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HIGHLIGHTS AND EDITORIAL COMMENTS

8-1 BREAST CANCER AND HORMONE-REPLACEMENT THERAPY IN THE MILLION WOMEN STUDY

This remarkable, country-wide study confirms that current use of HRT is associated with increased risk of incident and fatal BC. Between 1996 and 2001, one half of the million women age 50-64 in this UK cohort of were using HRT.

The risk is substantially less for estrogen-alone than for E-P combinations.

Use of HRT by women aged 50-64 in the UK over the past decade is estimated to have resulted in 20 000 extra cases of BC; 15 000 of these associated with E-P use; 5000 with use of estrogen alone. (Ie, *progestins are the major culprit*.)

Women who are presently taking estrogen-progestin may be told there is one additional chance in 150 of an invasive BC over 5 years; and one additional chance in 800 if they are taking estrogen alone.

Risk increases with duration of use. Past users (5 or more years previously) were not at increased risk.

8-2 ESTROGEN PLUS PROGESTIN AND THE RISK OF CORONARY HEART DISEASE.

E-P, in standard dose, does not confer cardiac protection. It may slightly increase risk of CHD, especially during the first year of use. Primary care clinicians may consider prescribing low-dose aspirin for primary prevention, at least during the first year. Treatment to improve lipid profiles reduces risk.

E-P should not be prescribed for the prevention of cardiovascular disease.

Any possible increase in incidence of CHD (about 6 extra cases per 10 000 patient-years) is minor compared with the risk for breast cancer.

8-3 IS OPPORTUNISTIC DISEASE PREVENTION IN THE CONSULTATION ETHICALLY JUSTIFIABLE?

Consultations in primary health care have been suggested as an ideal setting for health promotion and disease prevention. Doctors are expected to discuss preventive measures even when they are not among the reasons for the consultation. Opportunistic preventive medicine is considered a part of good medical practice. This article asks. . .Is this ethically justifiable?

The authors argue that doctors should maintain a clear focus on each patient's reasons for seeking help rather than be distracted by an increasing list of preventive measures. They maintain that, from a moral point of view, initiatives to improve health among people who are currently free of symptoms is fundamentally different from curative medicine—the condition for which the patient consults.

Physicians who offer a screening test carry a considerable responsibility. They must offer enough information about risks and benefits in order to enable the patient to give informed consent. Informed consent presupposes an

understanding of the limitations of the screening test. Every test carries a chance of misclassification of disease. A false positive test may result in further interventions that do not benefit the patient, and may cause harm.

"Once medical risk has been passed on to a person, it cannot be retracted. Respect for autonomy should therefore also honor the person's right *not* to be opportunistically confronted with knowledge about biomedical risks that are unrelated to his or her reasons for seeing the doctor."

"As the list of accessible preventive tests lengthens and thresholds for intervention are lowered, a doctor who adheres to all recommendations for provision of preventive services may ultimately be able to find something abnormal in everybody."

Think twice before advising screening tests.

8-4 A RISK SCORE FOR PREDICTION OF STROKE OR DEATH IN INDIVIDUALS WITH NEW-ONSET ATRIAL FIBRILLATION IN THE COMMUNITY: *The Framingham Heart Study*

This risk score for embolic stroke was derived from 5 risk predictors: advancing age, female sex, increasing systolic BP, prior stroke or TIA, and diabetes. The score can be used to estimate *absolute* risk of stroke (5% to 75% over 5 years) and help to negotiate treatment decisions with patients with AF at the time they are first diagnosed. . Risk may be stratified into mild, moderate or severe.

Although some physicians and patients may more readily accept and act on a numerical risk prediction, I believe primary care clinicians can just as accurately judge risk without creating a numerical 5-year "risk". Most patients with AF eventually end up receiving anticoagulation. It is nevertheless important to spare those at low risk from the potential adverse effects of warfarin therapy and use aspirin instead. Patients with AF, but without structural heart disease, (including no hypertension) are at relatively low risk, especially if they are under age 65.

To anticoagualate or not anticoagualate is a difficult and important decision. It remains a clinical-judgment call. For each patient, clinicians must strike an acceptable balance between risk of ischemic stroke and bleeding. In the absence of an absolute or important relative contraindication, the data seem compelling that warfarin therapy should be offered to most patients with AF. The difficulty is to know what threshold of stroke risk is low enough so that the potential risk of warfarin therapy outweighs its potential benefits. For most patients the potential benefits of stroke prevention will outweigh the potential risks of bleeding secondary to warfarin.

An article (*Annals Internal Medicine April 28 , 2003; 163: 936-43; Practical Pointers April 2003*) differs somewhat in suggesting that up to 1/3 of patients with AF can be classified as low-risk and treated with aspirin.

8-5 COMPARISON OF LOW-INTENSITY WARFARIN THERAPY WITH CONVENTIONAL-INTENSITY WARFARIN THERAPY FOR LONG-TERM PREVENTION OF RECURRENT VENOUS THROMBOEMBOLISM

"The intensity of anticoagulation for patients who have had unprovoked venous thromboembolism should not be reduced after the first three months of treatment." Such a reduction increases risk of recurrence. INR should remain at 2.0 to 3.0.

Risk of recurrent VTE was 0.7 per 100 patient-years in the INR 2.0 to 3.0 group vs 2.8 per 100 patient years in the INR 1.5 to 1.9 group.

In this study, there was no evidence that aiming for an INT of 1.5 to 1.9 (vs 2.0 to 3.0) reduced risk of bleeding.

I believe that in the "real world" of primary care, aiming for a higher INR will be related to an increased risk of bleeding. Indeed, bleeding risk is increased in patients who aim for the lower INR as compared with placebo.

An article in *NEJM April 10, 2003; 348; 1425-34* reported that a low-level INR (target 1.5 to 2.0; compared with placebo) in patients with unprovoked VTE was highly effective in preventing recurrence. It is likely that a higher target will be slightly more effective in prevention, but will lead to greater risk of bleeding. Again a clinical judgment call based on individual-patient characteristics and preferences.

8-6 D-DIMER LEVELS AND RISK OF RECURRENT VENOUS THROMBOEMBOLISM

After 3-months of anticoagulation for a first episode of unprovoked VTE, measuring D-dimer levels allowed identification of a subset of patients with very low risk of recurrence. Patients with a level of less than 250 ng/mL 3 weeks after discontinuation of oral anticoagulation were at low risk.

The cumulative probability of recurrent VTE at 2 years among those with levels < 250 was 3.7%. Among those with higher levels was 11.5%

A higher D-dimer is likely to be related to ongoing thrombosis-thrombolysis due to a thrombogenic potential**.**

8-7 PREVALENCE OF CONVENTIONAL RISK FACTORS IN PATIENTS WITH CORONARY HEART DISEASE.

At least 80% to 90% of patients with CHD have conventional risk factors (cigarette smoking, diabetes, dyslipidemia, and hypertension**).** This is probably an underestimate. Clinical medicine, public health policies, and research efforts should place significant emphasis on the 4 factors and lifestyle behaviors. Non-traditional risk factors and genetic causes deserve less emphasis.

"Although widely asserted, the belief that more than 50% of patients with CHD lack conventional risk factors is not supported by primary data." "In essence, patients without conventional risk factors are unlikely to develop CHD."

"The true prevalence of conventional risk factors is certainly higher than identified in our study."
Many patients with hypertension and diabetes are not aware of their condition. More stringent cutoffs for BP, lipids, and blood glucose have been increasingly recommended.

"It is increasingly clear that the 4 conventional risk factors and their resulting health risks are largely preventable by a healthy life-style."

Primary care clinicians have their hands full encouraging patients to deal with these conventional risk factors. We don't need more at this time.

8-8 EMERGING RISK FACTORS FOR ATHEROSCLEROTIC VASCULAR DISEASE.

This critical review highlights 4 emerging risk predictors: C-reactive protein, Lipoprotein (a), Fibrinogen, and Homocysteine.

"Their optimal use in routine screening and risk stratification remains to be determined."

"The explanatory power of the *major established* cardiovascular risk factors has been systematically underestimated." (*See previous abstract.)*

Primary care clinicians and their patients have not even begun to assess, prevent, and treat the established major, modifiable risk factors. Until we do, I believe we need no more risk factors.

We will, with interest, however, follow the basic science investigations aimed at determining the best mix of risk factors on which to base clinical interventions.

8-9 CARDIOVASCULAR RISK FACTORS AND INCREASED CAROTID INTIMA-MEDIA THICKNESS IN HEALTHY YOUNG ADULTS

Atherosclerosis is a slowly progressive process possibly starting at a young age. Preventive measures taken early in life might postpone the development of atherosclerosis and decrease risk of clinical cardiovascular disease **(CVD).**

Unfavorable cardiovascular risk factors (cigarette smoking, diabetes, dyslipidemia, and hypertension) were related to greater CIMT in young adulthood. Effort to change modifiable risk factors early in life may retard development of atherosclerosis and the onset of clinical cardiovascular disease later in life.

8-10 REGRESSION OF CAROTID AND FEMORAL ARTERY INTIMA-MEDIA THICKNESS IN FAMILIAL HYPERCHOLESTEROLEMIA

High dose simvastatin over 2 years reduced combined carotid/femoral IMT in more than two thirds of patients. The largest effect was on the femoral artery. This degree of reduction of IMT. . . "will likely have a significant clinical impact on the prevention of coronary artery disease".

Primary care clinicians might easily extrapolate these results to other patients with high cholesterol levels. Atherosclerosis is reversible.

8-11 BULIMIA NERVOSA

Has 3 key features: 1) Intense preoccupation with body weight and shape; 2) Repetitive episodes of binge eating--uncontrollable eating a large quantity of food in a defined period—usually less than 2 hours; 3) Routinely taking extreme measures to prevent weight gain: self induced vomiting, fasting, exercise, and misuse of laxatives and diuretics. Some patients take up to 50 laxative pills per day. Severe constipation with a laxative-dependence syndrome may result.

Anorexia nervosa differs. Patients with BN maintain a normal weight.

The challenge for primary care clinicians is to suspect and recognize BN in select young women who present with vague symptoms, anxiety and depression. The clinical clues cited may help. A metabolic package might very well reveal a metabolic alkalosis.

"Hypokalemia in an otherwise healthy young woman is highly specific for BN."

8-12 DIFFERENTIAL ASSOCIATION OF ORAL AND TRANSDERMAL OESTROGEN-REPLACEMENT THERAPY WITH VENOUS THROMBOSIS RISK.

Oral, but not transdermal ERT, was associated with risk of VTE in postmenopausal women. Transdermal administration avoids the first pass through the liver and blunts production of thrombogenic proteins by the liver.

A good example of the advantages of transdermal application of drugs.

8-13 ENDOCRINE TREATMENT OF PHYSIOLOGICAL GYNECOMASTIA

"Physiological" gynecomastia is due to an altered ratio between free estradiol (a stimulant) and testosterone (an inhibitor). Anti-estrogens such as tamoxifen (*Nolvadex*) have therefore been suggested as non-surgical treatment. Various published studies have used tamoxifen at a dose of 10 to 40 mg daily for several months. Resolution of the lump and pain has been reported in 80% of cases. Only minor and reversible side effects were reported.

8-14 EXPOSURE TO NON-STEROIDAL ANTI-INFLAMMATORY DRUGS DURING PREGNANCY AND RISK OF MISCARRIAGE

NSAIDs and aspirin were associated with an increased risk of miscarriage. Acetaminophen was not.

8-15 POOR GLYCEMIC CONTROL CAUSED BY INSULIN INDUCED LIPOHYPERTROPHY.

Prevalence of lipohypertrophy in patients with type 1 diabetes is estimated to be around 20% to 30%. It is due to a cellular response of adipocytes to the local effects of injected insulin. Immunological factors may be important. Frequent injection into the same site is related to incidence.

Injection repeatedly given into these sites may lead to problems of glycemic control. Insulin absorption can be significantly delayed.

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Current Use Of HRT Is Associated With Increased Risk Of Incident And Fatal BC

8-1 BREAST CANCER AND HORMONE-REPLACEMENT THERAPY IN THE MILLION WOMEN STUDY

Current and recent use of hormone replacement therapy **(HRT**) increases the risk of breast cancer **(BC**). However, the effect of HRT on mortality from BC is unclear. Use of HRT preparations containing estrogen-progestogen **(E-P)** combinations may be associated with a greater risk than preparations containing estrogen alone.

This million-woman cohort study investigated the relation between various patterns of use of HRT and BC incidence and mortality.

Conclusion: Current use of HRT is associated with increased risk of incident and fatal BC. The risk is substantially less for estrogen-alone than for E-P combinations.

STUDY

1. Recruited over one million women aged 50-64 in the UK between 1996 and 2001.

2. All provided information about their use of HRT and other personal details.
3. Estrogen-only users were subdivided according to the specific estrogen (equine estrogen, or estradiol), and whether it was administered as on oral, transdermal, or implanted formulation.
4. Users of combined E-P were subdivided into subgroups by the specific progestogen constituents and by sequential or continuous regimens.
5. Determined cancer incidence and death.

RESULTS

1. Half the entire cohort had used HRT.
2. Incident invasive BC was recorded in over 9300 women after an average follow-up of 2.6 years.
3. BC deaths occurred in over 600 women after an average of 4.1 years of follow-up.
4. Current users at recruitment were more likely than never-users to develop BC (Relative Risk = 1.66), and were more likely to die from BC (RR = 1.22).
5. Incident invasive BC over 5 years:

   All never users 2894/392 757 = 0.737%

   Current users of estrogen alone 991/115 383 = 0.858% Absolute difference = 0.121 NNT to harm = 826

   Current users of E-P 1934/142 870 = 1.35% Absolute difference = 0.613 NNT to harm = 159

   (*My calculations. About a five-fold higher incidence in the E-P group. RTJ*)
6. Use of HRT by women aged 50-64 in the UK over the past decade is estimated to have resulted in 20 000 extra cases of BC; 15 000 of these associated with E-P use.
7. In current users of each type of HRT, the risk increased with increasing total duration of use:10-years of use is estimated to result in 5 additional cancers per 1000 users of estrogen alone and 19 additional cases in users of combined E-P per 1000 users.
8. Past users (5 or more years previously) were not at increased risks of incident or fatal BC.
9. Results varied little between specific estrogens and progestogens and their doses, or between continuous or sequential regimens.
10. The extra deaths cannot yet be reliably estimated.

DISCUSSION

1. This confirms previous findings of increased risk of BC in current and recent HRT users. There was considerably less risk among users of estrogen alone compared with E-P users.
2. The only factor that modified the RR estimates was the body-mass index. Thinner women had a greater risk than obese women.
3. Incident BC was diagnosed on average 1.2 years after recruitment. Risk increased with increasing duration of use.
4. There was little or no increased risk in past users of HRT.
5. Endometrial cancer risk increased in women with an intact uterus who used estrogen alone. The main reason

to use E-P preparations in these women is to prevent endometrial cancer. “However, if the additional breast cancers and endometrial cancers associated with each type of HRT are added together, there seems to be little advantage to using estrogen-progestogen in preference to estrogen alone in women who still have a uterus.”

CONCLUSION

Current use of HRT is associated with an increased risk of incident and fatal BC. The risk is substantially greater for E-P combinations than for estrogen alone.

Lancet August 9, 2003; 362: 419-27 Original investigation by the Million Women Study Collaborators, correspondence to Valerie Beral, Radcliffe Infirmary, Oxford, UK . www.thelancet.com

An editorial in this issue of Lancet (pp 414-15), first author Toine Lagro-Janssen, University Medical Centre, Nijmegen, Netherlands comments:

A general practitioner would need to give combined HRT to 166 women for 5 years—or 53 women for 10 years—to see one extra case of BC.

Most women receiving HRT are in primary care. Despite stringent controls of drugs, how is it that heavy promotion of HRT has put millions of women at risk? Any preventive intervention in healthy people must be supported by the strongest evidence of benefit and virtually no evidence of risk. “Digression from this principle could be considered unethical.”

Primary care is the vital ingredient of clinical research before introduction of a new intervention.

For many general practitioners, the HRT story must present an all-too-familiar pattern. Those who claim special expertise place a new product in a positive light, overwhelming general practitioners with “evidence” of benefits. The drug industry promoted HRT to physicians and directly to patients, neglecting the risks. Now that the risks are firmly demonstrated, it is left to primary care providers to solve the problem.

HRT should be discouraged. For post-menopausal-related health problems, women should be well-informed about HRT and use it for no more than 6 months.

Women who are already using HRT should discontinue use.

Comment:

I was intrigued by the data suggesting that the classical reason for adding progestogen to estrogen (prevention of endometrial cancer) is negated by the increase in BC. This upsets the classical approach.

I believe that some women are so disturbed by menopausal symptoms (especially women who have had an oophorectomy that they will be more than willing to take the chance of adverse effects. RTJ

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E-P does not protect against CHD. It may increase risk. “This treatment is not a viable intervention for primary prevention.”

8-2 ESTROGEN PLUS PROGESTIN AND THE RISK OF CORONARY HEART DISEASE.

Final Report from the Women’s Health Initiative Investigation

Recent trials have suggested that estrogen + progestin **(E-P)** does not confer cardiac protection, and may actually increase risk of coronary heart disease. **(CHD)**

This article presents the final results of the Women's Health Initiative regarding the risks.

Conclusion: E-P does not protect against CHD. It may increase risk slightly.

STUDY

1. Randomized, primary-prevention trial entered over 16 000 generally healthy postmenopausal women age 50 to 79.
2. Randomized to: 1) *Prempro* -- estrogen + progestin (conjugated equine 0.625 mg + medroxyprogesterone 2.5 mg) once daily, or 2) placebo
3. Primary outcome = CHD (non-fatal myocardial infarction or death due to CHD).
4. Mean follow-up = 5 years.

RESULTS

1. Coronary outcomes over 5 years:

	E-P group (n = 8506)	Placebo (n = 8102)
CHD	188	147
Nonfatal MI	151	114
Death due to CHD	39	34

2. Absolute rates of CHD: 39 cases per 10 000 person-years for E-P group vs 33 cases in the placebo group.
3. No significant differences for coronary revascularization, angina, acute coronary syndrome, or congestive heart failure.
4. The number of cases of CHD was higher in the first year of E-P therapy: 42 vs 23. In following years, risk was less. After year 6, the risk of CHD the E-P group actually fell below the placebo group. (Ie, favoring E-P over placebo). Numbers were small.
5. Patients in the E-P group had improvements in lipids. The increased risk developed despite a lowering of conventional (surrogate) risk factors; total-cholesterol (- 5%); LDL-cholesterol (- 13%); glucose (- 2,.5%); insulin (- 7%) and an increase in HDL-cholesterol (+ 7%). In addition, weight, waist circumference, and waist/hip ratio decreased in the treatment group. (*One might assume that reduction of all of these risk factor reductions might reduce incidence of CHD. It did not*.)
6. Possible adverse effects on risk factors: triglycerides were raised by +7%; systolic BP increased by 1 mmHg.
7. However, in the E-P group, aspirin users and statin users had a lower risk than non users. Subjects with LDL-cholesterol under 125 mg/dL had a lower risk than those with LDL-c above 125. Those with HDL-cholesterol above 58 mg/dL had lower risk than those with levels below 58. (*Ie, some evidence of protection against CHD in these subgroups*.) However, in all these subgroups of women, no group except those with a higher LDL-c had evidence of a risk of CHD with E-P that differed significantly for that observed for all women.

DISCUSSION

1. In addition to the favorable changes in risk factors noted above in the E-P group, E-P favorably

improves endothelial vascular function fibrinogen levels, Lp(a) lipoprotein, plasminogen-activator and insulin. This might again lead to the conclusion that hormone therapy would decrease CHD risk.

2. However, estrogen also has adverse physiological effects; increased triglycerides, small-dense LDL particles, and C-reactive protein. It also has prothrombotic effects.
3. The addition of progestin attenuates some of the lipid benefits of estrogen, especially the increase in HDL-c, but does not seem to counter the prothrombotic effects.
4. The Woman's Health Initiative previously reported that the risks of E-P outweigh the benefits. The combined excess of CHD, stroke, venous thromboembolism, and breast cancer was not offset by a reduced risk of hip fracture and colorectal cancer. Study stopped early because overall risks exceeded benefits.
5. "This treatment is not a viable intervention for primary prevention."

CONCLUSION

E-P, in standard dose, does not confer cardiac protection. It may slightly increase risk of CHD, especially during the first year of use. It should not be prescribed for the prevention of cardiovascular disease.

NEJM August 7, 2003; 349: 523-34 Original investigation by the Women's Health Initiative Investigators, first author JoAnn E Manson, Brigham and Women's Hospital and Harvard Medical school, Boston Mass. www.nejm.org

Comment:

This study demonstrated a lack of benefit for prevention of CHD. It did not convincingly show that E-P increases risk.

Over the years, the presumed cardiovascular benefits of estrogen were in part based on biologically plausible surrogate markers (improvements in lipids and the fact that women in general do not begin to experience CVD until after the menopause--about a decade after men). The adverse cardiovascular effects may be caused by an increased tendency to thrombogenesis. This tendency may be countered by use of low-dose estrogen and low-dose aspirin. I would prescribe low-dose aspirin and low-dose estrogen for menopausal symptoms in women accepting E-P therapy, at least during the first year and treat dyslipidemia with statins and life-style therapy.

I believe many women who suffer menopausal symptoms will willingly accept the risks to obtain relief.

Remaining questions:

What is the effect of estrogen alone and low dose estrogen? Does low dose aspirin protect? Will transdermal estrogen be safer? (This might be a reasonable assumption. When given transdermally, the liver is by-passed and production of adverse thrombogenic proteins produced by the liver is limited.) Will prolonged use (over 5 years) be associated with a reduced risk of CHD?

Why is risk higher in the first year of use? RTJ

The Physician Who Offers Screening Tests Carries A Considerable Responsibility. Think Twice Before Advising Them

8-3 IS OPPORTUNISTIC DISEASE PREVENTION IN THE CONSULTATION ETHICALLY JUSTIFIABLE?

Consultations in primary health care have been suggested as an ideal setting for health promotion and disease prevention. Doctors are expected to discuss preventive measures even when they are not among the reasons for the consultation. Opportunistic preventive medicine is considered a part of good medical practice. This article asks. . .Is this ethically justifiable?

The authors argue that doctors should maintain a clear focus on each patient's reasons for seeking help rather than be distracted by an increasing list of preventive measures. They maintain that, from a moral point of view, initiatives to improve health among people who are currently free of symptoms are fundamentally different from curative medicine—the condition for which the patient consults.

The two disciplines imply different premises and have different obligations to the individuals whose lives they modify.

A "risk epidemic" has occurred in medical publishing. The range of tests that can be considered in general practice has become extensive. (*The authors list 13 conditions which can be screened for in primary care. There are more. RTJ*) Now, asymptomatic people are more likely to be labeled as at risk and needing medical intervention and follow-up. Lower thresholds for intervention in asymptomatic people are constantly promoted.

Doctors don't always follow clinical guidelines. (They are said to have "clinical inertia".) This is generally interpreted as a sign of low quality care. Lack of time is a frequent explanation. Preventive measures are considered to be effective enough to shift a large load of work away from treatment of manifest disease in the practice population. With the introduction of each new screening routine, the number of consultations will increase. It has been estimated that an average of 7 hours of the working day of a primary care clinician would be needed to provide all services recommended by the U S Preventive Services Task Force.

The physician who offers a screening test carries a considerable responsibility. He or she must offer enough information about risks and benefits in order to enable the patient to give informed consent. (Patients should understand the difference between relative and absolute risk.)

Informed consent presupposes an understanding of the limitations of the screening test. Every test carries a chance of misclassification of disease. A false positive test may result in further interventions that do not benefit the patient, and may cause harm.

Interventions which are effective in optimal settings may be of marginal benefit in everyday practice.

"Implementation of preventive medical measures on a large scale is thus not only becoming technically unmanageable, but a matter of increasing ethical concern in relation to individual patients."

Measurable pathophysiological disturbances should not necessarily be interpreted as the ultimate cause(s) of disease and suffering. External factors, such as social inequality and destructive human relations, greatly influence health and disease. A focus on biotechnological interventions may divert the dialogue between patient and doctor away from important social and relational issues relevant to health. "It is not necessarily good medicine to focus on the management of bodily risk factors in individuals who ask for help to take control of their lives."

"As the list of accessible preventive tests lengthens and thresholds for intervention are lowered, a doctor who adheres to all recommendations for provision of preventive services may ultimately be able to find something abnormal in everybody."

There is the potential for risk information to cast shadows of doubt and insecurity over people's lives, which means it may undermine their experience of integrity and health. "Once medical risk has been passed on to a person, it cannot be retracted. Respect for autonomy should therefore also honor the person's right *not* to be opportunistically confronted with knowledge about biomedical risks that are unrelated to his or her reasons for seeing the doctor."

BMJ August 30, 2003; 327: 498-500 "Education and Debate", Essay, first author Linn Getz, Landspitali Hospital, Reykjavik, Iceland. www.bmj.com/cgi/content/full/327/7413/498

Comment:

I enjoyed this thoughtful paper.

Some screening tests are routinely included and accepted in primary care practice--eg, weight, height (BMI), BP, cholesterol, and glucose. A routine biochemical profile is also readily accepted and may reveal abnormalities which lead to discussion and intervention. Routine health questionnaires can reveal concerns leading to further discussion. Other screening procedures can be introduced according to the patient's concerns. Much depends on the present culture. Much depends on individual patient preferences. When a screen is recommended, patients should understand the harms as well as potential benefits.

Primary care practice which builds trust and allows long-term care, may give the clinician opportunity to gradually introduce selective biomedical interventions.

We must not forget that there is no justification for any screening test for a disorder for which a substantiated clinically beneficial intervention is not readily available.

I believe some practices can be dedicated to "preventive medicine". This may be welcomed by many individuals. But, I agree with the authors—most primary care clinicians must be very selective in advising screening procedures. Patients are much more than collections of biomedical risks. RTJ

A Risk Score Can Be Used To Estimate Absolute Risk And Help To Negotiate Treatment Decisions With Patients.

8-4 A RISK SCORE FOR PREDICTION OF STROKE OR DEATH IN INDIVIDUALS WITH NEW-ONSET ATRIAL FIBRILLATION IN THE COMMUNITY: *The Framingham Heart Study*

Embolic stroke is a common complication of atrial fibrillation **(AF)**. Risk is variable, depending on characteristics of individual patients.

This study derived risk scores for stroke alone, and for stroke or death in community based individuals with *new*-onset AF.

Conclusion: These risk scores can be used to estimate absolute risk and help to negotiate treatment decisions with patients.

STUDY

1. Prospective, community-based observational cohort study identified over 700 patients (mean age = 75) with new-onset AF. None was being treated with warfarin at baseline.
2. New onset AF was diagnosed when AF or atrial flutter was first noted on an EKG obtained from the Framingham clinic visit, hospital charts, or physician office record.
3. Developed risk scores from patient outcomes for embolic stroke or death according to patient characteristics. The risk score was derived from 5 risk predictors: advancing age, female sex, increasing systolic BP, prior stroke or TIA (not in the setting of AF) , and diabetes. (*The cause of the increased risk in women is not known. It may be due to an increased thrombotic tendency.)*
4. Patients were censored once warfarin was started. (*Ie, this natural-history study concerned only those who were not taking warfarin*.)
6. Mean follow-up = 4 years.

RESULTS

1. During a mean follow-up of 4 years in patients who were not anticoagulated, stroke alone occurred in 83 patients; stroke or death occurred in 383.
2. Crude incidence rates were 3 per 100 person-years for stroke, and 13 per 100 patient-years for stroke or death. (*See figures on page 1052 and 1053* www.nhlbi.nih.gov/about/framingham/stroke.htm)
3. Example for risk of stroke within 5 years:
   A. The predicted highest risk (75% in 5 years) was for a female over age 93, with systolic BP over 179, with diabetes, and prior stroke or TIA.
   B. The predicted lowest risk (5% in 5 years) was for a male age 55-59, with a systolic BP under 120, without diabetes, and without prior stroke.
4. Risks for stroke or death were higher.

DISCUSSION

1. These risk scores can be used to estimate the absolute risk of a stroke in individuals diagnosed with new-onset AF. They can be used to stratify patents at particularly high or low risk.
2. Other risk predictors have included heart failure or left ventricular dysfunction.
3. The study did not include patients with prior stroke occurring in the setting of AF because there is broad consensus that these individuals are at high risk of events and should receive anticoagulation. (*The study concerned risks following new-onset of AF. Patients with stroke or TIA in the past associated with AF were excluded because the onset of AF was not "new". Presumably any prior stroke or TIA in the study patients was due to factors other than AF, not thromboembolism associated with AF*)
4. Individuals with a 10% or lower risk of stroke over 5 years may *not* realize additional benefit from warfarin compared with aspirin. Their risk of stroke may not exceed the risk of bleeding due to warfarin.
5. "A potential advantage of the Framingham scheme over existing risk schemes is the greater

flexibility provided by a point-scoring system because a given score may be attained by different combinations of patient characteristics."

6. Some patients in the study were receiving aspirin. Aspirin reduces the risk of thromboembolism in AF. Therefore, the stroke rates derived by the study may underestimate the risk in persons not taking aspirin.
7. The study did not distinguish between paroxysmal and sustained AF or between AF and atrial flutter. Stroke risk associated with paroxysmal AF is similar to that of sustained AF. A large proportion of patients with flutter subsequently develop AF.
8. The risks of thromboembolic complications of AF are highly variable. It is increasingly important to be able to risk-stratify patients. These risk scores enable prediction of the risk of stoke or death over a 5-year period in an individual patient at the time of diagnosis. (*Note that there was no indication in the study about the length of time AF existed before it was diagnosed. This will extend to period of risk assessment beyond 5-year. RTJ)*
9. "An understanding of absolute risk is fundamental to make clinical decisions involving patients with AF such as the decision to initiate anticoagulant therapy or to temporarily stop anticoagulation for surgical procedures."

JAMA August 27, 2003; 290: 1049-56 Original investigation, first author Thomas J Wang, Framingham Heart Study, Framingham Mass. www.jama.com

An editorial in this issue of JAMA (pp 1093-95) by Albert L Waldo comments and expands on the article:

Prevention of ischemic stroke in patients with AF remains a major challenge. Risk of stroke may be stratified by many factors, including age, previous thromboembolic embolic stroke, hypertension, diabetes, ventricular dysfunction, mitral stenosis, coronary heart disease, female sex, thyrotoxicosis, and cardiomyopathy.

Risk may be stratified further into mild, moderate or severe. Patients with AF, but without structural heart disease, (including no hypertension) are at relatively low risk, especially if they are under age 65.

For patients with AF who are at higher risk of ischemic stroke, warfarin is significantly better than aspirin for preventing stroke. The prevalence of AF and risk of AF-associated embolic stroke increase with age. Risk of intracranial bleeding while taking warfarin also increases with age. Risk of bleeding, particularly related to falls, frailty, or forgetfulness is the most noteworthy reason for reluctance to anticoagualate the elderly. "Patients with the greatest risk of ischemic stroke in the face of AF are the ones least likely to receive it." It is difficult to regulate the INR (between 2.0 and 3.0) in the elderly. One reason is the interaction of warfarin with the large numbers of other drugs they take.

For each patient, clinicians must strike an acceptable balance between risk of ischemic stroke and bleeding. In the absence of an absolute or important relative contraindication, the data seem compelling that warfarin therapy should be offered to most patients with AF. The difficulty is to know what threshold of stroke risk is low enough so that the potential risk of warfarin therapy outweighs its potential benefits. For most patients the potential benefits of stroke prevention will outweigh the potential risks of bleeding secondary to warfarin.

The advent of new anticoagulants such as the direct thrombin inhibitor ximelagatran may simplify decision-making.

Comment:

The risk score predicting 5-year risk of stroke is published in figure 1 p 1052 of the article. Risk varies according to the number of 5 risk factors, from 5% to 75%

The score implies an accuracy of prediction which I believe is not justified. It can be a useful tool as a first step to judge a ball-park figure of risk. Primary care clinicians may be able to judge risk of stroke empirically by simply listing the number of factors which increase risk in individual patients.

I spent considerable time abstracting this article. It is important because AF is so common and decisions about treatment, although difficult, are critical. As usual, individualization, along with patient-preference, is the key to the best decision-making.

Primary care clinicians must consider a vast variation in patients—clinical, social, family support, personal preference, availability of monitoring INR accurately—before deciding to anticoagualate or not. Simply adding up 1 + 2 + 3 + 4 + 5 won't do it. Not many patients with AF will fit the category of a risk of 10% or lower. According to the score, women age 72 and over already have a risk score of 10% even though they have no other risk factors.

The study does call to attention the variability of risk. But I doubt many primary care clinicians will find such risk scores helpful. A reasonable judgment for risk can be made from the evident clinical characteristics without trying to place a numerical value of 5-year risk. Obviously increasing age, diabetes, hypertension, heart failure, prior stroke or TIA are self evident markers of risk of embolic stroke. These are readily factored into a judgment about anticoagulation vs. use of aspirin.

Why are women at higher risk? RTJ

Conventional Anticoagulation Therapy (INR 2.0 TO 3.0) Was The Most Effective.

8-5 COMPARISON OF LOW-INTENSITY WARFARIN THERAPY WITH CONVENTIONAL-INTENSITY WARFARIN THERAPY FOR LONG-TERM PREVENTION OF RECURRENT VENOUS THROMBOEMBOLISM

Unprovoked ("idiopathic"; spontaneous) venous thromboembolism, **(UVTE)** is associated with a higher risk of recurrence after anticoagulation is discontinued than is VTE associated with a transient risk factor (eg, immobilization, surgery, trauma).

Previous studies have reported that, after an initial episode of UVTE, it is better to continue warfarin for an additional two years than to discontinue treatment after 3 months. Another study of anticoagulant therapy in patients who had two episodes of UVTE, reported that no patient had a recurrence while receiving extended warfarin therapy adjusted to an INR of 2.0 to 3.0. This suggests that anticoagulation of this intensity may be necessary for effective long-term prevention of recurrence. The risk of bleeding is a limitation of extended therapy.

This study asks…Is anticoagulation with warfarin in patients with UVTE with a target INR of 1.5 to 1.9 just as effective in preventing recurrence, but less likely to be associated with bleeding than conventional anticoagulation (INR 2.0 to 3.0)?

Conclusion: Conventional anticoagulation therapy (INR 2.0 TO 3.0) was the most effective.

STUDY

1. Randomized, double-blind study entered over 700 consecutive patients (mean age = 57). All had one or more episodes of UVTE. All had completed 3 or more months of conventional warfarin therapy (INR target 2.0 to3.0).
2. All episodes were unprovoked deep venous thrombosis or pulmonary embolism. No patient had a major risk factor for VTE (recent trauma, fracture, cancer, hospitalization with confinement to bed, or surgery).
3. Factor V Leiden was present in 171 (26%); prothrombin gene mutation present in 60 (9%).
4. Randomized, after the first 3 months to continued warfarin with 1) a target INR of 2.0 to 3.0 (conventional intensity), or 2) a target INR of 1.5 to 1.9 (low intensity).
5. Follow-up = an average of 2.4 years

RESULTS

1. Outcome	INR 2.0 to 3.0 (n = 369)	INR 1.5 to 1.9 (n = 369)
Recurrent VTE	6 (1.6%)	16 (4.3%)
	0.7 per 100 patient years	2.8 per 100 patient-years.
Major bleeding	8 (2 %)	9 (2 %)

2. No significant difference in frequency of overall bleeding between groups.
3. INR control was excellent. Mean INR in the low-intensity group was 1.8; in the conventional group, 2.4. In the remainder of the patients, INR fell above and below these levels to roughly the same extent. There was no instance where INR exceeded 4.0

DISCUSSION

1. Conventional-intensity warfarin (INR 2.0 to 3.0) was more effective than low-intensity warfarin (1.5 to 1.9) in preventing recurrence in patients with UVTE
2. The study found no significant increase in bleeding in the INR 2-0 to 3.0 group
3. As in other studies, factor V Leiden and prothrombin mutations were not associated with a higher risk of recurrent VTE when the patients were anticoagulated.

CONCLUSION

"The intensity of anticoagulation for patients who have had unprovoked venous thromboembolism should not be reduced after the first three months of treatment." When INR target was reduced to 1.5 to 1.9, risk of recurrence of UVTE exceeded that of patients kept on conventional therapy (INR 2.0 to 3.0).

. There was no evidence that, compared with low-dose anticoagulation, conventional dose increased the risk of bleeding. [1]

NEJM August 14, 2003; 349: 631-39 Original investigation by The Extended Low-intensity Anticoagulation for Thrombo-embolism (ELATE) investigators, first author Clive Kearon, McMaster University, Hamilton, Ontario, Canada. www.nejm.org

Comment:

1 I believe the authors overstate. In primary care practice, I believe that bleeding will be less common in patients who aim for a lower INR. It might be expected that, in "the real world", INR control, when aimed for a higher level, might be less exact, resulting in a higher relative frequency of bleeding.

See also "Long-term, Low-intensity Warfarin Therapy for the Prevention of Recurrent Venous Thromboembolism." NEJM April 10, 2003; 348: 1425-34 This study compared low-dose warfarin (target INR 1.5 to 2.0) *with placebo* (after the standard 3-month full warfarin therapy). All patients had a previous episode of UVTE. Effectiveness and safety was demonstrated over a 2-year period. Recurrent VTE was 2.6 per 100 person-years in the low-dose group vs 7.2 per 100 person-years in the placebo group. Major hemorrhage occurred in 5 of 255 patients in the low-dose group vs 2 of 253 patients in the placebo group. Ie, major hemorrhage occurs even when the target INR is low.

I was impressed by the relatively large numbers of patients with thrombophilia. This must be common in patients with UVTE. I was also impressed by the effectiveness of warfarin in preventing recurrence in these patients.

So, do you wish to use a low-dose regimen in some patients? They will indeed receive considerable benefit in reducing recurrence (even those with thrombophilia) compared with placebo, although not as much benefit as with full dose warfarin. Major bleeding will still occur, but, I believe will be much less common than with full-dose warfarin.

Choice will depend on many factors, including patients' age and personal preference. RTJ

After A First Episode Of VTE, And After The First 3 Months Of Anticoagulation, A Low D-Dimer Level Indicates Low Risk Of Recurrence

8-6 D-DIMER LEVELS AND RISK OF RECURRENT VENOUS THROMBOEMBOLISM

The risk of recurrence of unprovoked (spontaneous) venous thromboembolism **(VTE)** is minimal during oral anticoagulation. Risk increases as soon as anticoagulation is stopped. What is the optimal duration of therapy? What patients are at least risk of recurrence?

Widespread screening for thrombophilic risk factors may be helpful to identify patients in whom risk of recurrence outweighs risk of bleeding. Because the number of known risk factors is increasing, assessing the risk of recurrence in an individual patient is intricate. A single laboratory test that measures multifactorial thrombophilia is needed.

D-dimer is a global indicator of coagulation activity and fibrinolysis. Well-standardized assays are available and widely used in diagnosis of acute VTE. A high level (> 70^{th} percentile of controls) is associated with a more than doubling risk of a first VTE as well as a recurrence. One study reported a 2.5-fold higher risk of recurrence among patients with VTE and D-dimer levels higher than 500 ng/mL after discontinuation of oral anticoagulation.

This study assessed the relationship between risk of recurrent VTE and D-dimer levels.

Conclusion: After withdrawal of the first 3-months of oral anticoagulation, patients with a first unprovoked VTE and a D-dimer level less than 250 ng/mL have a low risk of VTE recurrence.

STUDY

1. Prospective cohort study entered over 600 patients who had a history of a first spontaneous VTE. All had been treated with oral anticoagulation for at least 3 months.
2. Measured D-dimer levels shortly after discontinuation of anticoagulation.
3. Followed frequently for recurrence of VTE over a mean of 38 months.
4. A high percentage of these patients had thrombophilic factors present (factor V Leiden, prothrombin mutation, and high factor VIII).

RESULTS

1. VTE recurred in 79 (13%) of 610 patients. Patients with a recurrence had significantly higher mean D-dimer levels compared with those without recurrence. (553 ng/mL vs 427 ng/mL).

2. D-dimer level (ng/mL)	< 250	250-499	500-749	> 750
Number of recurrences	16 (8%)	39 (16%)	11 (14%)	13 (19%)
Relative risk of recurrence	0.3	0.6	0.6	1.0

3. A total of 209 (34%) of 610 patients had D-dimer levels less than 250. VTE recurred in 8% of these patients. They had significantly fewer thrombotic risk factors such as factor V Leiden, and high factor VIII compared with patients with higher D-dimer levels.
4. The cumulative probability of recurrent VTE at 2 years among those with levels < 250 was 3.7%. Among those with higher levels was 11.5%.

DISCUSSION

1. Patients with a first spontaneous VTE and a D-dimer level of less than 250 ng/mL 3 weeks after discontinuation of oral anticoagulation were at low risk of recurrence.
2. Extensive screening for thrombophilic factors in patients with unprovoked VTE has become more common. Assessing the overall risk of recurrence is intricate. Many patients carry more than one thrombogenic risk factor. The effect of compound defects tends to be multiplicative rather than additive. Thus, a simple test that measures multifactorial thrombophilia is required.
3. D-dimer allows a global assessment of thrombotic tendency. It allows stratification into high and low-risk with regard to recurrence.

CONCLUSION

After a first episode of unprovoked VTE, measuring D-dimer levels allowed identification of a subset of patients with very low risk of recurrence. Patients with a level of less than 250 ng/mL 3 weeks after discontinuation of oral anticoagulation were at low risk of recurrence.

JAMA August 7, 2003; 290: 1071-74 Original investigation, first author Sabine Eichinger, University of Vienna, Austria. www.jama.com

Comment:

This study implies a prolonged period of anticoagulation is indicated in patients with high D-dimer. It also implies that patients with a continuing high D-dimer likely have continuing fibrin formation and fibrinolysis due to an underlying thrombogenic abnormality.

This study is provocative. Further experience is required to determine if the test used for this purpose has a valid place in clinical practice.

D-dimer assays have usually been used as an aid to diagnosis of acute venous thromboembolism. Deep-vein thrombosis can be ruled out in a patient who is judged clinically unlikely to have deep vein thrombosis and who has a negative D-dimer test. (*NEJM September 25, 2003; 349: 1227-35*). An editorial in the same issue of NEJM cautioned that hospital laboratories should validate their D-dimer assay method and ensure that operators are proficient in interpretation. RTJ

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The Great Majority Of Patients With CHD Have Conventional Risk Factors

8-7 PREVALENCE OF CONVENTIONAL RISK FACTORS IN PATIENTS WITH CORONARY HEART DISEASE.

Cigarette smoking, diabetes, dyslipidemia, and hypertension—the so called "conventional risk factors" **(CRF)--**are independent risk factors for coronary heart disease **(CHD)**. Treatment of these risk factors has been shown to reduce the risk of future cardiac events.

Although the importance of these risk factors is well established, it is commonly suggested that more than half of patients with CHD lack any of the factors. This implies that other factors play a significant role in the development of CHD, and that there is a substantial void in the current understanding of the pathogenesis of CHD. This has led to considerable research on non-traditional risk factors and genetic causes of CHD.

This study sought to determine the prevalence of the 4 conventional risk factors among patients with CHD.

Conclusion: 80% to 90% of patients with CHD have conventional risk factors.

STUDY

1. Analyzed data from over 122 000 patients with CHD. This included patients with ST-elevation myocardial infarction, with unstable angina, and those undergoing percutaneous coronary intervention **(PTCI).**
2. Determined prevalence of each CRF and the number of CRFs present among patients with CHD.
3. Main outcome measures = prevalence of each CRF compared between men and women and by age at trial entry.

RESULTS

1. Among patients with CHD, at least one risk factor was present in 85% of women and 81% of men.
2. In younger patients (men , age < 55; women age < 65), and most patients with unstable angina or presenting for PTCI, only 10% to 15% lacked any of the CRFs.
3. Premature CHD was related to cigarette smoking in men, and to cigarette smoking and diabetes in

women. Smoking decreased the age at the time of the first CHD event by nearly one decade.

4. Prevalence of CRF:	Women	Men
Current smoking	29%	42%
Diabetes	23%	15%
Hyperlipidemia	40%	34%
Hypertension	56%	38%

5. Number of risk factors

0	15%	19%
1	37%	43%
2	33%	28%
3	13%	9%
4	1%	1%

DISCUSSION

1. In patients with CHD, conventional risk factors were present at a much higher level than commonly believed. Only 15% to 20% lacked any of the factors.
2. Cigarette smoking played a critical role in the development of *premature* CHD.
3. Overall, the prevalence of risk factors was greater in women than in men. Because CHD typically presents 10 years later in women than in men, higher risk factor prevalence in women is necessary to lead to the development of CHD at the same age as in men. Diabetes virtually negates the usual protection women have against CHD.
4. “Although widely asserted, the belief that more than 50% of patients with CHD lack conventional risk factors is not supported by primary data.”
5. “In essence, patients without conventional risk factors are unlikely to develop CHD.”
6. “The true prevalence of conventional risk factors is certainly higher than identified in our study.” Many patients with hypertension and diabetes are not aware of their condition. More stringent cutoffs for abnormal BP, lipids, and blood glucose have been increasingly recommended. Self-report of risk factors has been shown to systematically underestimate the true prevalence of risk factors as measured objectively.
7. “It is increasingly clear that the 4 conventional risk factors and their resulting health risks are largely preventable by a healthy life-style.”

CONCLUSION

At least 80% to 90% of patients with CHD have conventional risk factors. This is probably an underestimate. Clinical medicine, public health policies, and research efforts should place significant emphasis on the 4 factors and lifestyle behaviors. Non-traditional risk factors and genetic causes deserve less emphasis.

JAMA August 20, 2003; 290: 898-904 Original investigation, first author Umesh N Khot, Cleveland Clinic Foundation, Cleveland Ohio. www.jama.com

Comment:

CHD is a preventable disease.

The exact cutpoints for the risk factors was not stated. It is evident that levels of systolic BP, LDL-cholesterol, and mean blood glucose below the currently defined upper normal limits of these risk factors carry an increased risk. See the following abstract. RTJ

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"Their optimal use in routine screening and risk stratification remains to be determined." Depend on the conventional established risk factors.

8-8 EMERGING RISK FACTORS FOR ATHEROSCLEROTIC VASCULAR DISEASE.

The search for additional etiologic agents for atherosclerotic vascular disease (**AVD**) continues. In recent years new candidates have been proposed. (*The article lists 35 in box p 933*)

This critical review highlights 4 emerging risk predictors:

C-reactive protein

Lipoprotein (a)

Fibrinogen

Homocysteine.

It reviews the epidemiological, basic science, and clinical trial evidence concerning these additional factors.

The available evidence supports, to a varying degree, independent associations between these factors and AVD. But, there is relatively little data regarding the additive yield of screening for these factors over that of validated global risk assessment strategies currently in use. There are few controlled intervention studies of therapies aimed at reducing these risk factors.

"Their optimal use in routine screening and risk stratification remains to be determined."

"The explanatory power of the *major established* cardiovascular risk factors has been systematically underestimated."

JAMA August 20, 2003; 290: 932-40 Original investigation, first author Daniel G Hackam, McMaster University, Hamilton, Ontario, Canada. www.jama.com

Comment:

Primary care clinicians and their patients have not even begun to assess, prevent, and treat the established major, modifiable risk factors. Until we do, I believe we need no more risk factors.

We will, with interest, however, follow the basic science investigations aimed at determining the best mix of risk factors on which to base clinical interventions. RTJ

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An Unfavorable Cardiovascular Risk Profile Was Associated With A Marked Increase In CIMT In Young Adulthood.

8-9 CARDIOVASCULAR RISK FACTORS AND INCREASED CAROTID INTIMA-MEDIA THICKNESS IN HEALTHY YOUNG ADULTS

Atherosclerosis is a slowly progressive process possibly starting at a young age. Preventive measures taken early in life might postpone the development of atherosclerosis and decrease risk of clinical cardiovascular disease **(CVD).**

High definition ultrasonography provides a non-invasive method to quantify arterial wall thickness and progression of atherosclerosis. In middle age, an increased carotid intima-media thickness **(CIMT)** is a strong predictor of CVD morbidity and mortality. Increased CIMT is strongly associated with atherosclerosis in other parts of the arterial system.

Autopsy evidence suggests a relationship between cardiovascular risk factors and arterial wall changes (from fatty streaks through transitional lesions to atheromatous lesions) in relatively young persons.

This study evaluated the relationship between conventional risk factors and increased CIMT in subjects age 27 to 30.

Conclusion: An unfavorable cardiovascular risk profile was associated with a marked increase in CIMT in young adulthood.

STUDY

1. Healthy young adults (age 27-30; n = 750; about equally male and female) completed a questionnaire on risk factors. All underwent blood tests and assessment of CIMT by ultrasound.
2. Correlated CIMT with risk factors.

RESULTS

1. Body mass index, age, pulse pressure, male sex, and LDL-cholesterol were independently associated with increased CIMT.
2. Total pack-years of smoking showed a linear trend with increased CIMT.
3. CIMT increased gradually and significantly with the number of risk factors present.
4. The estimated absolute risk for development of coronary heart disease **(CHD**) within 20 years (based on the Framingham data) was over two times higher in individuals with a CIMT in the highest quartile as compared with those in the lowest quartile.

DISCUSSION

1. Age, BMI, pulse pressure, LDL-cholesterol, and male sex were independent determinants of CIMT in these young adults.
2. Risk of CHD within 20 years rose gradually with increasing CIMT in these young adults. (As shown previously in older adults.) Men with 3 or more risk factors had 6% thicker CIMT than those with no risk factors. Women had a 4% greater thickness.
3. Modification of risk factors early in life may postpone development and progression of subclinical atherosclerosis, which in turn, would delay the onset of clinical manifestations of CVD later in life. Risk factors in children may be easier to change.

CONCLUSION

Unfavorable cardiovascular risk factors were related to greater CIMT in young adulthood. Effort to change modifiable risk factors early in life may retard development of atherosclerosis and the onset of clinical cardiovascular disease later in life.

Archives Int Med August 11/25 2003; 163: 1787-92 Original investigation by the Atherosclerosis Risk in Young Adults (ARYA) Study, first author Anath Oren, University Medical Center, Utrecht, Netherlands. www.arcchinternmed.com

Comment:

Lifestyle preventive measures are most effective when begun early in life. RTJ

Atherosclerosis Is Reversible.

8-10 REGRESSION OF CAROTID AND FEMORAL ARTERY INTIMA-MEDIA THICKNESS IN FAMILIAL HYPERCHOLESTEROLEMIA

Familial hypercholesterolemia **(FH)** affects approximately 1 in 400 individuals in the Netherlands. These individuals have elevated levels of LDL-cholesterol **(LDL-c)** due to mutations in the LDL-receptor gene. FH patients are at severe risk of premature cardiovascular disease **(CVD).** Modification of the risk requires aggressive lowering of LDL-c.

Intima-medial thickness **(IMT),** measured by ultrasonography, is a non-invasive surrogate marker for atherosclerotic disease. It is associated with increasing age, LDL-c, blood pressure, and smoking. Reducing risk factors may lead to regression of atherosclerosis as measured by IMT.

This study used high-dose simvastatin (*Zocor*) in patients with FH to reduce LDL-c levels. Would lowering LDL-c have any effect on IMT?

Conclusion: Simvastatin was associated with a reduction in IMT.

STUDY

1. Recruited 153 patients with FH (age range, 19 to 79; mean = 46). All patients received simvastatin 80 mg daily for 2 years.
2. Determined IMT of segments of the common carotid artery and femoral artery at baseline and at 2 years.
3. End point = change in the mean combined IMT of carotid and femoral arterial segments at 2 years.

RESULTS

1. Over the 2 years, total cholesterol declined by 36%; LDL-c by 44%, triglycerides by 25%. HDL-cholesterol rose by 7%.
2. The mean baseline arterial IMT was increased by at least twice that of normal controls. In the subset of patients with cardiovascular disease (24%), IMT was increased to a greater degree.
3. After 2 years, mean IMT declined by 0.08 mm. The largest decline was in the femoral artery (-0.3 mm)
4. An actual decrease in IMT occurred in 70% of all patients.
5. In the 30 patients receiving antihypertension drugs (calcium antagonists, ACE inhibitors, or beta-blockers), the

mean combined IMT was reduced to a greater extent compared with patients who were not receiving these drugs.

DISCUSSION

1. Even 1 year of treatment was sufficient to reduce mean IMT.
2. The decrease in IMT of the degree observed is likely to have a significant clinical impact of prevention of coronary artery disease.
3. Other studies reported that beta-blockers, added to statins in hypercholesterolemic patients, have a synergistic effect on decreasing IMT.
4. Safety and tolerability of the statin were excellent.

CONCLUSION

High dose simvastatin over 2 years reduced combined carotid/femoral IMT in more than two thirds of patients. The largest effect was on the femoral artery. This degree of reduction of IMT. . . "will likely have a significant clinical impact on the prevention of coronary artery disease".

Archives Int Med August 11/25; 163: 1837-41 Original investigation, first author Pernette R W de Sauvage Nolting, Academic Medical Center, Amsterdam , Netherlands. www.archinternmed.com

Comment:

Primary care clinicians might easily extrapolate these results to other patients with high cholesterol levels. Atherosclerosis is reversible. RTJ

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"Hypokalemia In An Otherwise Healthy Young Woman Is Highly Specific For BN."

8-11 BULIMIA NERVOSA

Binge eating generally begins during adolescence, with a peak of onset about age 18. Lifetime prevalence is 3%. It is essentially a disease of females.

It has 3 key features:

1) Intense preoccupation with body weight and shape.
2) Repetitive episodes of binge eating (uncontrollable eating a large quantity of food in a defined period—usually less than 2 hours.
3) Routinely taking extreme measures to prevent weight gain: self induced vomiting, fasting, exercise, and misuse of laxatives and diuretics. Some patients take up to 50 laxative pills per day. Severe constipation with a laxative-dependence syndrome may result.

Episodes can be spontaneous or planned. They can be triggered by stress.

Medical complications are caused by vomiting and laxative misuse. Dental caries on the lingual surface of the anterior teeth and pharyngeal soreness are due to repeated exposure to acidic gastric contents. Sialadenosis

(painless swelling to the salivary glands) develops after an intense cycle of purging. Dentists are in a good position to suspect and refer patients. Frequent vomiting may lead to gastroesophageal reflux. Dyspepsia is common.

Patients are usually in the normal weight range. (Contrast to anorexia nervosa.)

Routine screening for BN is not currently the standard of care, but may be prudent in college-age populations.

Suspect bulimia in young and middle aged women who present with weight and shape concerns (whether normal or overweight), or with common comorbid conditions such as depression, anxiety, or substance abuse. Look for physical effects of the illness: dental caries, menstrual irregularities, and unexplained hypokalemia and metabolic alkalosis. ("Hypokalemia in an otherwise healthy young woman is highly specific for BN.") Anorexia nervosa is not associated with risk of metabolic abnormalities, acid-base disturbance, or hypokalemia.

When asked directly about bulimic symptoms in a treatment setting, patients are usually relieved to have the opportunity to talk about them.

Treatment:

Effective treatment is available. However, few patients seek help. Delay in seeking treatment is caused by secrecy and shame

1) Antidepressants can reduce binge eating and purging, improve depression and attitudes toward food. Fluoxitine (*Generic; Prozac*) is the only selective serotonin reuptake inhibitor known to be effective treatment. There is insufficient evidence about its role in maintenance therapy.
2) Cognitive behavior therapy is equally effective. A therapist leads the patient to realize what her eating habits are and to change them. Therapists use many different techniques to help patients understand their problem and change their thinking and behavior.
3) Combined treatment is more effective than either alone.

BMJ August 16, 2003; 327: 380-83 Excerpts from "Best Treatments" by Regina Z Lilly, BMJ Unified, London; commentary by Phillipa Hay, University of Adelaide, Australia; Allison Tonks, BMJ Unified, London; and by a 32 year-old woman whose "Life Revolves Around Food And Exercise"
www.bmj.com/cgi/content/ full/327/7411/380

Comment:

See also: *NEJM August 28, 2003 349; 875-81* "Clinical Practice" review article by Philip S Mehler, University of Colorado Health Sciences Center, Denver. www.nejm.org

The challenge for primary care clinicians is to suspect and recognize BN in select young women who present with vague symptoms, anxiety and depression. The clinical clues cited may help. A metabolic package might very well reveal a metabolic alkalosis. RTJ

Short Term Transdermal Estrogen May Be A Good Choice For Disturbing Postmenopausal Symptoms In Women At Risk For VTE.

8-12 DIFFERENTIAL ASSOCIATION OF ORAL AND TRANSDERMAL OESTROGEN-REPLACEMENT THERAPY WITH VENOUS THROMBOSIS RISK.

Venous thromboembolism **(VTE)** is a complication of hormone replacement therapy **(HRT)** as well as breast cancer, coronary heart disease and stroke. Estrogen activates blood coagulation and might be thrombogenic.

Recent observations showed consistent associations between current users of ERT and increased risk of VTE. Most studies have been related to oral use. Transdermal ERT is widely used in Europe. It has little effect on blood coagulation.

This study examined the effects of the route of administration (oral vs transdermal) on risk of VTE.

Conclusion: Transdermal ERT was not associated with increased risk.

STUDY

1. Multicenter hospital-based case-control study recruited 155 consecutive cases of a first documented episode of idiopathic (unprovoked) VTE (92 with pulmonary embolism and 63 with deep venous thromboembolism):
   Cases—VTE present. Women with previous VTE were excluded.
   Controls--381 controls—no VTE, matched for center, age (62), and time of recruitment.

RESULTS

1. Comparison:	Cases	Controls
Current users of oral estrogen	21%	7%

2. Odds ratio for VTE among users of oral ERT compared with non-users was 3.5. Odds ratio for VTE among users of transdermal ERT compared with non-users was 0.9.
3. Likelihood of VTE in oral users was 4 times that of transdermal users.
4. Likelihood of VTE among users of oral VTE increased with duration of use.

DISCUSION

1. Risk of VTE was greater in patients receiving current oral ERT than in patient receiving transdermal ERT. Risk was highest in the first year of use of oral ERT.
2. Indeed, there was no association between *transdermal* ERT use and VTE.
3. Oral, but not transdermal estrogen leads to high hormone concentrations in the liver and promotes hepatic protein synthesis. This increases concentrations of some prothrombin fragments, generates thrombin, lowers antithrombin concentration, and increases resistance to activated protein C.
4. Transdermal estrogen has little or no effect on hemostasis. It causes none of these hemostatic changes.
5. The relation between *oral* ERT and VTE is biologically plausible.
6. For women at high risk of VTE who have disturbing menopausal symptoms, use of short-term transdermal estrogen might be an important clinical choice.

CONCLUSION

Oral, but not transdermal ERT was associated with risk of VTE in postmenopausal women.

Lancet August 9, 2003; 362: 428-32 Original investigation, first author Pierre-Yves Scarabin, INSERM Cardiovascular Epidemiology Unit U258 , Villejuif, France www.thelancet.com

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Tamoxifen Should Be Considered First Line Therapy.

8-13 ENDOCRINE TREATMENT OF PHYSIOLOGICAL GYNECOMASTIA

Gynecomastia is a common condition among normal healthy men of varying ages. Tenderness may be a symptom, but the usual reason for presentation is that young men don't like having breasts and older men are worried about cancer.

Diagnosis is primarily by clinical examination and, where necessary, ultrasound and needle biopsy. Traditional management includes simple analgesia, and surgery. The most common reason for requesting surgery is cosmetic. Surgery may leave scars and pigmentation.

The authors recognize two forms of gynecomastia: "lump" and "fatty'. Lump is a single firm retro-areolar lump, often tender. "Fatty" is a diffuse lesion in the whole breast area. Adolescents usually have lump; elderly men have fatty.

Most cases have no known cause. Testicular tumors are a very rare cause. Liver dysfunction and a wide variety of drugs may cause gynecomastia (eg, spirinolactone, estrogens, and cimetidine). In these patients, the gynecomastia is usually bilateral and diffusely fatty.

Primary breast cancer is rare, but an important differential diagnosis. It usually presents as a lump, not centrally placed, and often shows skin tether.

"Physiological" gynecomastia is due to an altered ratio between free estradiol (a stimulant) and testosterone (an inhibitor). Anti-estrogens such as tamoxifen (*Nolvadex*) have therefore been suggested as non-surgical treatment. Various published studies have used tamoxifen at a dose of 10 to 40 mg daily for several months. Resolution of the lump and pain has been reported in 80% of cases. Only minor and reversible side effects were reported.

At present, tamoxifen should be considered first line therapy.**1**

BMJ August 9, 2003; 327: 301-02 Editorial by Hamed N Klan, and R W Blamey, Nottingham City Hospital, UK www.bmj.com/cgi/content/full/7410/301

Comment:

1 I presume raloxifene (*Evista*) would work just as well.

I remember years ago referring a patient with gynecomastia for surgical removal. The surgeon called me back and recommended I take the patient off digoxin. It worked. The surgeon was much smarter than I was. RTJ

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NSAIDs and Aspirin Were Associated With An Increased Risk Of Miscarriage

8-14 EXPOSURE TO NON-STEROIDAL ANTI-INFLAMMATORY DRUGS DURING PREGNANCY AND RISK OF MISCARRIAGE

NSAIDs are often used by pregnant women. Adverse effects on the gastrointestinal tract and kidney are well known. This study asks. . ."Are there also adverse effects on pregnancy?"

Conclusion: NSAIDs and aspirin were associated with an increased risk of miscarriage. Acetaminophen was not.

STUDY

1. Prospective cohort study recruited over 1000 pregnant women immediately after their positive pregnancy test. Mean gestational age at entry was 40 days.
2. Determined NSAID, aspirin, and acetaminophen use.
3. Main outcome measure = pregnancy outcomes up to 20 weeks of gestation.

RESULTS

1. 53 women (5% of cohort) reported prenatal NSAID and aspirin use around time of conception or during pregnancy.
2. Use around the time of conception and during pregnancy was associated with an adjusted 80% increased risk of miscarriage.
3. Outcomes: miscarriage occurred in 162 women:

Non-users (n= 980)	149 (15% had a miscarriage)
Users (n=53)	13 (25% had a miscarriage)

(Absolute difference = 10%; NNT (harm one patient) = 10)

4. Of 162 patients with miscarriage, 8% used NSAIDs; of 871 without miscarriage, 5% used NSAIDs.
5. Associations with aspirin were similar.
6. The association was stronger if the initial NSAID or aspirin use was around the time of conception, or if use lasted more than a week.
7. Acetaminophen was not associated with increased risk.

DISCUSSION

1. NSAIDs and aspirin inhibit prostaglandin biosynthesis in most organ systems. Acetaminophen inhibits prostaglandin synthesis only in the central nervous system.
2. Prostaglandins may be needed for successful implantation of the embryo. Abnormal implantation may predispose to miscarriage.
3. The newer cyclo-oxygenase 2 inhibitors have been reported to increase peri-implantation and post-implantation losses and reduce fetal survival in animals.

4. Suppression of prostaglandin production by NSAIDs may have an adverse effect on placental perfusion and circulation, thus increasing likelihood of fetal loss.
5. These findings require confirmation.

CONCLUSION

Although these findings require confirmation, women should be aware of this potential risk of miscarriage and avoid use of NSAIDs and aspirin around the time of conception.

BJM August 16, 2003; 327: 368-71 Original investigation, first author De-Kun Li, Kaiser Foundation Research Institute, Oakland CA. www.bmj.com

Comment:

This study is provocative, not conclusive. We depend at times on suggestive, but unproved interventions. "Purists" may say wait for more conclusive proof of harm and continue prescribing NSAIDs.

I believe that most primary care clinicians would act on this inconclusive data and advise pregnant women not to take NSAIDs. RTJ

Injections Repeatedly Given Into These Sites May Lead To Problems Of Glycemic Control

8-15 POOR GLYCEMIC CONTROL CAUSED BY INSULIN INDUCED LIPOHYPERTROPHY.

Insulin lipohypertrophy is characterized by a benign "tumor-like" swelling of fatty tissue secondary to subcutaneous insulin injections.

This brief paper describes two patients with diabetes—one with type 1; one with type 2. Both were using insulin. Both reported increasingly poor control. They were injecting the insulin into areas of insulin induced lipohypertrophy. Control of the diabetes improved dramatically when these sites were avoided and they began to rotate injection sites.

Diabetic lipodystrophies, particularly lipoatrophy, were common local complications of insulin when bovine and porcine insulins were used. With the introduction of human recombinant insulins, lipoatrophy has become uncommon, but lipohypertrophy remains a major problem. The more rapid acting insulin lispro may cause less lipohypertrophy because its absorption is faster and there is less time to expose adipocytes.

Prevalence of lipohypertrophy in patients with type 1 diabetes is estimated to be around 20% to 30%. It is due to a cellular response of adipocytes to the local effects of injected insulin. Immunological factors may be important. Frequent injection into the same site is related to incidence.

Injections repeatedly given into these sites may lead to problems of glycemic control. Insulin absorption can be significantly delayed leading to erratic glycemic control.

The sites can be unsightly. The only available treatment is liposuction. Avoiding injection into the sites may reduce their size over time.

Sites of injection should be examined yearly, and palpated rather than just visually examined. Sites are often asymmetrical because injections are often given by the dominant hand.

Rotation of sites of injection is mandatory. Indeed, patients with lipohypertrophy should be advised to reduce their insulin dose once they begin to rotate, as they may develop hypoglycemia resulting from improved absorption from a new site.

BMJ August 16, 2003; 327: 383-84 "Lesson of the Week" first author Tahseen A Chowdhury, Royal London Hospital, UK www.bmj.com.cgi/content/full/327/7411/383

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