5 years in reducing glycemic levels and slowing the progression of diabetic nephropathy. The present study followed the DCCT cohort for an additional 8 years to determine if the benefits of intensive vs conventional treatments on kidney function would persist.

Conclusion: Benefits were persistent. In the group actively controlled for 6.5 years, incidence of hypertension and albuminuria remained lower for 8 years thereafter despite deteriorating glucose control.

STUDY:

1. The EDIC study began in 1993, following the DCCT closeout. It compared the original intensive-treatment group vs the original conventional-treatment group for an additional 8 years.
2. Over 1300 participants entered this observational study.
3. Main outcome = development of microalbuminuria, hypertension, or increase in creatinine levels.

RESULTS

1. Outcomes at 8 years according to original assignment:	Intensive group	Usual treatment
New cases of microalbuminuria	6.8%	15.8%
New cases of clinical albuminuria	1.4%	9.4%
Prevalence of development of hypertension	29.9%	40.3%
Reached a creatinine of 2 mg/dL or greater	5 patients	19 patients

2. Mean HbA1c maintained during DCCT (up to 1993) was 7.2% vs 9.1% in controls. The mean values throughout the 8-years of the EDIC study were 8..0% vs 8.2%. *(Patients lost their enthusiasm for strict control over the years.)*

DISCUSSION

1. The persistent beneficial effects on albumin excretion and the reduced incidence of hypertension 8 years after 6.5 years of very strict glycemic control suggest that previous intensive treatment of diabetes with near-normal glycemia has an extended benefit in delaying progression of diabetic nephropathy.
2. The difference in HbA1c between groups in the DCCT trial over 6.5 years averaged 1.8%. This better control continued to produce benefit regarding nephropathy for at least 7 to 8 years thereafter although the difference in mean HbA1c between the two former treatment groups averaged only 0.2%.
3. In addition, there were clear benefits of intensive treatment on future development of hypertension over the ensuing 8 years.

4. The differences between the original DCCT intensive-treatment group vs the conventional-treatment group are virtually all explained by the differences in glycemia established during the 6.5 years of the DCCT trial. "This lends support to the hypothesis that a 'metabolic memory' effect had occurred.".
5. The advanced glycation end product pathway is capable of producing tissue changes that could outlast a particular level of hyperglycemia. Natural history studies have documented a decade-plus exposure to hyperglycemia before the first manifestations of diabetic nephropathy occur. Thus intensively treated participants had few manifestations of nephropathy during the DCCT due to their relatively low level of HbA1c. The near normal hyperglycemic control for 6.5 years may have simply delayed the development of indicators of diabetic nephropathy during the 8 more years of follow-up.

CONCLUSION

The persistent beneficial effects on albumin excretion and the reduced incidence of hypertension 8 years at the end of the DCCT suggest that pervious intensive treatment of diabetes with near-normal glycemia during the 6.5 year DCCT had an extended benefit in delaying progression of diabetic nephropathy.

JAMA October 22/29, 2003; 290: 2159-67 Original investigation by the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications Research Group (EDIC), Bethesda MD.

Comment:

I believe primary care clinicians will have little difficulty extrapolating these benefits to patients with type 2 diabetes. The greater the number of days with normal glucose levels, the longer the delay in development of microvascular complications. RTJ

10-7 SHOULD DOCTORS PRESCRIBE ALCOHOL TO ADULTS ?

"There is no more emblematic standard of good health in the United States than the food guide pyramid. It is widely recognized if not well followed. The pyramid advises Americans to eat lots of grains and fruits and vegetables, some meat and dairy, and a small amount of fat and sugars."

"One day soon, it may advise adult Americans to have a drink of beer, wine, or spirits every day as well. The idea is not as radical as it seems. "

The policy makers at the U.S. Department of Health and Human Services are reconsidering their stance on alcohol—which in the past has consisted of mentioning the health benefits of alcohol while emphasizing the adverse effects—as they update the U.S. dietary guidelines. With the policy experts talking ever more seriously about endorsing moderate drinking, is it time for physicians to consider selective prescription of alcohol for patients?

Epidemiological evidence from more than 100 observational studies over the past 3 decades has shown that moderate alcohol consumption helps prevent heart disease. Other health benefits include reduced risk for ischemic stroke, peripheral vascular disease, and diabetes. Risk of heart disease among moderate drinkers is 35% or so lower than in non-drinkers. "Alcohol clearly has a sizable effect, and it's not so easy to ignore that."

About one third of adults in the USA abstain. As a result, they miss the health benefits of alcohol.

Of course, alcohol can be very dangerous. A main concern is that moderate drinking will transform to excessive drinking. Most current guidelines recommend moderate drinking only for people who already drink, and urge abstainers *not* to start drinking for their health. Some physicians now believe clinicians should discuss alcohol consumption with all patients and inform those without contraindications of the benefit of regular moderate consumption. "For appropriate patients who do not drink, or do so only occasionally, and who wish to do so, encouraging a glass of wine or other alcoholic beverage with dinner every night may be the best advice you can give them." (*Based on epidemiological studies, the type of alcohol consumed is not important RTJ.)*

Some authorities, however, do not believe we should base important clinical changes on observational studies alone.

The editorialist comments that the well publicized "French Paradox" which describes the lower risk of cardiovascular disease in France where consumption of wine is high and fat consumption is similar to the USA. Publicizing it did not have any consistent effect on drinking in the USA.

The risk of turning non-drinkers into excessive drinkers by prescribing one glass of wine daily is impossible to know. The American Heart Association cautions persons who do not drink NOT to start drinking.

Barriers to a controlled trial of alcohol vs no alcohol are too daunting to become a reality.

Actually, physician's recommendation, or an addition to the food pyramid encouraging moderate lifetime alcohol consumption is unlikely to change American's drinking habits.

Annals Int Med October 21, 2003; 139: 711-14 "Current Clinical Issues", editorial by Jennifer Fisher Wilson,

Comment

The epidemiological data seems overwhelming. Some authorities state that abstinence is a risk factor.

What would be the legal risk to clinicians who write a prescription for "one glass of wine with dinner daily"? If the patient exceeds the stated dose, could the clinician be held liable for adverse effects any more than if the patient experienced adverse effects after exceeding the dose of any drug contrary to the prescription?

Clinicians may be more secure in prescribing alcohol for secondary prevention. And patients may be more likely to accept it. RTJ

More Bang For The Buck Taken At Night

10-8 TAKING SIMVASTATIN IN THE MORNING COMPARED WITH EVENING

Most manufactures of statin drugs recommend that they be taken at night. This is based on physiological studies which show that most cholesterol is synthesized when dietary intake is lowest.

A study of atorvastatin (*Lipitor*) however, showed no difference. Thus, doubt remains.

This study determined if simvastatin (*Zocor*) taken in the morning had significantly different effects from taking it in the evening.

Conclusion: Simvastatin taken in the evening produced lower cholesterol levels.

STUDY

1. Randomized and followed 60 patients (mean age 66) who were stable on 10 or 20 mg simvastatin taken at *night* to: 1) dosing in the morning and 2) dosing in the evening.
2. Measured fasting lipid profiles at baseline and at 8 weeks
3. Primary outcome = change in fasting cholesterol between baseline and 8 weeks.

RESULTS

1. At 8 weeks, total cholesterol was 14 mg/dL lower in the evening group, then in the morning group, and LDL cholesterol 10 mg/dL lower.
2. No significant change in HDL or triglycerides.

DISCUSSION

1. The degree of lowering produced by dosing in the evening has implications for prevention of coronary heart disease.
2. The difference may not apply to statins with longer elimination half life (eg, atorvastatin).

CONCLUSION

Simvastatin is probably best taken at night because concentrations of total cholesterol and low density cholesterol are significantly lower than when it is taken in the morning.

BMJ October 4, 2003; 327: 788 Original investigation, first author Alan Wallace, Grangewood Surgery, Houghton le Spring, Tyne and Wear, UK

Comment:

Lowering LDL-c by 10 mg/dL is clinically significant. This is achieved with no additional cost or inconvenience. Clinicians will easily extrapolate this advantage to other statins. RTJ

10-9 INHALED INSULIN PROVIDES IMPROVED GLYCEMIC CONTROL IN PATIENTS WITH TYPE 2 DIABETES MELLITUS INADEQUATELY CONTROLLED WITH ORAL AGENTS.

Functional defects in the pancreatic beta cells are crucial to the development of type-2 diabetes **(DM-2).** They occur early in the course of the disease. Oral agents depend on pancreatic beta cell function for their action. Their maximal efficacy is limited by dose-response considerations and by declining beta cell function. A high proportion of patients with DM-2 has poor glycemic control despite therapeutic doses of oral agents.

Physicians and patients often resist initiation of insulin because of fear of injections, difficulty in administration, the number required to achieve good control, and the perception that commencing insulin reflects a significant worsening of the disease.

Recently, a dry powder inhaled insulin **(IN-I)** system has been developed. It provides a new method of treatment. The pulmonary route exploits the large vascular bed and permeability of the alveoli to deliver insulin

directly into the blood stream. IN-I has a rapid onset of action, actually faster than injected regular insulin and insulin lispro. Its duration of action is about 6 hours. This is between insulin lispro (5 hours) and regular insulin (7 hours). IN-I is rapidly and reproducibly absorbed from the lung. It is likely to be a suitable agent for control of meal-related glucose excursions. It may improve patient satisfaction.

This proof of concept study was designed to determine if IN-I would improve control in patients with DM-2 who failed to achieve adequate control on oral agents.

Conclusion: IN-I added to oral agents improved control.

STUDY

1. Entered 68 patients (mean age 51) with DM-2 inadequately controlled despite therapy with a sulfonylurea and/or metformin. (HbA1c = 8% to 12%)
2. Randomized to: 1) Premeal inhalations of IN-I + continued oral agents, or 2) Oral agents alone. Premeal IN-I was delivered in 1 to 2 inhalations of 1-mg or 3-mg doses (Each inhalation is equivalent to 3 IU or 9 IU injected regular insulin--9 to 27 IU daily).
3. Administration of IN-I was preceded by a blood glucose measurement and insulin dose was adjusted weekly based on glucose monitoring results. A target postprandial glucose was in the range of 100 mg/dL to 160 mg/dL
4. Follow-up = 12 weeks.

RESULTS

1. At week 12, there was a significantly greater reduction in HbA1c for the IN-I + oral agents group than in the oral agents alone group—a mean reduction in HbA1c of 2.3 %. HbA1c remained stable in the control group—about 10%
2. One third of the IN-I + oral agents group achieved a HbA1c less than 7% vs none in the oral agents alone group. (Mean HbA1c dropped from about 10% to 7.5% in the IN-I group.)
3. Fasting plasma glucose improved significantly more in the IN-I + oral agents group compared with the oral agents alone group (a 55 mg/dL reduction). Postprandial increase in glucose was also significantly lower in the IN-I group—from a mean increase of about 120 mg/dL at baseline to an increase of about 80 mg/dL. Two hour postprandial glucose remained stable in the oral-alone group.
   (Data extracted from figure 2 , p 2280)
4. One report of severe hypoglycemia occurred in the INH + oral group.
5. A greater weight increase occurred in the IN-I group.
6. Pulmonary function was unchanged. No patient discontinued therapy because of adverse events.

DISCUSSION

1. Addition of IN-I to existing oral drugs in patients with DM-2 improved glycemic control.
2. This is consistent with a previous study which found that adding fast acting insulin lispro to oral agents improved control to a greater degree than oral agents alone.

3. Adding premeal IN-I reduced the postprandial glucose burden and augmented the disposal of meal-related glucose. It also lowered fasting glucose substantially and decreased HbA1c.
4. IN-I was well tolerated. It incurred a risk of hypoglycemia to no greater degree than that expected with combined oral drugs and subcutaneous insulin. Pulmonary function remained unchanged over 12 weeks.
5. A large number of patients with DM-2 are not well controlled by oral agents alone. Addition of insulin improves control. However, about one quarter of patients have psychological problems with injecting insulin. A questionnaire at the end of this study revealed a high patient satisfaction with IN-I: 97% opted to continue in a 1-year extension of the therapy.

CONCLUSION

The addition of preprandial inhaled insulin to existing oral agents improved glycemic control without the need for injections in patients with type 2 diabetes who failed to achieve satisfactory control with oral agents alone.

Archives Int Med October 27, 2003; 2277 -82 Original investigation by the inhaled Insulin Phase II Study Group, first author Stuart R Weiss, San Diego Endocrine and Medical Clinic, California.

Comment:

Dry powder aerosol delivery system by Nektar therapeutics, Pfizer, and Aventis.

This is an early proof of concept study. Primary care clinicians will watch for developments with great interest. Cost is to be determined. RTJ

10-10 COMBINATION ESTROGEN-PROGESTIN ORAL CONTRACEPTIVES.

(Review articles are too long to abstract concisely. I enjoy reading them and sometimes abstract a few points which are new to me, or which I consider important and deserving emphasis. RTJ)

At present, the doses of estrogen contained in O-Cs are 2 to 5 times less and the progestin content is 5 to 10 times less than originally formulated. This reduces the risk of venous thrombosis without any loss of effectiveness. Most preparations now contain 20 to 50 ug of ethinyl estradiol. Several different doses of progestin with varying directions for use are available.

The substantial benefits of O-Cs include avoidance of the dangers of pregnancy as well as a reduction in risk of ovarian cancer, acne, dysfunctional uterine bleeding, and possibly endometrial cancer.

Risks include venous thromboembolism and arterial vascular disease (myocardial infarction and stroke). The challenge for clinicians is to identify women in whom the risks outweigh the benefits. Both the American College of Obstetricians and Gynecologists and the WHO have published guidelines which differ only slightly:

Variable	Risk
Smoker	Unacceptable
Hypertension	Risk outweighs benefit if systolic 140-159/90-99 and unacceptable if > 160/100.

History of stroke, ischemic heart disease or venous thromboembolism	Unacceptable
Diabetes	Acceptable if no other cardiovascular risk and no end organ damage
Hypercholesterolemia	Acceptable if LDL-c under 160 and no other cardiovascular risk factors
Migraine headache Without associated neurological deficits	Acceptable
Breast cancer history	Unacceptable.
Thrombophilia (deficient protein C or protein S, presence of factor V Leiden, or prothrombin mutation)	Unacceptable. (Although screening not recommended.)

Despite at least 60 epidemiological studies of breast cancer associated with O-C use, the risk remains controversial. A recent study of 4500 women in the USA showed no increase.

"Even when the health risks are taken into account, the net health benefit of oral-contraceptive use is great, especially given the effect on risk of ovarian cancer and effectiveness in preventing pregnancy."

Hypertension and smoking are the most common contraindications to be considered.

NEJM October 9, 2003; 349: 143-50 "Clinical Practice", review article by Diana B Petetti, Kaiser Permanente Southern California, Pasadena.

10-11 CURRENT SMOKING, SMOKING CESSATION, AND THE RISK OF SUDDEN CARDIAC DEATH IN PATIENTS WITH CORONARY ARTERY DISEASE.

Sudden cardiac death **(SCD)** constitutes about one quarter of all coronary artery disease **(CAD)-**related major events and more than half of all CAD-related deaths. Ventricular arrhythmia is believed to be the most common direct cause.

Nicotine produces a marked elevation in serum catecholamines and is potentially arrhythmogenic and may predispose to cardiac arrest.

This study assessed the effect of continued cigarette smoking and smoking cessation on risk of SCD in patients with established CAD.

Conclusion: Cessation was related to a significant reduction in SCD.

STUDY

1. Followed over 3000 patients with a previous myocardial infarction or stable angina.
2. Prospectively followed for a mean of 8 years.
3. Primary end point = incidence of SCD according to smoking status.

RESULTS

1. Outcomes—8 years	Current smokers (n = 370)	Quitters (n = 1821)	Never smokers (n = 931)
Sudden cardiac death:	8.1%	4.6%	4.6%
All cause mortality	24.9%	13.8%	14.9%

2. In absolute terms, smoking cessation and never smoking resulted in a 3.5% lower risk of SCD over 8 years compared with those who continued to smoke. [NNT(8 years to prevent one SCD) = 30]. And a 11% reduction in all-cause death. [NNT = 10].
3. Interestingly, the benefit of quitting in those who formerly smoked was just as great as the benefit of never smoking.

DISCUSSION

1. Continued smoking was associated with a significant increase in risk of SCD.
2. In smokers who quit, risk is significantly reduced and compares with the risk of those who never smoked.
3. The decline in risk associated with cessation was immediate and not time dependent. This supports the view that the risk is due to direct toxic effects.
4. The risk of continuing smoking on SCD is even more pronounced than other risk factors—age, sex, New York Heart Association functional class, BP, and dyslipidemia.
5. The risk in smokers was not related to the amount of smoking. The great majority of continuing smokers smoked less than one pack a day.

CONCLUSION

Continued smoking after a myocardial infarction significantly increased risk of sudden cardiac death. Cessation lowered risk immediately to match the risk of non-smokers. Cessation is one of the most effective preventive measures.

Arch Int Med October 27, 2003; 163: 2301-05 Original investigation first author Ilan Goldenberg, Chaim Sheba Medical Center, Tel-Hashomer, Israel.

Comment:

Cessation is certainly one of the most effective preventive measures. Despite being informed of the risks, many patients continue to smoke. Primary care clinicians who succeed in getting recalcitrant smokers to stop achieve a major therapeutic intervention. Would asking them to read a copy of this article help? RTJ

10-12 RESTLESS LEG SYNDROME SYMPTOMS IN PRIMARY CARE.

Restless leg syndrome **(RLS)** is a sleep disorder that accounts for a significant proportion of patients with sleep complaints. Diagnostic criteria have been updated several times, the latest in 2002.

Currently, to be considered positive for RLS, four criteria must be met:

1. Urge to move the legs, usually accompanied by an unpleasant sensation in the legs.
2. Symptoms must be aggravated by rest.
3. Symptoms must be alleviated by movement, in particular, walking.
4. Must be worse in the evening or at night either currently or in the past when the condition first started.

The diagnosis is based on clinical symptoms. Primary care clinicians can provide both the diagnosis and the treatment for most cases. However, few primary care clinicians diagnose the syndrome.

This study was designed to determine the prevalence of RLS in a specific primary care practice.

Conclusion: RLS was highly prevalent. Awareness of the syndrome should be heightened.

STUDY

1. A primary care practice conducted a prospective population-based study surveying all adult patients presenting to the practice for RLS using a validated RLS diagnostic questionnaire.
2. Over a 1-year period, over 2000 patients completed the questionnaire.

RESULTS

1. Twenty four percent of these patients were positive for all 4 of the essential symptoms.; 15% reported the symptoms at least weekly.
2. The symptom complex was reported more often by women. More women than men reported early onset of the syndrome.
3. Patients with RLS were significantly older. Symptoms increased by age until about age 60; thereafter prevalence declined.
4. Most patients in the series had symptoms at least once a month. Some patients rarely had compatible symptoms. Frequency is a poor surrogate for severity of the symptoms.
5. Successful therapies are available. (*The article did not concern treatment.)*
6. This study suggests that a large number of RLS patients may be seen by primary care clinicians.

Archives Int Med October 27, 2003; 163: 2323-29 Original study, first author Deborah A Nichols, Stanford University Center of Excellence for Sleep Disorders, Stanford, California.

Comment:

I suspect RLS is not noted often in primary care because clinicians do not ask. Clinicians may be more likely to ask about it if the patients complains about sleep disturbance.

What about treatment? I accessed Restless Leg Syndrome on WebMD. Healthwise, Inc, Boise Idaho presented an overview of treatments:

Try conservative methods first: Stretching, walking, and regular exercise may help.

Treat other medical conditions which may predispose to RLS: eg, iron deficiency may be associated with RLS.

RLS may be temporary during pregnancy and be relieved by delivery. Here conservative treatment and reassurance are needed.

Drugs may be used if symptoms are frequent and severe and interrupt sleep. The FDA has not reviewed them for specific use in RLS:

Dopamine precursors (eg, levodopa; *Laradopa*)

Dopamine agonists (eg bromocriptine; *Parlodel*)

Anticonvulsants

Benzodiazepines.

Opioids

The variety of drugs used speaks for the lack of studies to determine preference. Drug therapy in practice would likely be based on cautious trial and error. RTJ

A Review Article

10-13 GOUT

(Review articles are too long to abstract concisely. I enjoy reading them and sometimes abstract a few points which are new to me, which I had forgotten, or which I consider important and deserving emphasis.)

Statistically normal uric acid levels (7 mg/dL in men and 6 mg/dL in pre-menopausal women) are close to the limits of urate solubility, This imposes a delicate physiologic urate balance. Hyperuricemia is central to gout, but does not inevitably cause disease. Indeed, urate levels are frequently normal during attacks.

Factors other than serum urate contribute to clinical gout in an additive manner—hypertension, thiazide and loop diuretics, obesity, and high alcohol intake. Gout is also associated with insulin resistance.

Uric acid stones are common in presence of both excessive production and excretion of urate. Overproduction of uric acid combined with acid urine (more prevalent in gout) contributes also to formation of calcium oxalate stones.

The differential diagnosis is broad. Definitive diagnosis requires direct identification of urate crystals in the joint and the exclusion of infection.

Prevalence of gout is rising in postmenopausal women, associated with use of diuretic-treated hypertension and renal insufficiency. Initial symptoms of gout may be subtle in this subpopulation. Tophi may occur in osteoarthritic small joints of the hand.

Treatment of *acute* gouty arthritis:

NSAIDs are considered first-line therapy. They usually relieve symptoms within 24 hours. Cyclo-oxygenase-2 inhibitors are just as effective as generics.

Systemic corticosteroids and intra-articular corticosteroids (large joints) are effective. Primary treatment with corticosteroids can be associated with rebound arthritis flairs. Adjunctive low-dose colchicine has been advocated.

What about colchicine? Acute symptoms respond to colchicine within hours when initiated within 24 hours. Self treatment (one 0.6 mg tablet every hour up to 3 hours—maximum of 3 tablets) may curtail acute episodes. Patients may be given a supply available for self-treatment. However, the therapeutic ratio of benefits to adverse effects is poorer for colchicine than for other drugs.

Long-term or *prophylactic* treatment:

Lifestyle changes: Sometimes levels return to normal without use of drugs if the patient stops drinking alcohol, switches from thiazides, or, if obese, loses weight. Conventional low purine diets are unpalatable and typically are only moderately effective..

Drug therapy:

NSAIDs

Colchicine (low-dose 0.6 mg twice daily) is frequently used in patients with intact renal function for 6 months while anti-hyperuricemic therapy is used. However, even low-dose daily colchicine may be associated with severe adverse effects. Intravenous colchicine should not be used.

Lowering uric acid levels: The principal indications for long-term uric acid lowering therapy are subcutaneous tophi, frequent attacks, or documented overproduction of uric acid. *Intermittent* anti-hyperuricemic therapy with drugs lacks efficacy. It is standard practice to avoid using anti-hyperuricemic drugs during an acute attack. Although most patients have substantially reduced renal urate clearance (probenecid may used for these patients). . . "It is common and acceptable practice to use the xanthine oxidase inhibitor allopurinol (*Generic; Zyloprim*), which inhibits uric acid synthesis whether or not the patient overproduces urate." "Irrespective of the cause of hyper-uricemia, allopurinol is the most frequently used anti-hyperuricemic agent." Its once-daily administration is convenient and effective regardless of the cause of the hyperuricemia.

NEJM October 23, 2003; 349: 1647-55 "Clinical Practice", review article by Robert A Terkeltaub, University of California, San Diego.

Comment:

The recommendations for colchicine surprised me. I thought use had been greatly restricted over the years. I would use other agents first.

Use of allopurinol for both over-production and decreased renal clearance makes therapy simpler. RTJ

Exercise In Patients With AD May Benefit Some.

10-14 EXERCISE PLUS BEHAVIORAL MANAGEMENT IN PATIENTS WITH ALZHEIMER DISEASE.

The deleterious effects of Alzheimer disease **(AD)** on physical functioning are less well known than the effects on cognitive, emotional, and behavioral functioning. A number of studies link AD with physical deterioration. When compared with age-matched controls, AD patients show more signs of undernutrition, higher risk of falls and fractures, and a more rapid decline in mobility. Reduced muscle mass has been associated with loss of independence.

Improving physical conditioning in patients with AD may extend their independent mobility and enhance their quality of life despite progression of the disease. Even the oldest adults can improve cardiovascular function and increase flexibility, balance, and strength.

This study assessed the effect of exercise training on AD patients. Caregivers were taught how to manage behavioral problems and how to apply the exercise program.

Conclusion: In patients with AD, exercise training improved physical health and lessened depression.

STUDY

1. Randomized, controlled trial entered 153 community-dwelling patients with AD (mean age = 78).
2. Patient-caregiver dyads were assigned to: 1) combined exercise and caregiver training, or 2) routine medical care. This "Reducing Disability in Alzheimer Disease (RDAD) program was conducted in patients' homes over 3 months.
3. The exercise component included aerobic/endurance activities, strength training, balance, and flexibility training. The goal was for patients to engage for 30 minutes daily in moderate-intensity exercise.
4. Caregivers were given specific instructions about how to identify and modify patient behavioral problems that impaired day-to-day function and adversely affected patient-caregiver interactions. They were taught the skills to identify and modify precipitants of patients' distress. They were encouraged to identify pleasant activities for their patients, encourage positive interactions and to increase physical and social activity. Mean age of caregivers = 70. The great majority were female, and spouses.
5. Main outcome = change in physical health and function measured by a health survey and affective status measured by depression scales.
6. Follow-up at 3 months and 2 years.

RESULTS

1. Outcomes at 3 months:

   More patients in the RDAD group exercised at least 60 minutes weekly and had fewer days of restricted activity.

   Patients in the RDAD group had improved scores for physical functioning. Those in the control group had worse scores.

   RDAD patients were less depressed.

2. Outcomes at 2 years:

RDAD patients continued to have better physical functioning scores and showed a trend (19% vs 50%) for less institutionalization due to behavioral disturbance.

3. Withdrawals were common (41% vs 43%). The same number were institutionalized. But the number institutionalized for behavioral problems was considerably less in the RDAD group.

DISCUSSION

1. An integrated treatment program designed to train demented patients and their caregivers in exercise and behavioral management techniques was successfully implemented in a community setting.
2. Caregivers were able to learn how to encourage and supervise exercise participation.
3. Patients achieved increased levels of physical activity, decreased rates of depression, and improved physical health and function. Their number of restricted activity days decreased. .
4. Post-test physical function improvements were maintained for up to 2 years.
5. The investigators did not assess the degree to which caregivers felt satisfied with what they were learning, nor was there any assessment of outcomes on caregivers.

CONCLUSION

Exercise training combined with teaching caregivers behavioral management techniques improved physical health and depression in patients with Alzheimer disease.

JAMA October 15, 2003; 290: 2015-22 Original investigation, first author Linda Teri, University of Washington, Seattle.

Comment:

A complete RDAD treatment manual is available from Linda Teri, PhD, University of Washington, Psychosocial and Community Health, PO Box 358733 Seattle Washington 98195 lteri@u.washington.edu

This is a difficult program to complete. Withdrawals for a number of reasons were high. I believe it would be possible only if the patient trusts and is emotionally bonded to the caregiver and the caregiver is dedicated, loving, patient and empathetic.

Walking with the patient would also help the caregiver gain and maintain fitness.

Worth a try? RTJ

10-15 PROGNOSTIC IMPORTANCE OF PHYSICAL EXAMINATION FOR HEART FAILURE IN NON-ST-ELEVATION ACUTE CORONARY SYNDROMES: ***The Enduring value of Killip Classification***

Increasingly sophisticated laboratory and diagnostic testing has led to diminished attention to the importance of the physical examination . An important reason for this diminished interest has been that studies have documented limitations of the physical examination when compared with more sophisticated methods.

Increasing evidence suggests that assessment of the presence and severity of heart failure by physical examination provides significant independent prognostic information. For example, in chronic heart failure (HF), the presence of an S1 gallop and elevated jugular venous pressure independently predict mortality.

In ST-*elevation* myocardial infarction **(MI),** the presence and severity of heart failure **(HF)** at the time of presentation have been formally categorized by use of the well-known Killip classification,, originally proposed in 1967. Subsequently, the Killip classification has been validated to predict mortality in patients treated with thrombolytic agents and in those treated by primary percutaneous coronary intervention.

This study asks—Is the classification relevant among patients with *non*-ST –elevation acute coronary syndromes?

Conclusion: The Killip classification is a powerful independent predictor of all-cause mortality in patients with *non*-ST –elevation acute coronary syndromes

STUDY

1. Analyzed information from over 26 000 patients with *non*-ST –elevation acute coronary syndromes documented in 4 large trials.
2. Killip classification was based on severity of HF (rales) and systolic BP at randomization:

   Killip I—no evidence of HF

   Killip II—mild HF, with rales involving 1/3 or less of the posterior lung fields and a systolic BP 90 mm HG or higher.

   Killip III—pulmonary edema with rales involving more than 1/3 of the posterior lung fields, and systolic BP of 90 or more.

   Killip IV—cardiogenic shock with any rales and systolic BP under 90.

   (For the purpose of this analysis, III and IV were combined because of the few numbers in class IV.)
3. Determined association between Killip class and all-cause mortality.

RESULTS

1. Patients in class II, II, and IV were generally older, and had more co-morbidities, (diabetes, prior MI, prior congestive HF, severe lung disease, chronic renal insufficiency, prior stroke) than those in class I.
2. More had elevation of cardiac enzymes and ST depression, higher heart rates, and lower systolic and diastolic BP.
3. Higher class was associated with higher mortality:

All-cause mortality	30 days (%)	6 months (%)
Killip I	2.8	5
Killip II	8.8	14.7
Killip III and IV	14.4	23

4. Killip II, III, and IV constituted 11% of the overall population, was associated with 30% of deaths.
5. Five factors—age, Killip classification, heart rate, systolic BP and ST depression—provided more than 70% of the prognostic information for 30-day and 6-month survival.
6. The relation between Killip class and mortality was evident for unstable angina as well as *non*-ST –elevation MI

DISCUSSION

1. Assessment for the presence and severity of HF through Killip classification in patients with *non*-ST–elevation acute coronary syndromes provides powerful independent information regarding short-term and long-term mortality.
2. Killip III and IV is the most powerful predictor of mortality. It uniquely provides independent prognostic information that is unavailable by other means.
3. "The physical examination should be viewed as an evidence-based aspect of the assessment of patients with *non*-ST–elevation acute coronary syndromes as well as in those with ST-elevation MI."
4. The mechanism behind the increased risk associated with the Killip classification is not known. Recent studies suggest that diastolic dysfunction and a propensity to develop delayed left ventricular dilation may play a role.
5. Cardiogenic shock at the time of initial presentation is far less common in patients with *non*-ST-elevation acute coronary syndromes than in those with ST-elevation MI. Instead, cardiogenic shock tends to develop during hospitalization, often secondary to recurrent ischemia or infarction. Once it develops, it is associated with an extremely high mortality rate. This delay in presentation of shock in *non*-ST –elevation acute coronary syndromes creates a fortuitous window, during which early revascularization may prevent shock.

CONCLUSION

Killip classification is a powerful independent predictor of all-cause mortality in patients with *non*-ST – elevation acute coronary syndromes.

Age, Killip class, heart rate, systolic BP and ST depression should receive particular attention in the initial assessment of *non*-ST –elevation acute coronary syndromes.

JAMA October 22/29 2003; 290: 2174-81 Original investigation, first author Umesh N Khot, Cleveland Clinic Foundation, Cleveland Ohio

Comment:

Old timers will welcome this reaffirmation and usefulness of simple physical signs. RTJ

A New More Sensitive Marker For Patient Vulnerability

10-16 PROGNOSTIC VALUE OF MYELOPEROXIDASE IN PATIENTS WITH CHEST PAIN

Myeloperoxidase in an abundant leukocyte enzyme. In patients with sudden death from cardiac events, it is elevated in culprit lesions that have fissured or ruptured. Numerous lines of evidence suggest links between myeloperoxidase and both inflammation and cardiovascular disease. Inflammation has been linked to all stages of the development of vulnerable plaque, from initial lipid deposition to rupture. Leukocyte activation and degranulation are found in patients with unstable angina. Extensive monocytes and neutrophil infiltration is seen in fissured, thrombosed plaques in patients with acute coronary syndromes. The activation of leukocytes prompts the secretion of myeloperoxidase.

At presentation, many patients with chest pain have normal levels of creatine kinase isoenzymes or troponins but subsequently have a myocardial infarction **(MI)**.

This study tested the hypothesis that plasma myeloperoxidase levels serve as a novel marker of plaque vulnerability in persons presenting with chest pain.

Conclusion: Plasma myeloperoxidase independently predicted early risk of MI and adverse cardiac events at 30 days and 6 months.

STUDY

1. Assessed value of plasma levels of myeloperoxidase in over 600 sequential patients presenting to the emergency department within 24 hours of onset of chest pain of suspected cardiac origin.
2. Diagnosis of acute coronary syndrome was based on presence of MI, or unstable angina. Defined MI by rise in troponin T levels. Unstable angina was ascertained by presence of angina at rest or by sudden increase in episodes of previously stable angina, ST-segment depression, and T-wave inversion.
3. Assessed patients for major adverse cardiac outcomes (MI, need for revascularization, or death) related to myeloperoxidase levels.
4. Determined the normal myeloperoxidase level by testing healthy subjects.

RESULTS

1. High initial myeloperoxidase levels predicted immediate risk of MI even in patients negative for troponin T.
2. Increased myeloperoxidase levels at presentation independently predicted risk of major adverse cardiac events within 30 days and 6 months.
3. In patients without evidence of myocardial necrosis (those with consistently normal troponin T levels), myeloperoxidase also independently predicted risk of major adverse coronary events.

DISCUSSION

1. Clinical criteria, ECG criteria, and conventional laboratory tests, including troponin T, do not adequately predict the risk of cardiovascular events in patients presenting with acute coronary syndromes.
2. C-reactive protein and other markers have been advocated as a more accurate means of gauging risk, but additional tools are needed to predict vulnerability of coronary arteries to major events in the near term. Myeloperoxidase is an excellent candidate. It predicts cardiovascular risks independently of C-reactive protein and other markers of inflammation.
3. Even in patients in whom MI is ruled out on the basis of normal serial troponin T levels, elevated myeloperoxidase levels at presentation predicted subsequent major events.
4. Myeloperoxidase levels were significantly elevated at baseline (even within 2 hours after onset of symptoms). Troponin T levels take longer to rise. Thus, myeloperoxidase may be useful in early triage in the emergency department.
5. “Our findings suggest that myeloperoxidase serves as a marker of the vulnerable plaque and one that

can be used to identify patients at imminent risk for major adverse cardiac events, independently of evidence of myocardial necrosis."

CONCLUSION

In patients presenting to the emergency department within 24 hours of onset of chest pain of suspected cardiac origin, a single measurement of myeloperoxidase independently predicted early risk of myocardial infarction, as well as the risk of major adverse cardiac events in the ensuing 30 days and 6 months. It identified patients at risk in the absence of myocardial necrosis.

NEJM October 23, 2003; 349: 1595-604 Original investigation, first author Marie-Luise Brennan, Cleveland Clinic Foundation, Cleveland, Ohio

Comment: I presented this abstract as a preliminary observation. More experience is required to determine cut points for myeloperoxidase levels and to determine clinical applications. The study is provocative.

Do we need a new marker? I believe so, if it is more predictive.

Primary care clinicians—watch for developments. RTJ

10-17 THE GREATEST THREAT TO WOMEN'S HEALTH

Which disease kills the greatest number of women worldwide? Some might answer cancer; some malaria, tuberculosis, or HIV/AIDS. They are all wrong.

In fact, heart attacks and stroke kill twice as many women as all cancers combined. They are 4 times as likely to die from coronary disease as from breast cancer. Moreover, contrary to conventional wisdom, women are more likely to die from cardiovascular disease than men.

The WHO has reported that one-third of global deaths are due to cardiovascular disease (defined as coronary heart disease, cerebrovascular disease, hypertension, heart failure, and rheumatic heart disease). Most of these global deaths are in countries with low to medium incomes. By 2010, cardiovascular disease will be the leading cause of death in developing countries. "Yet, more than half of all deaths and disability from heart disease and stroke can be prevented."

Getting women to stop smoking, eat healthily, drink alcohol only in moderation, lose weight if appropriate, and take regular exercise involves changing behaviors that are often ingrained from childhood. Promoting images of women with cardiovascular disease in TV dramas (men are almost always portrayed as the victims of heart disease), newspaper articles and magazines would help.

The great majority of women have never discussed heart disease with their primary care provider. Most women over age 65 have never had a consultation about heart disease, even though these older women are at greatest risk.

"Advising women, as well as men, about their risks of cardiovascular disease should, we urge, be mandatory for all primary care practitioners."

Lancet October 11, 2003; 362: 1165 Editorial from The Lancet staff