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TRANS FATTY ACIDS—A MAJOR RISK FACTOR FOR CARDIOVASCULAR DISEASE

HIGH LEVELS OF INDUSTRIALLY PRODUCED TRANS FAT IN POPULAR FAST FOODS

THE INFLUENCE OF ESTROGEN ON MIGRAINE

ASSESSING GLYCEMIA USING SELF-MONITORING BLOOD GLUCOSE AND HbA_{1C}

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BREAST CANCER IN THE FAMILY—CHILDREN'S PERCEPTIONS

SHOULD ACE INHIBITORS BE PRESCRIBED FOR ALL PATIENTS WITH CHD?

ADIPOSITY OF THE HEART REVISITED

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This document is divided into two parts

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

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

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

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

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

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

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HIGHLIGHTS AND *EDITORIAL COMMENTS* APRIL 2006

4-1 TRANS FATTY ACIDS AND CARDIOVASCULAR DISEASE: Review Article

Trans fats are formed during "partial hydrogenation" of vegetable oils (an industrial process). This converts the oil into semisolid form for use in margarines, commercial cooking, and manufacturing processes. The food industry favors trans fats because their shelf life is long, they are stable during deep-frying, and may enhance palatability of baked goods and sweets.

The average consumption of trans fats in the USA is 2% to 3% of total calories consumed.

The Department of Agriculture made limiting intake of trans fats a key recommendation in the new food pyramid. Consumption should be limited to below 1% of total energy intake.

The FDA has ruled that the nutrition labels of conventional foods and supplements must indicate the content of trans fats. (*Consumers should remember to check the "Nutrition Facts' on labels. RTJ*)

These actions were prompted by evidence that trans fats increase the risk of coronary heart disease by several different mechanisms:

A. Adverse effect on serum lipids.

B. Promotion of systemic inflammation.

C. Trans fats may also cause endothelial dysfunction.

"On a per-calorie basis, trans fats appear to increase the risk of CHD more than any other macronutrient." Even at low levels of consumption (1 to 3 percent of calories), a substantially increased risk occurs.

Trans fats have no intrinsic health value above their caloric value. Thus, their intake may result in considerable potential harm with no apparent benefit.

The potential harm is clear. Adverse effects are seen even at low intakes—1% to 3% of total energy (~ 20 to 60 calories; 2 to 7 grams for a person consuming 2000 calories daily).

"Thus, complete or near complete avoidance of industrially produced trans fats—consumption of less than 0.5 percent of total energy intake—may be necessary to avoid adverse effects."

Avoidance will depend on consumers' decisions to choose foods free of trans fats. This depends on knowledge of the type and quantity of oils used. *(Again, read the label. In restaurants, choose foods less likely to contain trans fats. RTJ)*

About 20% of CHD events could be prevented by total avoidance of trans fats and replacement with cis unsaturated fats.

Elimination of trans fat (as much as possible) should be considered a major goal for reducing risk of CHD. Obviously, daily consumption of 2 grams (over 1% of total calorie intake) is very easy.

Fifty Percent of The Servings Contained More Than 5 Grams Per Serving—The Amount Associated With A 25% Increase in Risk Of Ischemic Heart Disease

4-2 HIGH LEVELS OF INDUSTRIALLY PRODUCED TRANS FAT IN POPULAR FAST FOODS

"The daily intake of about 5 grams of trans fats is associated with a 25 percent increase in the risk of ischemic heart disease."

This study determined the content of industrially produced trans fat in fast foods purchased in 2004 and 2005 in 20 countries. The table (p 1651) illustrates the amounts of trans fat in McDonald's and KFC outlets in a large serving of french fries and chicken.

The content of trans fat in a large serving of french fries varied from less than 1 gram in Denmark to 7 grams in New York City and 12 grams in Hungary. Fifty percent of the servings contained more than 5 grams—the amount of daily intake associated with a 25% increase in risk of ischemic heart disease.

Large variations were observed within the same chain in the same country.

As the general public becomes more aware to the risks, I believe that fast food companies and food manufacturers can (and may have to) lower the trans fat content of their foods. The fact that the trans fat content varies markedly in different countries and even within a given country suggests that consumers will accept foods prepared with oils containing lower amounts of trans fats.

McDonalds is trying. I recently picked up several brochures describing their efforts to promote balanced eating. Their "McDonald's Nutrition Facts" lists foods prepared with "partially hydrogenated" cooking oils.

Tables list trans fat content	*Grams*
Plain hamburger	*0.5*
Big Mac	*1.5*
Small french fries	*2.5*
Large french fries	*6.0*
Biscuit	*5.0*
Deluxe breakfast	*11*
Warm cinnamon roll	*4.5*
Baked apple pie	*4.5*
Chocolate chip cookie	*1.5*

I enjoy McDonalds and KFC. I believe they will attempt to lower trans fat content. I will watch developments carefully, while I avoid ingestion of trans fats as much as possible.

"The 'Femaleness" Of The Migraine Condition Is Inescapable." Triptans Appear To Be Useful In Prevention

4-3 THE INFLUENCE OF ESTROGEN ON MIGRAINE: A Systematic Review

Migraine attacks at or about the time of menses affects about 50% to 60% of female migraineurs.

The International Headache Society defines *menstrual migraine* as 1) migraine attacks, *without aura*, occurring *exclusively* at the time of menses (day -2; day -1; day 1; day +2 and day +3).

In some women, attacks occur, not only at the time of menses, but, in addition, at other times in the cycle. This is termed "*menstrually-related migraine*" Some attacks may be preceded by aura.

A sudden drop in plasma concentrations of estrogens may precipitate attacks. Estradiol levels are high just before menses, and then suddenly drop. In pregnancy, estrogen levels increase throughout each trimester, and sharply decline postpartum. In one study, 80% of women with migraine without aura reported no attacks in the third trimester. Nearly all reported return of migraine after delivery.

Compared with other migraines, menstrual migraine is usually more resistant to treatment, of longer duration, and associated with more functional disability.

Treatment:

1) Estrogen: "If estrogen withdrawal precipitates a migraine attack, estrogen supplementation should prevent migraine attacks." Some small studies have reported benefit. Results of studies, however, are conflicting. The level of evidence is poor.

2) Triptans: While the level of evidence from clinical trials is poor for estrogen, clinical trials using 5-HT receptor agonists for menstrual migraine have been more robust. With the understanding that menstrual migraine attacks are often predictable, short-term *preventive* administration may be helpful. One trial used sumatriptan (*Imitrex* 25 mg 3 times daily) beginning 2 to 3 days before expected migraine onset and continued for 5 days resulted in complete relief in about 50% of treated cycles and reduction in severity in others.

3) Alternative treatments: The article presents a treatment algorithm which contains approaches other than triptans for migraine in women:

A. For acute attacks: simple analgesics (acetaminophen and NSAIDS); rescue therapy with corticosteroids or opiates,

B. Daily preventive therapy: Anticonvulsants; beta-blockers; tricyclic antidepressants; calcium channel blockers.

Epidemiological, pathophysiological, and clinical evidence link estrogen to migraine. The evidence for estrogen as a preventive therapy for menstrual migraine is inconsistent. Triptans appear to be useful in prevention of the headache as well as therapy for acute attacks.

For women who experience a consistent relationship between headaches and menses, prophylactic therapy with triptans may be especially helpful and welcome.

Clinical Review: "Approaches Are Available That Promote Successful Management" And a Peek into the Future

4-4 ASSESSING GLYCEMIA IN DIABETES USING SELF-MONITORING BLOOD GLUCOSE AND HEMOGLOBIN A_{1C}

Self-monitoring blood glucose **(SMBG)** reveals the immediate hour-to-hour glucose, which normally varies only about 50% throughout the day, but may vary 10-fold in patients with diabetes. It shifts the focus of diabetes management from the doctor's office into the hands of the patient. It allows patients to take control of their own diabetes.

This systematic literature search assessed the evidence underlying the use of SMBG, and HbA1c. It considers: SMBG:

Does SMBG positively affect patient care?

How often to test?

Goals of testing

Optimal timing

Future clinical applications

HbA1c:

How effective is reduction ?

Standardization

Use for screening for diabetes

New certified rapid assay

Future clinical applications.

Read the abstract.

I believe SMBG and HbA1c levels are useful and rewarding applications. It depends on how they are used. Proper use depends on close patient-health professional cooperation. There is a learning curve. I believe individualization is the key.

Is The Folate-Homocysteine Relationship Invalid?

4-5 HOMOCYSTEINE TRIALS:

This issue of NEJM presents two randomized trials on the effect of supplements (combined folic acid, B6, and B12) on outcomes in patients with existing atherosclerotic disease. (*Secondary prevention*) Both report no benefit, and even suggest some harm. Both were conducted in elderly patients.

An editorial in the same issue comments:

> Epidemiological studies over the past 25 years have provided ample support for the association of mild hyper-homocysteinemia with elevated risk for atherothrombosis. (*Practical pointers has abstracted several.*)
>
> But, the results of the trials cited above leads. . . "to the unequivocal conclusion that there is no clinical benefit from the use of folic acid and vitamin B12 (with or without the addition of vitamin B6) in patients with *established* vascular disease."

Is epidemiology again misleading us as it did for the putative benefit of estrogen in prevention of cardiovascular disease?

I do not think so. I am not ready to give up on the folate-homocysteine connection. I believe that limiting trials to elderly patients with established atherosclerotic disease, in an effort to reverse it, is asking too much. It may be misleading. The benefit may lie in primary prevention—ie, beginning folate supplementation at an early age to retard development of lipid accumulation and plaque formation in arteries. .

I still believe the benefit/harm-cost ratio of folate, B12, and B6 may be high. Although the benefit may be questionable (I believe this is unsettled), the harm-cost is nil, and considerably increases the ratio.

"Topical Permethrin is A Reasonable First Line Therapy"

4-6 SCABIES; Review Article

The mite is an obligate parasite that completes its entire life cycle on humans. Mites cannot fly or jump. The more parasites on a person, the greater the likelihood of transmission, either direct (skin-to-skin—the predominant method) or indirect (through infested bedding, clothing or other fomites).

The diagnosis rests largely on the history and examination of the patient as well as the family and close contacts. Generalized and intense itching (worse at night) usually spares the face and head. Lesions are located mostly in the finger webs, on flexor surfaces of wrists and elbows, axillae, buttocks, genitalia, and breasts of women.

One study reported that the presence of diffuse itching and visible lesions, associated with either 1) two or more typical locations of scabies, or 2) a household member with itching has a 100% sensitivity and a 97% specificity for the diagnosis.

The infected person and close contacts should be treated at the same time, regardless of whether symptoms are present.

Permethrin (5% cream) is given as a single overnight application. A meta-analysis reported it was more effective than lindane. The CDC recommends it as first line treatment.

Topical treatments may be poorly tolerated by some patients. They are messy, may be difficult to apply, and may cause burning and stinging. Ivermectin (*Stromectal*: 3 mg tablets) has been used for several parasitic infections. Several controlled trials have assessed efficacy of a single dose (200 ug per kg). One trial compared ivermectin with permethrin. Ivermectin cured 70%; permethrin cured 98%. A second dose of ivermectin two weeks later cured 95%. When oral therapy is prescribed, the CDC recommends a dose of 200 ug/kg repeated two weeks later. Trials suggest that ivermectin is safe.

Scabies is prevalent among the homeless and among persons visiting free clinics, which are supported by many communities.

"All Screening Programs Do Harm; Some Do Good As Well"

4-7 SHOULD WE SCREEN FOR DEPRESSION? A Review of Screening Programs

This article presents 9 key criteria of UK National Screening Committee for screening.

(Read the abstract and the article. RTJ)

For screening for depression, the article concludes: "Opportunistic screening and population level screening for depression do *not* fulfill the criteria of the UK Screening Committee."

The use of these criteria indicates that screening for depression is unlikely to be a clinically effective or cost effective way to improve the mental wellbeing of the population. Screening alone cannot improve the management and outcome of depression unless systems to manage the depression are available.

I believe this presents an important consideration for primary care. The criteria considerably restrict screening.

Strictly defined, screening applies only to persons who have no signs or symptoms of the condition in question. This implies that the condition screened for, in the population selected, reflects only the prevalence of that condition in that population.

The borderline between screening and testing is ill defined.

I believe that most screening in primary care practice is applied to persons who have at least some pre-test probability of having the condition screened for. The "screen" then becomes a "test". A positive result would indicate a higher post-test probability of having the condition.

I believe screening in the USA is overdone. Primary care clinicians should be circumspect. They should make the patient aware of risks (including creation of considerable ongoing anxiety) as well as benefits of a screen. The patient should be willing to proceed to further investigation and treatment if the screen is positive. Adequate referral and treatment should be available.

I note that some entrepreneurs still come to town offering "Life Line Screening". All residents are invited to participate. The screens (for a fee) include "stroke/carotid artery screening, abdominal aortic aneurysm screening, and peripheral artery disease screening". This type of screening meets few of the UK National Screening Committee key criteria. I believe they do more harm than good.

Reduced Deaths and Reinfarction without Increase in Bleeding A New Era in Anticoagulation?

4-8 EFFECTS OF FONDAPARINUX ON MORTALITY AND REINFARCTION IN PATIENTS WITH ACUTE ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION: The Oasis-6 Randomized Trial

Despite many therapeutic advances, mortality in patients with acute ST-elevation myocardial infarction (**STEMI)** remains high. Antiplatelet therapy, thrombolysis, and angiotensin-converting enzyme inhibition improve prognosis. Primary percutaneous coronary intervention (**PCI**) offers benefits over thrombolytic therapy, but access to this procedure is limited.

Trials of unfractionated heparin, direct thrombin inhibitors, and enoxaparin (a low-molecular-weight heparin) have thus far failed to demonstrate mortality reductions. Reviparin (also a low-molecular–weight heparin) has been shown to reduce mortality and reinfarction, but bleeding is increased when it and other agents are used with aspirin and thrombolytic therapy.

This large randomized trial evaluated the effect of fondaparinux (*Arixtra*; a synthetic pentasaccharide which rapidly inhibits factor Xa) when initiated early and given up to 8 days.

One group of patients received a fixed dose of fondaparinux (2.5 mg subcutaneously daily for 8 days) or placebo; another group received fondaparinux or 2 days of unfractionated heparin + placebo.

Overall, at 30 days and at 3 to 6 months, death and reinfarction occurred less frequently in the fondaparinux group. (NNT = 66 and 70).

Benefits were evident in those receiving no reperfusion therapy and in those receiving thrombolysis. No benefit in those undergoing PCI.

Severe bleeding was less likely in the fondaparinux group. (Overall, 1.0% vs 1.3%)

"Unlike other antithrombotic agents, such as low-molecular-weight heparin, direct thrombin inhibitors,

or intravenous antiplatelet agents, fondaparinux reduced death and reinfarction without increasing bleeding or hemorrhagic stroke."

"Addition of fondaparinux to thrombolytic therapy probably represents an attractive, effective, and safe option as an initial adjunctive antithrombotic agent in STEMI in patients not undergoing primary PCI."

I wondered if the name of the drug (ending in X) was related to its effect of factor X. Note also the X in Arixtra.

The standard dose and the reduced risk of bleeding are notable benefits.

See also "Comparison of Fondaparinux and Enoxaparin in Acute Coronary Syndromes" (OASIS-5 NEJM April 6, 2006; 354: 1464-75) This study compared fondaparinux (2.5 mg daily) with enoxaparin (Lovenox), a low-molecular weight heparin, in over 20 000 patients with unstable angina or myocardial infarction without ST elevation. Major bleeding occurred less frequently in the fondaparinux group. At 30 days, and long-term, mortality and morbidity favored fondaparinux.

Fondaparinux has been reported to be more effective than enoxaparin in preventing venous thromboembolism. (See Practical Pointers February 2006.)

An editorial, first author Raymond J Gibbon (NEJM April 6, 2006; 354; 1524-27) suggests that 2 specific activities of fondaparinux may be responsible for the reduced risk of bleeding: 1) inhibition of factor Xa within the clot, and 2) lack of inhibition of platelet function.

No Increase In Risk of BC. An Increase in Need for Repeat Mammography

4-9 EFFECTS OF CONJUGATED EQUINE ESTROGENS ON BREAST CANCER AND MAMMOGRAPHY SCREENING IN POSTMENOPAUSAL WOMEN WITH HYSTERECTOMY

Epidemiologic studies have suggested an increased risk of breast cancer **(BC)** in women receiving estrogen.

This trial compared incidence of BC in hysterectomized women who received estrogen-alone vs placebo

The Women's Health Initiative **(WHI)** enrolled over 10 500 postmenopausal women (age range 50-79; majority over age 60). All had a prior hysterectomy. Randomized to: 1) 0.625 mg combined equine estrogen (**CEE**; *Premarin*) or 2) placebo. Follow-up = 7 years.

After a mean of 7-years, the hazard ratio of invasive BC in women receiving estrogen-alone was 0.80 compared with those receiving placebo. [95% confidence interval = 0.62 to 1.04—not quite statistically significant.]

	CEE (n = 5310)	Placebo (n = 5429)	Absolute difference	NNT (7y)
Invasive BC	104 (2.0%)	133 (2.5%)	0.5%	200
Ductal carcinoma	61 (1.1%)	88 (1.6%)	0.5%	200

The number of women recalled for repeat mammography was higher in the CEE group. At one year, 9% had mammograms with abnormalities which required follow-up vs 5.5% in the placebo group. Absolute difference = 4.5%. (NNT = 22) This pattern continued throughout 7 years (36% vs 28%) Absolute difference = 8%. (NNT = 15)

In this trial, incidence of invasive BC did not differ significantly (statistically) between women receiving

CEE vs placebo over 7 years. “This outcome was surprising considering prior evidence that CEE increased risk of BC.”

The major consideration–estrogen-alone does <u>not</u> increase risk of BC.

The evolution of hormone replacement therapy for menopausal symptoms is fascinating.

I believe that primary care clinicians can now inform symptomatic post-menopausal women:

A. Combined E + P does slightly increase risk of CHD, stroke, BC, and thromboembolism. Women at risk may wish to avoid E+P treatment (although there is no good alternative to estrogen). Alternatively, women at increased risk may wish to accept preventive therapy to reduce risk. And to take low doses for limited duration.

B. Estrogen-alone does not increase risk of BC. It may slightly increase risk of stroke and thromboembolism. Again, they may wish to accept preventive therapy to reduce risks, and take low doses of estrogen for limited periods.

You Really Can’t Keep It A Secret—Don’t Try.

4-10 BREAST CANCER IN THE FAMILY—CHILDREN’S PERCEPTIONS OF THEIR MOTHER’S CANCER AND ITS INITIAL TREATMENT

This study explored the accounts of mothers with breast cancer **(BC),** and their children (age 6 to 18) , to identify children’s awareness and understanding of their parent’s cancer; their reactions to the diagnosis; and what information they would have liked to have been given and seemed to need. And to contrast children’s accounts with the mother’s perceptions of their children’s knowledge.

All children (except two of the youngest) said they had heard of cancer before their mother’s illness

Some mothers thought their children did not know that cancer could be life-threatening, and were shocked when the children’s comments or questions revealed concerns that she might die.

Children often suspect there is something wrong before they are told—from changes in the mother’s mood and overheard conversations.

The reactions of younger and older children were remarkably similar. They described emotional upset, shock, tears, fear and anxiety. Some expressed anger at God, and at the mother herself. Some mothers found it hard to cope with an apparently selfish reaction.

Some children saw surgery and anesthesia as potentially fatal.

Some children considered chemotherapy, with its debilitating side effects and hair loss, was the worst aspect of treatment. Hair loss was a key issue for children across the age range.

Only children under 10 years said that they had been given enough information. Girls wondered whether they might be more likely to develop breast cancer.

Parents may underestimate their children’s need for information and try to protect them. “However, the more the children are prepared and informed, as appropriate for their age and development, the more it seems to help them cope.

“Although children cannot be protected from adverse events, the quality of the relationship and

communication between family members are important for preventing adverse longer term consequences."

When serious illness strikes, primary care clinicians have a responsibility to support the family as well as the patient.

4-11 ANGIOTENSIN-CONVERTING ENZYME INHIBITORS IN PATIENTS WITH CORONARY HEART DISEASE AND ABSENCE OF HEART FAILURE OR LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

"Angiotensin-converting enzyme inhibitors (**ACE**) . . . **"**are an undisputed treatment in patients who have congestive heart failure **(HF),** or in patients with coronary heart disease **(CHD)** and concomitant left ventricular dysfunction."

This meta-analysis assessed long-term effects of ACE in patients who have CAD and no signs of HF or severe left ventricular dysfunction. (Stable coronary artery disease.)

Treatment ACE inhibitors included ramipril, quinapril, enalapril, perindopril, and trandolapril.

Overall results:	Active treatment	Placebo	Absolute difference	NNT (4-y)
	n = 16 328 (%)	n = 16 034 (%)	(% in 4.4 years)	
All-cause death	1215 (7.4)	1392 (8.7)	1.3	77
CV death	673 (4.1)	819 (5.1)	1.0	100
MI	1048 (6.4)	1258 (7.8)	1.4	71
Stroke	342 (2.0)	445 (2.7)	0.7	142

Use of ACE inhibitors for long-term secondary prevention in patients with established CHD, who are without LV dysfunction or heart failure, was associated with a reduction in all-cause mortality and major cardiovascular events.

Note that elevated BMI, smoking, hypertension, and dyslipidemia were present in many patients at baseline. The study did not consider influence of these factors on outcomes. Apparently, many of these factors were not treated or were under treated. The study concentrated on taking a pill or not taking a pill.

I believe correcting these risk factors would improve prognosis much more than taking a pill once a day.

What about cost? My pharmacy quotes $2.23 for one 10-mg ramipril (Altace). This would cost the patient about $3260.00 over four years. You may ask. . . "Would you pay over $3000.00 for a one in 100 chance of avoiding death from a cardiovascular cause over 4 years? And at the same time incurring considerable adverse effects from the drug?

ABSTRACTS APRIL 2006

"No Apparent Nutritional Benefit and Considerable Potential for Harm"

4-1 TRANS FATTY ACIDS AND CARDIOVASCULAR DISEASE: Review Article

Trans fatty acids (trans fats) are unsaturated fats. They contain at least one double bond. The double bond is in the trans configuration.

H

CH3-C-C-. . .C = C-C-. . .COOH The H atom is on opposite sides of the double bond. This straightens the

H chain and makes the oil semi-solid and more plastic.

In the cis configuration, the H atoms are on the same side.

H H

CH3-C-C-. . . C = C-C-. . . COOH ……. This bends the chain and maintains the oily characteristics.

Trans fats are formed during "partial hydrogenation" of vegetable oils (an industrial process). This converts the oil into semisolid form for use in margarines, commercial cooking, and manufacturing processes. (The process does not add a hydrogen atom, it merely changes its position.)

The food industry favors trans fats because their shelf life is long, they are stable during deep-frying, and may enhance palatability of baked goods and sweets. Major sources are deep-fried fast foods, bakery products, packaged snacks, margarines, and crackers. Naturally occurring trans fats do occur, but in smaller amounts (about 0.5% of total energy intake). These trans fats occur in meat and milk, produced by action of bacteria in the stomachs of ruminants. (Public health implications of consuming trans fats from ruminant products are relatively limited.)

The average consumption of trans fats in the USA is 2% to 3% of total calories consumed.

The Department of Agriculture made limiting intake of trans fats a key recommendation in the new food pyramid. Consumption should be limited to below 1% of total energy intake.

The FDA has ruled that the nutrition labels of conventional foods and supplements must indicate the content of trans fats. (*Consumers should remember to check the "Nutrition Facts' on labels. RTJ*) The FDA regulations allow producers of foods that contain less than 500 mg per serving to list the contents as 0. Consumers who read labels, and try to restrict intake, might unwittingly consume substantial quantities through multiple servings. (Eg, several pats of trans fat-containing margarine.)

These actions were prompted by evidence that trans fats increase the risk of coronary heart disease by several different mechanisms:

A. Adverse effect on serum lipids: As compared with the consumption of an equal number of calories from saturated fat, or cis un-saturated fats, consumption of trans fats raises levels of LDL-cholesterol, increases levels of triglycerides, reduces levels of HDL-cholesterol, and increases the total cholesterol / HDL-cholesterol ratio.

B. Promotion of systemic inflammation (increased activity of tumor necrosis factor, interleukins and

C-reactive protein). These factors are independent risk factors for atherosclerosis, sudden death from cardiac causes, diabetes, and heart failure. On the basis of the positive association between C-reactive protein levels and the risk of cardiovascular disease, the difference in C-reactive levels seen with intake of 2.1% of total calories (the median intake) as compared with 0.9% would correspond to an increase in risk of approximately 30 percent.

C. Trans fats may also cause endothelial dysfunction.

"On a per-calorie basis, trans fats appear to increase the risk of CHD more than any other macronutrient." A substantially increased risk occurs at low levels of consumption (1 to 3 percent of calories).

Trans fats have no intrinsic health value above their caloric value. Thus, their intake may result in considerable potential harm with no apparent benefit.

Reducing intake of trans fats:

The potential harm is clear. Adverse effects are seen even at low intakes—1% to 3% of total energy (~ 20 to 60 calories; 2 to 7 grams for a person consuming 2000 calories daily).

"Thus, complete or near complete avoidance of industrially produced trans fats—consumption of less than 0.5 percent of total energy intake—may be necessary to avoid adverse effects."

Intake can be reduced by choosing foods free of trans fats—a daunting task at present.

Physicians and other health care providers can support institutional changes to reduce use in food services.

In restaurants, bakeries, and other retail outlets, food labels are not obligatory and are rarely seen. If trans fats are increasingly eliminated from packaged foods, most trans fats will be consumed from these sites.

Avoidance will depend on consumers' decisions to choose foods free of trans fats. This depends on knowledge of the type and quantity of oils used. *(Again, read the label. In restaurants, choose foods less likely to contain trans fats. RTJ)*

About 20% of CHD events could be prevented by total avoidance of trans fats and replacement with cis unsaturated fats.

NEJM April 13, 2006; 354: 1601-13 "Medical Progress", Review article, first author Dariush Mozaffarian, Harvard Medicinal School, Boston, Mass

Examples of trans fatty acid content of national brand foods prepared with partially hydrogenated vegetable oils in 2002:

	Grams/typical serving	% of daily energy for 2000 kcal diet
French fries	4.7-6.1	2.1-2.7
Breaded fish burger	5.6	2.5
Breaded chicken nugget	5.0	2.3
Tortilla (corn) chips	1.6	0.7
Popcorn (microwave)	1.2	0.5
Pie	3.9	1.8
Danish or sweet roll	3.3	1.5

Doughnuts	2.7	1.2	
Vegetable shortening	2.7	1.2	(per tablespoon)
Hard margarine	0.9-2.5	0.4-1.1	
Soft margarine	0.3-1.4	0.1-0.6	
Pancakes	3.1	1.4	
Crackers	2.1	1.4	

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"Fifty Percent Of The Servings Contained More Than 5 Grams Per Serving"

4-2 HIGH LEVELS OF INDUSTRIALLY PRODUCED TRANS FAT IN POPULAR FAST FOODS

"The daily intake of about 5 grams of trans fats is associated with a 25 percent increase in the risk of ischemic heart disease."

This study determined the content of industrially produced trans fat in fast foods purchased in 2004 and 2005 in 20 countries. The table (p 1651) illustrates the amounts of trans fat in McDonald's and KFC outlets in a large serving of french fries and chicken.

The content of trans fat in a large serving of french fries varied from less than 1 gram in Denmark to 7 grams in New York City and 12 grams in Hungary. Fifty percent of the servings contained more than 5 grams—the amount of daily intake associated with a 25% increase in risk of ischemic heart disease.

The cooking oil for french fries in McDonalds in New York City contained 23% trans fat. Oils used in many European countries contained about 10%, some as low as 5% (1% in Denmark).

Large variations were observed within the same chain in the same country.

It is possible to consume 10 to 25 grams of trans fatty acids in one day. It is likely that habitual customers will have an average daily intake above 5 grams. This is a matter of concern, particularly for low income people who already have an increased risk of ischemic heart disease owing to other lifestyle factors.

In 2004, Demark introduced legislation greatly restricting the use of industrially produced trans fatty acids. Their experience demonstrates that this health risk can be eliminated without any notable effect on the consumer.

NEJM April 13, 2006; 354: 1650-52 Editorial, first author Steen Stender, Gentofte University Hospital, Hellerup, Denmark

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"The 'Femaleness" Of The Migraine Condition Is Inescapable." Triptans Appear To Be Useful In Prevention

4-3 THE INFLUENCE OF ESTROGEN ON MIGRAINE: A Systematic Review

Migraine represents a substantial health care burden

Migraine attacks at or about the time of menses affects about 50% to 60% of female migraineurs.

The International Headache Society defines *menstrual migraine* as 1) migraine attacks, *without aura*, occurring *exclusively* at the time of menses (day -2; day -1; day 1; day +2 and day +3).

In some women, attacks occur not only at the time of menses, but, in addition, at other times in the cycle. This is termed "*menstrually-related migraine*" Some attacks may be preceded by aura.

Among female migraineurs, the true prevalence of pure menstrual migraine is less than 12%; menstrually-related migraine occurs in about 50%.

Compared with other migraines, menstrual migraine is usually more resistant to treatment, of longer duration, and associated with more functional disability.

What is the relation of migraine to "femaleness" and to estrogen?

1) Pre-pubertal girls and boys have about equal prevalence of migraine (4%). As girls mature, the prevalence increases to about 18% for women and 6% for men. (Genetic predisposition for migraine appears equally in men and women.) The great majority of women with migraine report onset between ages 10 to 39.

2) A sudden drop in plasma concentrations may precipitate attacks. Estradiol levels are high just before menses, and then suddenly drop. In pregnancy, estrogen levels increase throughout each trimester, and sharply decline postpartum. In one study, 80% of women with migraine without aura reported no attacks in the third trimester. Nearly all reported return of migraine after delivery. Some studies report that incidence of migraine is low during breast feeding.

3) Among menopausal women with a previous history of migraine who received supplemental estrogen, withdrawal of the estrogen was associated with increasing attacks. Among women who had no history of migraine, no headaches occurred when estrogen was withdrawn.

4) As women age and estrogen levels decline, prevalence of migraine attacks also declines.

5) Women with a history of menstrual migraine have an increased sensitivity to estrogen. Low levels of estrogen supplementation may paradoxically induce and attack.

6) Continuing high levels of estrogen, or complete withdrawal of estrogen, protects against migraine attacks.

Treatment:

1) Estrogen: "If estrogen withdrawal precipitates a migraine attack, estrogen supplementation should prevent migraine attacks." Some small studies have reported benefit. Results of studies, however, are conflicting. The level of evidence is poor.

2) Triptans: While the level of evidence from clinical trials is poor for estrogen, clinical trials using 5-HT receptor agonists for menstrual migraine have been more robust. They play a significant role in moderating migraine by mediating vasoconstriction and inhibiting vasoactive peptide synthesis. They are effective in treatment of acute menstrual migraine attacks. They are a valuable treatment strategy particularly in patients who have infrequent migraine attacks, and when attacks are otherwise unpredictable. However, not all patients benefit from acute treatment. Alternative treatments are warranted, particularly in more severe, recurrent migraine.

With the understanding that menstrual migraine attacks are often predictable, short-term *preventive* administration may be helpful. One trial, which used sumatriptan (*Imitrex* 25 mg 3 times daily) beginning 2 to 3 days before expected migraine onset and continued for 5 days, reported complete relief in about 50% of treated cycles and reduction in severity in others.

Similar benefit has been reported with prophylactic use of naratriptan (*Amerge*) and frovatriptan (*Frova*) around the time of expected headaches.

3) Naproxen: Short term naproxen (550 mg twice daily) beginning a week before expected menses and continued through day 6, was effective preventive therapy in one trial.

4) Alternative treatments: The article presents a treatment algorithm which contains approaches in addition to triptans for migraine in women:

A. For acute attacks: simple analgesics (acetaminophen and NSAIDS); rescue therapy with corticosteroids or opiates,

B. Daily preventive therapy: Anticonvulsants; beta-blockers; tricyclic antidepressants; calcium channel blockers.

Comorbidities are commonly associated with migraine: depression, panic disorder, and phobias are increased 2- to 3-fold. The potential interaction between these comorbidities and estrogen remains to be established.

Conclusion: Epidemiological, pathophysiological, and clinical evidence link estrogen to migraine. The evidence for estrogen as a preventive therapy for menstrual migraine is inconsistent. Triptans appear to be useful in prevention of the headache as well as treatment for acute attacks.

JAMA April 19, 2006; 295: 1824-30 "Clinical review" by Jan Lewis Brandes, Vanderbilt University School of Medicine, Nashville, TN.

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Clinical Review: "Approaches Are Available That Promote Successful Management" And a Peek into the Future

4-4 ASSESSING GLYCEMIA IN DIABETES USING SELF-MONITORING BLOOD GLUCOSE AND HEMOGLOBIN A_{1C}

"Good glycemic control reduces the incidence and progression of micro-vascular disease in both type-1 **(DM-1)** and type-2 **(DM-2)** diabetes." "The impact of *hyper*-glycemia on cardiovascular (macro-vascular) disease is also becoming increasingly evident." Although the Diabetes Control and Complications trial found an increased incidence of *hypo*-glycemia accompanying intensive glycemic control, participants rated their overall quality of life as improved.

Self-monitoring blood glucose **(SMBG)** reveals the immediate hour-to-hour glucose, which normally varies only about 50% throughout the day, but may vary 10-fold in patients with diabetes.

This systematic literature search assessed the evidence underlying the use of SMBG, and HbA1c.

STUDY

1. MEDLINE search retrieved articles relevant to SMBG and HbA1c from 1976-2005, including randomized trials, comprehensive reviews, meta-analyses, and published guidelines.

RESULTS

1. SMBG shifts the focus of diabetes management from the doctor's office into the hands of the patient. It allows patients to take control of their own diabetes.

2. Operator-related errors are a more significant source of error than are instrument-related errors.
   Constant communications between patient and health-care professionals is essential.
   (Primary care clinicians should be knowledgeable about the particular machine used, and check on the patient's proper usage RTJ.)

3. Most meters today are calibrated to provide plasma glucose equivalent readings.

4. Cost is considerable.

5. Does SMBG positively affect patient care?
   A. Many studies have sought the answer. Sources of bias are difficult to overcome.
   B. There is no reason to think that testing without acting upon the results would be helpful. When patients monitor regularly, they should be taught how to react immediately on the results and communicate the results to their professional.
   C. Sixteen trials are outlined in the table on page 1690. Only nine indicated that SMBG significantly improved HbA1c. The larger, more recent trials support the conclusion that SMBG, if effectively translated into action, improves glycemia. One large cohort study of 24 000 patients reported that SMBG improved HbA1c up to 1%. The data are most conclusive for insulin-using patients in whom SMBG is part of a complete regimen to improve glycemia. Results indicate that SMBG does reduce long-term complications of DM-1. Evidence for DM-2 is less definitive.

6. How often to test? No definitive studies are available to answer. For DM-1, the ADA recommends three times daily. No specific recommendation for DM-2. Frequency may be gauged by the stability of the glucose.

8. Goals: The ADA recommends adults with DM-1 and DM-2 aim for a pre-prandial plasma glucose of 90 to 130. And peak post-prandial of less than 180. The author's practice is to individualize treatment goals.

9. Optimal timing is controversial. One detailed analysis reported that the "extended post-lunch" (5 PM) values better predicted HbA1c levels with better specificity and sensitivity than fasting glucose.
   In less well controlled DM-2, a 3-point daily testing system [eg, 8 AM (fasting) ; one postprandial (10 AM); and one postprandial (5 PM)]. In DM-1, a 4- to 8- point daily system was recommended. In diabetic pregnancy, when the object is to approach euglycemia for the benefit of the developing fetus, post-prandial testing has proven efficacy for both woman with pregestational DM-1, and gestational diabetes. The author's practice is to rely on fasting, pre-prandial, and bedtime SMBG unless there are special circumstances. If nocturnal hypoglycemia is present, it is appropriate to test in the middle of the night and to make appropriate treatment adjustments.

10. SMBG can be used most effectively by using data management features available on some meters which calculate means, variance, and trends by time of day over weeks of months. Meters can now easily download results into a personal computer. Data can be quickly printed. The time of day and date must be accurately entered. Illustrations on page 1692 picture examples of repeated glucose measurements: 1) higher in the

morning (dawn phenomenon); 2) higher at 12 noon and 6 PM; and 3) generally higher over several weeks. All led to regimen change which improved diabetes control.

HbA1c:

1. HbA1c Is formed by the addition of glucose to the beta-chain of hemoglobin. Glucose attaches to the terminal valine and forms a stable compound. Since the life to the erythrocytes is 120 days, HbA1c measures long-term (month-to month) glucose control. Recent changes in glycemic control are over-represented: 50% of HbA1c is determined by the glycemia during the one month preceding, and 25% in the past 30 to 60 days, and 25% in days 60-120.
2. Many conditions exist that alter HbA1c independent of the assay method. Any process that shortens erythrocyte lifespan decreases HbA1c; and any process that creates an older erythrocyte cohort will increase it.
3. The Diabetes Control and Complications Trial reported that a HbA1c of 6% corresponded to a mean plasma glucose of 135 mg/dL. Each 1% increase corresponded to an increase in mean plasma glucose of 35 mg/dL. A reduction in mean HbA1c by 1.8% in an intensively treated group (9.1% to 7.3%) resulted in a highly significant reduction in development of retinopathy, micro-albuminuria, and neuropathy. Even a relatively short period of intensive control has long-lasting beneficial effects. A follow-up study reported a lower risk of *macro*-vascular complications as glycemia improved.
4. Standardization was a problem in the past. Now, a national standardization program is in place and is used by 99% of laboratories in the USA.
5. Recently, a certified rapid HbA1c assay for home and office testing of HbA1c has become available. This enables immediate feedback and allows timely therapy changes.. However, no evidence exists to evaluate home HbA1c testing. Expert opinion suggests routine testing twice yearly, and quarterly testing in those not meeting goals.
6. Whether HbA1c could be accepted as a means of screening or diagnosing diabetes remains controversial. It is still not accepted. The *specificity* of detecting undiagnosed diabetes was 97% in one study (Only 3% without diabetes were diagnosed as having diabetes; false positives.)

THE FUTURE:

Continuous glucose monitoring (CGM) is in its infancy. It is likely to change diabetes management. With use of CGM, extreme fluctuations in blood glucose are readily apparent, and alarms can be set to alert patients. The monitor measures glucose concentration in subcutaneous interstitial fluid which reflects changes in blood glucose.

For HbA1c, the International Federation of Clinical Chemistry has developed a new, more specific reference method. It measures glycation of valine residues on hemoglobin. The reference range is about 1.3% to 1.5% lower than the National Glycohemoglobin Standardization Program values. The normal range would be about 2% to 4% rather than the present 4% to 6%. A conversion equation has been developed. It is likely that this new method will become the anchor for glycated hemoglobin assays worldwide. There is a danger of confusion by patients.

JAMA April 12, 2006; 295: 1688-97 "Clinical Review", first author Christopher D Saudek, Johns Hopkins University School of Medicine, Baltimore, MD

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Is The Folate-Homocysteine Relationship Invalid?

4-5 HOMOCYSTEINE TRIALS:

This issue of NEJM presents two randomized trials on the effect of supplements (combined folic acid, B6, and B12) on outcomes in patients with existing atherosclerotic disease. (Secondary prevention)

1) "Homocysteine Lowering with Folic Acid and B Vitamins in Vascular Disease"

Randomized over 5500 patients (mean age = 69) with established vascular disease or diabetes to daily supplements or placebo for 5 years. Although mean homocysteine levels fell in the supplement group, there was no benefit in reducing the composite of death from cardiovascular causes, myocardial infarction, and stroke. In the folic acid group, there was actually an *increase* in hospitalizations for unstable angina.

2) "Homocysteine Lowering and Cardiovascular Events after Acute Myocardial Infarction"

Randomized over 3500 patients (mean age = 63) who had experienced a myocardial infarction to supplements or placebo for a median of 40 months. Again, no benefit. Indeed, the investigators report a possible harmful effect (a trend to increased risk).

An editorial in the same issue comments:

McCully first proposed that homocysteine causes atherosclerosis in 1969. This was based on autopsies of young people with homocysteinuria. Later the hypothesis was modified to include the effect of mild hyper-homocysteinemia, caused by dietary deficiencies of vitamin cofactors required for the metabolism of homocysteine, as a risk factor for atherothrombosis.

In developed countries, these vitamins are partially removed from foods during processing, and typical diets are rich in the precursor amino acid methionine (derived from animal protein). These conditions result in elevated homocysteine levels.

Epidemiological studies over the past 25 years have provided ample support for the association of mild hyper-homocysteinemia with elevated risk for atherothrombosis. (*Practical pointers has abstracted several.*)

But, the results of the trials cited above leads. . . "to the unequivocal conclusion that there is no clinical benefit from the use of folic acid and vitamin B12 (with or without the addition of vitamin B6) in patients with *established* vascular disease."

The editorialist suggests that the metabolic network of homocysteine and methionine is complicated, and we may be oversimplifying it. . Further exploration of the pathways and their association with atherothrombotic mediators will be needed. We should consider alternative approaches to reduce homocysteine concentrations.

NEJM April 13, 2006; 354: 1629-32 Editorial by Joseph Loscalzo, Brigham and Women's Hospital, and Harvard Medical School, Boston, Mass

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"Topical Permethrin is A Reasonable First Line Therapy"

4-6 SCABIES; Review Article

(I abstracted a few highlights. RTJ)

The mite is an obligate parasite that completes its entire life cycle on humans. Only females burrow into the skin. About 5 to 15 females live on a host infected with classic scabies. "The number can reach hundreds, or even millions in cases of crusted scabies." (As in an immunocompromised host.)

Mites cannot fly or jump. The more parasites on a person, the greater the likelihood of transmission, either direct (skin-to-skin—the predominant method) or indirect (through infested bedding, clothing or other fomites). Scabies is seen in clinics for sexually transmitted infections.

The diagnosis rests largely on the history and examination of the patient as well as the family and close contacts. Generalized and intense itching usually spares the face and head. Lesions are located mostly in the finger webs, on flexor surfaces of wrists and elbows, axillae, buttocks, genitalia, and breasts of women.

Itching is worse at night. One study reported that the presence of diffuse itching and visible lesions, associated with either 1) two or more typical locations of scabies, or 2) a household member with itching has a 100% sensitivity and a 97% specificity for the diagnosis.

Treatment:

The infected person and close contacts should be treated at the same time, regardless of whether symptoms are present.

1) Topicals

A. Permethrin (5% cream) is given as a single overnight application. A meta-analysis reported it was more effective than lindane. (Although there was considerable heterogeneity between studies.) The CDC recommends it as first line treatment. Mass treatment has been effective in controlling scabies in communities in which it is endemic.

B. Lindane (1% lotion or cream) Potential neurotoxicity with repeated applications has limited use. (It is no longer available in the U.K.)

2) Oral

Ivermectin (*Stromectal* 3 mg tablets) has been used for several parasitic infections. Several controlled trials have assessed efficacy of a single dose (200 ug per kg). One trial compared ivermectin with permethrin. Ivermectin cured 70%; permethrin cured 98%. A second dose of ivermectin two weeks later cured 95%. Trials suggest that ivermectin is safe.

Topical treatments may be poorly tolerated by some patients. They are messy, may be difficult to apply, and may cause burning and stinging.

Spread of classical scabies without direct person-to-person contact is rare. However, the recovery of mites from furniture and bedding supports the use of environmental measures, even though data are lacking to confirm efficacy. Clothes and linens should be machine washed at 60^0 C. Insecticide powder is reserved for materials that cannot be laundered.

There is uncertainty; questions remain. Topical treatments may be poorly tolerated. Optimum dose of ivermectin remains uncertain. One dose of 200 ug/kg may not be sufficient. An alternative is a single dose of 400 ug/kg or a repeat 200 ug/kg dose at two weeks. (When oral therapy is prescribed, the CDC recommends a dose of 200 ug/kg repeated two weeks later.)

Topical permethrin is a reasonable first line therapy in the USA.

"The patient should be followed to confirm resolution of itching which may take up to four weeks."

NEJM April 20, 2006; 354: 1718-27 Review article by Olivier Chosidow, Universite of Pierre et Marie Curie, Paris, France.

Permethrin (*Generic*—5 % cream) for treatment of scabies comes in 60 g tubes. It is safe. It is rinsed off after 12 hours. A second administration one week after the first is often prescribed. The correct application is crucial. After a tepid shower, it should be applied from head to toe, including the scalp. (Scalp involvement may be a cause for relapse.) . Avoid mucocutaneous junctions.

Ivermectin comes in 3 mg (3000 ug) and 6 mg tablets. Confusion may occur. Choose the correct dose based on weight of the patient: 200 ug/kg = 100 ug/pound. One mg per 10 pounds; 3 mg per 30 pounds. This would equal 5—3 mg tablets for a 150 pound patient. It is, however, a reasonably safe drug. A second dose 14 days later is recommended. For patients with extensive involvement, multiple doses may be given in combination with topical therapy.

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"All Screening Programs Do Harm; Some Do Good As Well"

4-7 SHOULD WE SCREEN FOR DEPRESSION? A Review of Screening Programs

This article lists the UK National Screening Committee key criteria for screening:

- The condition should be an important health problem.
- The epidemiology and clinical course of the disease should be adequately understood.
- The screening test should be safe, simple, precise, and validated. A suitable cut-off value should be defined and agreed.
- An effective treatment should be identified through the screening program, with evidence that early treatment leads to better outcome.
- Clinical management of the condition, and patient's outcomes should be optimized for all heathcare providers before the screening program is offered.
- High quality randomized, controlled trials should provide evidence that the screening program effectively reduces morbidity.
- The screening program should be clinically, socially, and ethically acceptable.
- The benefit should outweigh the harm.
- The cost should be economically balanced in relation to the expenditure on medical care.

For screening for depression, the article concludes :

"Opportunistic screening and population level screening for depression do *not* fulfill the criteria of the UK Screening Committee."

The use of these criteria indicates that screening for depression is unlikely to be a clinically effective or cost effective way to improve the mental wellbeing of the population. Screening alone cannot improve the management and outcome of depression unless systems to manage the depression are available.

Screening alone cannot improve the management and outcome of depression. Screening for depression is an unhelpful diversion from more fundamental questions about the most efficient and effective way of organizing and delivering care.

The ratio of costs to benefits is too high.

This does not mean that screening has no part to play. Several studies have shown that integrated management programs for depression (some of which incorporate screening) are more effective than usual care. But systems to manage depression must be in place. In primary care and general practice hospitals these systems are inadequate.

Population strategies aimed at reducing morbidity are more efficient when targeted at minimizing the chronic effect of existing depression rather than identifying more minor psychiatric morbidity.

"Screening for depression should only be considered as a part of a package of enhanced care. Without this, moves to implement screening will be associated with increased costs and no benefit."

BMJ April 29, 2006; 332: 1027-30 "Analysis and Comment" first author Simon Gilbody, University of York, UK

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Reduced Deaths and Reinfarction without Increase in Bleeding A New Era in Anticoagulation?

4-8 EFFECTS OF FONDAPARINUX ON MORTALITY AND REINFARCTION IN PATIENTS WITH ACUTE ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION: The Oasis-6 Randomized Trial

Despite many therapeutic advances, mortality in patients with acute ST-elevation myocardial infarction (**STEMI)** remains high. Antiplatelet therapy, thrombolysis, and angiotensin-converting enzyme inhibition improve prognosis. Primary percutaneous coronary intervention (**PCI**) offers benefits over thrombolytic therapy, but access to this procedure is limited.

The role of additional antithrombotic agents is unclear, especially among patients not receiving reperfusion therapy. Trials of unfractionated heparin, direct thrombin inhibitors, and enoxaparin (a low-molecular-weight heparin) have thus far failed to demonstrate mortality reductions. Reviparin (also a low-molecular–weight heparin) has been shown to reduce mortality and reinfarction, but bleeding is increased when it and other agents are used with aspirin and thrombolytic therapy.

This large randomized trial evaluated the effect of fondaparinux (*Arixtra*; a synthetic pentasaccharide which rapidly inhibits factor Xa) when initiated early and given up to 8 days.

Conclusion: In patients with STEMI, fondaparinux reduced mortality and reinfarction, without increasing bleeding and strokes.

STUDY

1. Multi-hospital (n = 447), multi-country (n = 41) double-blind trial randomized over 12 000 patients with STEMI presenting within less than 12 to 24 hours of symptom onset. Patients were divided into 2 strata:
    1) Stratum 1:
        A. Fondaparinux 2.5 mg subcutaneously once daily for 8 days. or
        B. A control group received usual care + matching placebo for 8 days. (For various reasons, unfractionated heparin was considered contraindicated in these patients.)
    2) Stratum 2:
        A. Fondaparinux 2.5 subcutaneously for 8 days, or
        B. A control group received usual care + placebo for 8 days + unfractionated heparin for 24 to 48 hours.
2. Patients were taking a variety of drugs, including aspirin, beta-blockers, and ACE inhibitors.
3. Many received primary percutaneous coronary intervention (PCI) and thrombolytic drugs,
4. Main outcome = composite of death or reinfarction at 30 days. Final follow-up at 3 or 6 months.

RESULTS

1. Overall—at 30 days:	Placebo or unfractionated heparin (%)	Fondaparinux (%)
Death or reinfarction	11.2	9.7 (NNT = 66)
Death	8.9	7.8
Reinfarction	3.0	2.5
2. At 3 to 6 months:		
Death or reinfarction	14.8	13.4 (NNT = 70)
Death	11.6	10.5
Reinfarction	4.6	3.8

(Deaths were chiefly cardiac.)

3. Subgroup analysis—death or reinfarction at 30 days (control vs fondaparinux)
    No reperfusion therapy – 15.5% vs 12.2% (NNT = 30)
    Thrombolysis – 13.6% vs 10.9% (NNT = 37)
    PCI – no benefit from fondaparinux.

    (Note that, in the subgroups not undergoing reperfusion, and in those receiving thrombolysis, benefits were greater than the benefits overall.)
4. Benefits from fondaparinux were also evident at 9 days
5. Severe bleeding:
    Overall, at 9 days, a tendency to fewer severe bleeds in the fondaparinux group (61 vs 79); and fewer cardiac tamponade (28 vs 48).
    In the stratum 1, those receiving placebo actually experienced more severe bleeding than those receiving fondaparinux (1.6% vs 1.0%). *[No explanation available except possibly play of chance.]*

DISCUSSION

1. "The OASIS-6 trial demonstrates a moderate reduction in mortality and reinfarction with the use of fondaparinux compared with usual care."
2. "Unlike other antithrombotic agents, such as low-molecular-weight heparin, direct thrombin inhibitors, or intravenous antiplatelet agents, fondaparinux reduced death and reinfarction without increasing bleeding or hemorrhagic stroke."
3. "Addition of fondaparinux to thrombolytic therapy probably represents an attractive, effective, and safe option as an initial adjunctive antithrombotic agent in AMI in patients not undergoing primary PCI."
4. The use of a single daily fixed dose of fondaparinux (2.5 mg subcutaneously) without any monitoring or dose adjustment simplifies the regimen and permits use in a range of settings.

CONCLUSION

In patients with acute STEMI not undergoing PCI, fondaparinux given for 8 days reduced mortality and reinfarction without increasing bleeding and strokes.

JAMA April 5, 2006; 295: 1519-30 original investigation, by the Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS-6) Trial Group, Corresponding author Salim Yusuf, McMaster University, Hamilton, Ontario, Canada.

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No Increase In Risk of BC. An Increase in Need for Repeat Mammography

4-9 EFFECTS OF CONJUGATED EQUINE ESTROGENS ON BREAST CANCER AND MAMMOGRAPHY SCREENING IN POSTMENOPAUSAL WOMEN WITH HYSTERECTOMY

Combined estrogen + progestin has been reported to produce more health risks than benefits[1]

A trial of estrogen-alone in hysterectomized women reported an increased risk of stroke after 7 years of use[2]. And no increase (and no reduction) in coronary heart disease.

Epidemiologic studies have suggested an increased risk of breast cancer **(BC)** in women receiving estrogen.

This trial compared estrogen-alone vs placebo on incidence of BC in hysterectomized women.

Conclusion: Estrogen-alone for 7 years did *not* increase BC incidence.

STUDY

1. The Women's Health Initiative **(WHI**) enrolled over 10 500 postmenopausal women (age range 50-79; majority over age 60). All had a prior hysterectomy.
2. Randomized to: 1) 0.625 mg combined equine estrogen (**CEE**; *Premarin*) or 2) placebo. Follow-up = 7 years.

RESULTS

1. After a mean of 7-years, the hazard ratio of invasive BC in women receiving estrogen-alone was 0.80 compared with those receiving placebo. [95% confidence interval = 0.62 to 1.04—not quite statistically significant.]

	CEE (n = 5310)	Placebo (n = 5429)	Absolute difference	NNT (7y)
Invasive BC	104 (2.0%)	133 (2.5%)	0.5%	200
Ductal carcinoma	61 (1.1%)	88 (1.6%)	0.5%	200

   At the end of the study, only 54% were taking the assigned study medication. When only women who were adherent in taking the study medications were considered, the incidence of invasive BC was much lower in the CEE group. (Hazard ratio = 0.69)

   There was an apparent *protective* effect of CEE as judged by 5-year estimated BC risk; history of benign breast disease; and number of first-degree relatives with BC.

2. The number of women recalled for repeat mammography was higher in the CEE group. At one year, 9% had mammograms with abnormalities which required follow-up vs 5.5% in the placebo group. Absolute difference = 4.5%. (NNT = 22) This pattern continued throughout 7 years (36% vs 28%). Absolute difference = 8% (NNT = 15).

DISCUSSION

1. In this trial, incidence of invasive BC did not differ significantly (statistically) between women receiving CEE vs placebo over 7 years. "This outcome was surprising considering prior evidence that CEE increased risk of BC."
2. There was a suggestion that CEE was associated with a decrease in risk of BC in women who were adherent to the protocol.
3. This is in clear contrast to risk when estrogen and progestin are combined in women with a uterus. Prior evidence suggested that combined progestin + estrogen increases risk of BC.
4. However, in postmenopausal women who have BC, reduction of estrogen levels by aromatase inhibitors (exemestane; *Aromasin*) and estrogen-receptor modulators (tamoxifen; *Nolvadex*) has anti-cancer effects. "These data are consistent with breast cancer cells being susceptible to estrogen fluctuations either above of below that tolerated by normal breast glandular tissues." [3]
5. The likelihood of incurring repeat mammography was higher in the CEE group. (One in 15) CEE increased mammograms (and biopsies) in women for whom radiologists recommended short-term follow-up. (*Estrogen increases breast density*.) This is associated with emotional and economic costs.
6. "Initiation of CEE-alone should be based on careful consideration of potential risks and benefits in a given individual."

CONCLUSION

CEE-alone for 7 years did not increase incidence of BC in hysterectomized postmenopausal women. CEE-alone may actually decrease risk of early stage invasive and ductal BC.

CEE-alone was associated with an increase in recommendations for repeat mammography

JAMA April 12, 2006. 295: 1647-57 Original investigation by the Women's Health Initiative Estrogen-alone Trial, first author Marcia L Stefanic, Stanford Prevention Research Center, Stanford CA.

1 For years, observational studies reported that hormone replacement therapy reduced risk of coronary heart disease, although many commented that bias in the form of the "healthy user effect" may have skewed the evidence. The WHI trial, in 2002 [JAMA 2002: 288: 321-33], reported that combined estrogen-progestin did not protect against cardiovascular disease, but actually increased risk slightly (up to 8 events per 10 000 women per year). As a result, many clinicians advised women to discontinue hormone replacement therapy and many women then continued to suffer menopausal symptoms.

I believe there is no doubt combined estrogen-progestin increases risk of breast cancer. It seems established that estrogen-alone does not increase risk. Progestin must be the culprit.

2 I believe the data do indicate that estrogen-alone slightly increases risk of stroke and thromboembolism.

3 Anxiety, bother, and cost of mammography are not trivial. Hysterectomized women with troublesome menopausal symptoms must balance relief of symptoms vs increased chance that repeat mammography might be advised. This is an individual choice.

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You Really Can't Keep It A Secret—Don't Try.

4-10 BREAST CANCER IN THE FAMILY—CHILDREN'S PERCEPTIONS OF THEIR MOTHER'S CANCER AND ITS INITIAL TREATMENT

Little has been published about communication with children when their parent is newly diagnosed as having cancer. Communication is important for the children's psychological adjustment. Children are exposed to an enormous amount of information about cancer. We know little about whether they notice this information, and how they make sense of it.

This study explored the accounts of mothers with breast cancer **(BC),** and their children, to identify children's awareness and understanding of their parent's cancer; their reactions to the diagnosis; and what information they would have liked to have been given and seemed to need. And to contrast children's accounts with the mother's perceptions of their children's knowledge.

STUDY

1. Recruited 37 mothers and 31 of their children (age 6 to 18). All the mothers had stage I-III BC that involved surgery (lumpectomy or mastectomy), supplemented by chemotherapy and radiotherapy as necessary.
2. Conducted detailed interviews with the mothers about their experience of talking about their illness with their family. And their perspectives of their children to the diagnosis.
3. A child psychiatrist saw the children at home, without their parents present, and conducted an interview about their experience of their mother's illness.

RESULTS

1. Children's awareness of cancer:

   All children (except two of the youngest) said they had heard of cancer before their mother's illness. Sources included the media, awareness of celebrities with cancer, direct experience with someone who had cancer, and science lessons at school. ("I thought that there was no cure for it; that you just died basically"—A 10-year old girl.)

   Several children seemed to be markedly affected by TV showing people with cancer who subsequently died ("I do wonder if I'm going to get it."—A 15-year old girl.)

   Many linked smoking with cancers of all kinds, and were troubled when their family or friends continued to smoke. Children with school friends whose mothers had recovered from cancer drew encouragement from the survival.

2. Mother's awareness of their children's knowledge:

   Some were sure that their child was aware that cancer could be life-threatening

   Others thought their children did not know that cancer could be life-threatening, and were shocked when the children's comments or questions revealed concerns that she might die. (A 7-year old—"Mummy, some people die when they have cancer".)

3. Children learning about mother's diagnosis:

   Children often suspect there is something wrong before they are told—from changes in the mother's mood and overheard conversations.

   The reactions of younger and older children were remarkably similar. They described emotional upset, shock, tears, fear and anxiety. Some expressed anger at God, and at the mother herself. Some mothers found it hard to cope with an apparently selfish reaction.

   Some children were worried about stress on their mother. ("Stress makes it worse, doesn't it? I thought if she gets stressed out too much, it might make it worse." – A 14 year old.)

4. Reactions to mother's treatment:

   Some saw surgery and anesthesia as potentially fatal.

   Some were shocked when first seeing their mother's drowsiness, and by seeing blood on the sheets from drainage tubes.

   Few were concerned about the loss of the breast.

   Some children considered chemotherapy, with its debilitating side effects and hair loss, was the worst aspect of treatment. Hair loss was a key issue for children across the age range.

5. What did children wish to know?

   Mothers wanted to strike a balance between containing their child's anxiety, and being honest.

   Only children under 10 years said that they had been given enough information.

   Girls wondered whether they might be more likely to develop breast cancer.

   "Usually when they (the doctors) wanted to say something, they would make me and my sister go somewhere

else while they talked to my dad and mum. But, I think it would have been better if they kind of spoke to all of us so, like, we knew exactly what was going on instead of just hearing it from mum and dad." –12 year old girl.

DISCUSSION

1. Even very young children were often aware of cancer as a disease before their mother's diagnosis. This awareness was often skewed. Many associated cancer with death. Children who knew of someone else with cancer mistakenly assumed that their mother's experience would be the same.
2. Parents find communicating the news about the cancer to their children stressful .

Even if children are not told, they draw meaning from their observations of the changes within the family.

Children are affected by changes in the parents' facial expressions and, particularly, by parental depression.

Evidence shows that giving children appropriate information about the disease reduces anxiety.

Parents may underestimate their children's need for information and try to protect them. "However, the more the children are prepared and informed, as appropriate for their age and development, the more it seems to help them cope.

Judging children's reactions can be difficult. Their reactions may belie their feelings.

"Although children cannot be protected from adverse events, the quality of the relationship and communication between family members is important for preventing adverse longer term consequences."

BMJ April 29, 2006; 332: 998-1001 Original investigation, first author Gillian Forrest, University of Oxford, UK

See BMJ April 29 2006 for additional comment and recommended websites to help parents deal with communication and providing support for their children.

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Should Be Systematically Used In <u>All</u> Patients With Documented CAD ? Should Be Systematically Used In <u>All</u> Patients With Documented CAD ?

4-11 ANGIOTENSIN-CONVERTING ENZYME INHIBITORS IN PATIENTS WITH CORONARY HEART DISEASE AND ABSENCE OF HEART FAILURE OR LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

"Angiotensin-converting enzyme inhibitors (**ACE**) . . . **"**are an undisputed treatment in patients who have congestive heart failure **(HF),** or in patients with coronary heart disease **(CHD)** and concomitant left ventricular dysfunction."

In patients who have CHD without heart failure or left ventricular dysfunction, randomized trials have yielded discrepant results.

This meta-analysis assessed long-term effects of ACE in patients who have CAD and no signs of HF or severe left ventricular dysfunction. (Stable coronary artery disease.)

Conclusion: ACE inhibitors reduce total mortality and morbidity and major endpoints in these patients.

STUDY

1. Systematic search found 7 randomized placebo-controlled trials meeting the specifications of the investigators (~ 34 000 patients, mean age ~ 63, followed for a mean of 4.4 years). All trials included patients with documented CHD. No patient had signs or symptoms of HF or documented LV dysfunction (ejection fraction < 0.35).
2. Five trials included only patients with documented CHD. One trial included patients with documented CHD, or patients with diabetes + one or more risk factors. One trial included patients with CHD, or with a history of transient ischemic attack, or a history of intermittent claudication.
3. Treatment ACE inhibitors included ramipril, quinapril, enalapril, perindopril, and trandolapril. Many patients (but far from all) were taking beta-blockers, antiplatelet agents, diuretics, and calcium blocker*s*.

RESULTS

1. Overall	Active treatment n = 16 328 (%)	Placebo n = 16 034 (%)	Absolute difference (% in 4.4 years)	NNT (4-y)
All-cause death	1215 (7.4)	1392 (8.7)	1.3	77
CV death	673 (4.1)	819 (5.1)	1.0	100
MI	1048 (6.4)	1258 (7.8)	1.4	71
Stroke	342 (2.0)	445 (2.7)	0.7	142
Cardiac arrest	46	82		
Hospitalized for unstable angina	993	1019		
Myocardial revascularization	2622	2788		
Hospitalized for HF	330	429		
New onset of diabetes[1]	437 (2.7)	554 (3.4)	0.7	142

(I had to calculate the absolute differences and NNT from their data. The results were reported in terms of odds ratios (between 0.77 and 0.86) which are misleading. RTJ)

2. No obvious relationship between the different pharmacological properties of the 5 drugs and clinical benefit.
3. Active treatment was associated with 3 to 6 mm/Hg drop in systolic BP.

DISCUSSION

1. The investigators comment that . . . **"**There was no obvious relationship between the magnitude of blood pressure reduction and clinical events in the trials. Blood pressure reduction per se is not necessarily associated with cardiovascular protection in patients who have stable CAD and preserved LV function."[2]
2. Dosage: The doses of ACE used in each of the trials differed. Trandolapril 2 to 4 mg; ramipril 10 mg; perindopril 8 mg. "The two trials with definitely positive results used the highest doses." Even rather low doses of ACE were effective in reducing risk of heart failure. "There is evidence that only the larger doses of ACE inhibitors can slow the progression of atherosclerotic disease."

CONCLUSION

Use of ACE inhibitors for long-term secondary prevention in patients with established CHD, who are without LV dysfunction or heart failure, was associated with a reduction in all-cause mortality and major cardiovascular events.

"These results, along with those previously reported in patients who have CAD with LV dysfunction or heart failure, suggest that ACE inhibitor therapy should be systematically used in all patients with documented CAD."

Archives Int Med April 10, 2006; 166: 787-96 Meta-analysis, first author Nicholas Danchin, Hopital Europeen Georges Pompidou, Paris, France.

1 The slight reduction in incidence of diabetes is interesting. This contrasts to the slight increase in incidence related to thiazide diuretic therapy.

2 I believe this is a stretch.

Proposing That Fat Accumulations In The Myocardium Are Toxic.

4-12 ADIPOSITY OF THE HEART, REVISITED: A Narrative Review

Under healthy conditions, most triglyceride is stored in adipocytes. The amount of triglyceride stored in non-adiposite tissues (pancreas, liver, and myocardium) is minimal and tightly regulated. When this regulation is disrupted, triglycerides may accumulate excessively in these organs (steatosis). The accumulation may culminate in irreversible cell death (lipotoxicity) and lead to several clinical syndromes: non-alcoholic hepatic steatosis; pancreatic B-cell failure; and dilated cardiomyopathy

Investigations are now revisiting the hypothesis that excessive deposits of lipids within myocardial tissue (that is, cardiac lipotoxicity) is an important, but forgotten, cause of non-ischemic dilated cardiomyopathy. Imaging techniques now permit precise and reproducible quantification of intra-cellular triglyceride in various human organs, including the myocardium. This presents a novel mechanism that may act independently of coronary artery disease to cause dilated cardiomyopathy.

"Myocardial lipid content may be a biomarker and a putative therapeutic target for cardiac disease in obese patients."

However. . . "A direct association between myocardial lipid content and left ventricular performance has yet to be reported."

This, of course, is not a practical point at this time. I could not resist abstracting it. Indeed, I am old enough to remember when the concept of the fatty heart was taught in medical school.

This makes sense. If fat can accumulate in the liver, why not in the myocardium?

Watch for further developments.

Proposing That Fat Accumulations In The Myocardium Are Toxic.

4-12 ADIPOSITY OF THE HEART, REVISITED: A Narrative Review

In the USA, morbidity and mortality rates have relentlessly increased as the obesity epidemic continues unabated. Hospitalizations for congestive heart failure have increased.

The concept of fatty degeneration of the heart was first described by Laennec in the early 1800s. Later the condition became known as myocardial steatosis, and was used to explain the greater risk of heart disease and death in obese persons. In 1933 the topic was revisited by Smith and Wiilus[1]. They reported that, on autopsy, lipids were seen to infiltrate the myocardium in many patients. This old hypothesis considered that fat is a direct cardiotoxin; that fatty degeneration of the heart is a common consequence of obesity; and is a possible cause of dilated cardiomyopathy.

Later, the concept was called into question, and its importance was downgraded.

Traditionally, obesity has been considered to be an *indirect* cause of heart disease. Obese persons present with several risk factors, including dyslipidemia, hypertension, and diabetes. These risk factors predispose patients to myocardial infarction, and ischemic cardiomyopathy. In addition, obesity is related to hemodynamic changes—increased heart rate and stroke volume. This hyperdynamic circulation may be a compensatory adaptation to increased adipose mass. In extreme obesity, it can progress to non-ischemic dilated cardiomyopathy.

Under healthy conditions, most triglyceride is stored in adipocytes. The amount of triglyceride stored in non-adipose tissues (pancreas, liver, and myocardium) is minimal and tightly regulated. When this regulation is disrupted, triglycerides may accumulate excessively in these organs (steatosis). The accumulation may culminate in irreversible cell death (lipotoxicity) and lead to several clinical syndromes: non-alcoholic hepatic steatosis; pancreatic B-cell failure; and dilated cardiomyopathy. Recently, a study of patients with heart failure who underwent cardiac biopsy demonstrated that patients who were obese had intramyocardial lipid levels 5 or 6 times higher than controls.

This article reviews recent basic animal research that demonstrates direct toxic effects of lipid accumulation on the myocardium. Investigations are now revisiting the hypothesis that excessive deposits of lipids within myocardial tissue (that is, cardiac lipotoxicity) is an important, but forgotten, cause of non-ischemic dilated cardiomyopathy. Novel magnetic resonance techniques are now available which permit precise and reproducible quantification of intra-cellular triglyceride in various human organs, including the myocardium. This presents a novel mechanism that may act independently of coronary artery disease to cause dilated cardiomyopathy.

Investigators have begun to study the role of myocardial steatosis in the development of obesity-specific cardiomyopathy in humans. Myocardial fat content increases with the degree of adiposity. This may contribute to the adverse structural and functional cardiac adaptations seen in obese individuals, acting independently of coronary artery disease to cause dilated cardiomyopathy. Myocardial triglyceride content appears to increase progressively as BMI increases. The investigators speculate that the increase in myocardial lipids is not toxic initially, but becomes detrimental after decades of sustained lipid excess.

“Myocardial lipid content may be a biomarker and a putative therapeutic target for cardiac disease in obese patients.”

However. . . “A direct association between myocardial lipid content and left ventricular performance has yet to be reported.”

Annals Int Med April 4, 2006, 144; 517-24 Review article—one of a series of Physiology in Medicine, first author Jonathan M McGavock, University of Texas Southwestern Medical Center, Dallas.

1 Archives Int Med 1933; 52: 811-931 Smith and Willius presented an article “Adiposity of the Heart”. The present authors borrowed the title for this review.