PRACTICAL POINTERS

FOR
PRIMARY CARE

ABSTRACTED MONTHLY FROM THE JOURNALS

JANUARY 2005

JAMA, NEJM, BMJ, LANCET

ARCHIVES INTERNAL MEDICINE

ANNALS INTERNAL MEDICINE

PUBLISHED BY PRACTICAL POINTERS, INC.

EDITED BY RICHARD T. JAMES JR. MD

400 AVINGER LANE, SUITE 203

DAVIDSON NC 28036 USA www.practicalpointers.org

Rjames6556@aol.com

PRACTICAL POINTERS HOPES FOR YOUR SUPPORT

***Practical Pointers for Primary Care* is now in its 20th year.**

Over this time, it has been supported financially solely by the publisher as a public service. Now, due to increasing costs and a shrinking purse, *Practical Pointers Inc.* will accept small contributions from "subscribers" who have found the publication helpful and wish it to continue.

Correspondence to:

Practical Pointers, Inc.
c/o Richard James, Publisher
400 Avinger Lane #203
Davidson NC 28036

Contributions are free of income tax as donations to a tax-exempt not-for-profit public service corporation, and as a medical-education expense.

HIGHLIGHTS AND *EDITORIAL COMMENTS* JANUARY 2005

Treat the Patient, Not the Blood Pressure—Not the Cholesterol.

1-1 TREATMENT WITH DRUGS TO LOWER BLOOD PRESSURE AND BLOOD CHOLESTEROL BASED ON AN INDIVIDUAL'S ABSOLUTE CARDIOVASCULAR RISK.

Absolute risk of a cardiovascular disease is the probability that an *individual* patient will have an event over a defined period. It is determined by a synergistic effect of *all* CVD risk factors present in the individual. It may be true that, in a large group of individuals with a systolic BP of 160, the CVD risk is twice as high as in a large group with a systolic of 110 (*relative risk*). In an individual, however, absolute risk depends on much more than a single risk factor. Indeed, absolute differences in risk can vary more than 20-fold in patients with the same BP.

"Cardiovascular treatment benefit is directly proportional to the pre-treatment absolute risk."

A new approach to preventive therapy is to modestly reduce all modifiable risk factors rather than concentrating on reaching "target levels' of one or two.

This is a sea change in our approach to lowering risk.

Please read the full abstract.

Why do we Underuse Treatments That are Beneficial in Trials?

1-2 EXTERNAL VALIDITY OF RANDOMIZED CONTROLLED TRIALS: To Whom do the Results of this Trial Apply?

Randomized controlled trials **(RCTs)** and systematic reviews must be *internally* validated. (Ie, the design and conduct of RCTs must keep the possibility of bias to a minimum). To be clinically useful, however, the results must be relevant to a definable group of patients in a particular clinical setting. This is termed *external validity.*

The most frequent criticism by clinicians of RCTs, systematic reviews, and guidelines is the lack of external validity. This explains the widespread underuse in routine practice of treatments that are beneficial in trials and recommended by guidelines.

Assessment of external validity requires clinical rather than statistical expertise.

The response to, and compliance with, treatment can be influenced strongly by the doctor-patient relationship, placebo effects, and patient preferences. The importance of these factors outside of trials should not be underestimated. Note the popularity of "alternative" therapies in which such factors are the only active ingredients.

The primary care clinician is a final arbiter of external validity. (Would this application be clinically useful for Mrs. Jones?)

Beware of surrogate outcomes in RCTs, of composite outcome measures, underreporting of adverse effects, and reports by pharmaceutical companies.

Primary care difficult, challenging, and so rewarding.

Is the Evidence "Generalizable" to my Patient?

1-3 EVIDENCE-BASED PRACTICE AND THE INDIVIDUAL

Is my patient so different from those in the trial that its results cannot help me make my treatment decision? The more family practitioners feel they know their patients, the less likely they are to apply external evidence to guide management.

Disingenuous surrogate markers and misleading composite outcomes may create good advertising material, but cannot obscure data and hinder genuine patient-centered care.

Let us not neglect the central role of individual patients as decision-makers in their own care. “It is the responsibility of healthcare workers to communicate objective evidence in a manner which allows recipients to make an informed choice, and then to respect that choice.”

“Now and then, clinicians will have to accept and explain that uncertainty is an inherent facet of the uniqueness of human nature. Evidence helps to quantify that uncertainty, but cannot remove it.”

If Confirmed, This Represents An Enormous Public Health Benefit.

1-4 FOLATE INTAKE AND THE RISK OF HYPERTENSION AMONG U.S. WOMEN

Oral folic acid supplementation improves endothelial function. Folate may have beneficial effects on blood pressure by increasing nitric oxide synthesis in endothelial cells, and by reducing plasma homocysteine levels. (Homocysteine by itself can cause endothelial cell injury.)

This study assessed the association of folate intake with incident hypertension in 2 large groups of women.

Younger women (mean age 36 at baseline):

Identified 7373 incident cases of hypertension (8%) over 8 years.

Subjects whose daily consumption was at least 1000 ug of total folate (diet + supplement) had a relative risk of developing hypertension of 0.54 compared with women who consumed less than 200 ug daily.

Absolute risk reduction of incident hypertension was about 8 cases per 1000 person-years.

Older women (mean age 55 at baseline):

Identified 12347 incident cases of hypertension (19%) over 8 years.

Relative risk of hypertension (1000 ug folate daily *vs* less than 200 ug) = 0.82.

Absolute risk reduction of incident hypertension was about 6 per 1000 person-years.

The most significant relationship was associated with supplemental (not dietary) folate intake.

(Bioavailability of supplemental folate is twice that of food folate.)

Younger women achieved the most benefit. Younger women whose intake was at least 1000 ug experienced 1/3 the risk of developing hypertension over 8 years. (*Ie, start supplementation early. RTJ*)

High intake of folate was associated with a decreased risk of incident hypertension, especially in younger women. Supplemental folate was independently beneficial.

If confirmed as true, this has enormous public health benefit.

The benefits of folate extend to prevention of spina bifida and coronary heart disease. The benefit/harm-cost ratio is very high.

Aromatase Inhibitor Safer and More Effective Than Tamoxifen

1-5 RESULTS OF THE ATAC (ARMIDEX, TAMOXIFEN, ALONE OR IN COMBINATION) TRIAL OF 5 YEARS' ADJUVANT TREATMENT FOR BREAST CANCER

This study compared the aromatase inhibitor anastrozole with tamoxifen over 5 years.

Compared with tamoxifen, anastrozole led to significant improvements for disease-free survival, and time-to-recurrence, especially in women whose BC was hormone-receptor-positive. Benefits were also demonstrated in hormone-receptor-negative patients.

Benefits were therefore *in addition* to the risk reduction previously shown in tamoxifen vs placebo trials. (*Ie, anastrozole vs placebo would have shown greater absolute benefits compared with tamoxifen vs placebo*)

The incidence of contralateral BC was substantially reduced by anastrozole as compared with tamoxifen. (This was also an improvement over the benefit of tamoxifen alone vs placebo as demonstrated in previous studies.)

Withdrawals were significantly fewer in the anastrozole group (11% vs 14%).

Drug-related serious adverse events were also fewer (5% vs 9%).

Anastrozole was associated with significant reductions in endometrial cancer, thromboembolic events, ischemic cerebrovascular events, vaginal bleeding, and hot flushes.

Arthralgias and fractures were more frequent in the anastrozole group. (*The authors suggest concomitant bisphosphonate therapy because of this finding*.)

It is reasonable to switch patients currently on tamoxifen to an aromatase inhibitor. It is not appropriate to wait until after a 5-year period of treatment with tamoxifen. The most effective and well-tolerated therapy should be offered at the earliest opportunity

Anastrozole should be considered the preferred *initial* adjuvant endocrine therapy for post-menopausal women with hormone-receptor positive localized BC.

Aromatase is the enzyme which catalyses conversion of androgens to estrogens in females. Aromatase inhibitors block production of estrogen.. There are three 3rd generation compounds under investigation: exemestane, anastrozole, and letrozole. The action of exemestane is irreversible.

A similar study reported in NEJM March 11, 2004 reported similar benefits when exemestane was substituted for tamoxifen after 2 to 3 years.(See Practical Pointers March 2004 [3-9])

I believe this represents a major improvement in therapy of BC, and likely an improvement in prevention.

I wonder—would there be any benefit in treatment of ductal carcinoma in situ?

Proposing an ABCDE Memory Device to Simplify Adherence to Guidelines

1-6 A SIMPLIFIED APPROACH TO THE MANAGEMENT OF NON-ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROMES

The study assembled a comprehensive plan through an "ABCDE" approach. The intention was to provide a memory device to overview therapies and lifestyle changes that are clinically useful for patients with NSTE-ACS.

Elements of the plan:

A Antiplatelets; Anticoagulation; ACE inhibitors; Angiotensin II blockers.

B Beta-blockers; Blood pressure control

C Cholesterol management; Cigarette cessation

D Diet; Diabetes management

E Exercise.

This practical approach allows physicians to more effectively create disease management protocols, define roles and responsibilities for different medical personnel, and ensure implementation of evidence-based short-and long-term medical and risk-reducing strategies.

This plan is almost identical to a check list presented in the Archives Int Med July 2004 for secondary prevention of cardiovascular disease. (See Practical Pointers July 2004 [7-8])

I believe check lists can be a valuable addition to primary care. In the hurried pace of practice, we all omit (simply forget to consider) aspects of treatment and lifestyle which should be addressed at almost every patient visit. A mneumonic check list is a practical approach.

Some clinicians may make their own. I tried to create a mneumonic check list for diabetes:

D Diet; Depression

I Insulin

A Aspirin; ACE inhibitors

B BMI; BP

E Exercise

T Tests (blood glucose; HbA1c; lipids; microalbuminuria; liver function; ejection fraction)

E Eye (retinopathy); Extremities (foot health; foot pulses; peripheral neuropathy)

S Sulfonylureas, Statins, and other oral drugs; Smoking

Plus (Add others which might be indicated.)

Adherence was Poor. Those Who Adhered for One Year Lost Weight

1-7 COMPARISON OF THE ATKINS, ORNISH, WEIGHT WATCHERS, AND ZONE DIETS FOR WEIGHT LOSS AND HEART DISEASE RISK REDUCTION

This study assessed adherence rates and effectiveness of 4 diets in producing weight loss and reducing cardiac risk factors:

1. Atkins	Low carbohydrate—20 g carbohydrate daily
2. Zone	High protein, low glycemic load
3. Weight Watchers	Balanced diet—total daily ”points” in a range determined by current weight (Aimed for 24 to 32 points daily.)
4. Ornish	Low fat, vegetarian diet containing 10% of calories as fat.

About half of the subjects in each group failed to complete the 1-year course. The most common reasons were “too hard to follow” and “not yielding enough weight loss”. Adherence was particularly low for Atkins and Ornish.

At 1 year, completers lost more than those who failed to complete (-3. 9 kg for Atkins and -6.6 kg for Ornish)

Each diet significantly reduced LDL/HDL-cholesterol ratio by about 10%. The Atkins diet did not lower LDL-cholesterol significantly. The Ornish diet did not increase the HDL-cholesterol. No diet significantly altered

triglyceride levels. Reductions of total cholesterol, C-reactive protein, and insulin levels were significantly associated with the degree of weight loss.

Under realistic conditions a variety of popular diets can reduce weight and several cardiac risk factors. But only about half of the subjects in this study sustained a high adherence level.

The problem is not the diet, it is the patient's inability to follow it. Recidivism would be higher still at 5 or 10 years. The bloom seems to be coming off the Atkins diet.

The authors suggest that one way to improve dietary adherence in clinical practice may be to use a broad spectrum of diet options to better match individual patient's food preferences, lifestyles, and cardiovascular risk factors. They suspect adherence would have been better if subjects had been given the option to choose their diet. I wonder—would switching from one type of diet to another every few months increase compliance?

A Particularly Ominous Public Health Issue

1-8 FAST-FOOD HABITS, WEIGHT GAIN, AND INSULIN RESISTANCE

This study investigated the association between fast-food habits of young U.S. adults and changes in body weight and insulin resistance over a 15-year period.

At baseline, weekly visits to fast-food restaurants = 2.4 for men and 1.7 for women. Younger subjects made more visits. There was a direct and independent monotonic association between fast-food frequency and weight and insulin resistance. Subjects who visited three times a week had a mean weight about 2 kg higher than those who visited less than once a week.

Over 15 years, frequent visitors gained more weight compared with those who visited less than once a week. Insulin resistance was directly associated with visits of 3 times a week. There was a direct and independent monotonic association between fast-food frequency and weight and insulin resistance. Compared with subjects whose fast-food visits were less than once a week, those who visited over 2 times weekly gained an extra 4.5 kg and had a 104% greater increase in insulin resistance.

Fast-food habits have strong, positive and independent association with weight gain and insulin resistance in young adults. This suggests an increased risk of type 2 diabetes and obesity.

I am sure that this does not surprise anyone.

The study points out some differences between blacks and whites, and between males and females. See the text.

"Overload your truck & it will break down."

The fast-food industry is beginning to make some adjustments in their menus. This is difficult for a highly competitive industry. To stay in business, the competition must be met. Customers will frequent the establishments offering the best tasting foods and the largest portion size. The solution lies, not in forcing the fast-food to change their menus, but by making a sea-change in public awareness and compliance with a "healthy diet"—an almost impossible task which will take years to accomplish even partially.

Stool Antigen Test is Recommended

1-9 TEST AND TREAT FOR DYSPEPSIA: But Which Test?

The National Institute for Clinical Excellence **(NICE)** of the UK recommends that patients with *persistent or recurrent uncomplicated dyspepsia* should have a non-invasive test for *Helicobacter pylori*. If the test is positive they should receive eradication (triple antibiotic) therapy

Now the stool antigen test is available. It detects *H pylori* antigens passed in feces. A commercial monoclonal antibody test is available. It is reported to be as accurate as the urea breath test. It can be introduced with ease into routine laboratory practice. It is less expensive and less time consuming than the urea breath test. It is useful also in confirming eradication of the infection.

"We need to have an easy, accurate diagnostic test and the stool antigen test is just that."

There are some advantages of "test and treat":

Will treat an unsuspected peptic ulcer. And reduce risk of subsequent ulcer disease.

Will reduce or eliminate symptoms in some patients (~ 10%). Since about 50% of patients with functional dyspepsia will be positive, eradication will remove symptoms in only 5% of patients with dyspepsia.

Remove a risk factor for gastric cancer.

Physician's Power Can be Enhanced, Diminished, Used Well or Ill, but It Cannot be Disowned.

1-10 CONSENT OR OBEDIENCE? Power and Authority in Medicine

This essay considers the role of inappropriate obedience as a source of abuse in the teaching hospital and the effect of obedience on patients' autonomy and consent.

Patients provide consent not only about big issues, but, in the course of an illness, sick patients consent innumerable times to interventions that they would rather not undergo.

Serious illness is marked by losses of normal function in many dimensions of existence, including the ability to reason and to act (without which "autonomy" loses meaning). Sick patients do not reason their way to decisions based on their appraisals of the relevant information, but because an authority helps them to decide.

A power comes from the hospital setting and the trappings of medical authority. "Such power can be enhanced, diminished, used well or ill, but it cannot be disowned."

Bearing in mind the effect of sickness on function, we should accept the propensity of sick patients to seek our approbation, celebrate our expertise, and acknowledge the legitimacy of our authority by doing as they think we wish. These tendencies present us with difficult responsibilities.

"The biggest thief of autonomy is sickness."

I enjoyed this thoughtful essay.

We live in a world in which authority leads multitudes to follow blindly and commit unspeakable atrocities. The resistance of one man is a badge of courage.

I believe physicians apply their power to some extent in every patient encounter. Physicians, wield your power carefully and always with the aim of benefit to the patient.

The USPSTF Now Recommends One-Time Screening in Select Subsets of Men

1-11 SCREENING FOR ABDOMINAL ANEURYSM

The U.S. Preventive Services Task Force **(USPSTF)** now recommends one-time ultrasonographic screening for abdominal aortic aneurysm **(AAA)** for men ages 65 to 75 who presently smoke or who have smoked in the past.

The task force makes no recommendation for or against screening men who have never smoked. It recommends *against* routine screening for women.

One-time screening is sufficient.

Is there any medical treatment? Will beta-blockers decrease the rate of expansion by reducing the stress caused by the steep increase in wall expansion during systole? Many patients in this age group with AAAs would be candidates for beta-blocker therapy because of an increase in risk factors for CVD, including sub-optimal BP control.

As always, primary care clinicians must judge benefits vs harms of individual patients. The availability of expert, safe surgery is a major factor influencing the recommendation.

Advice for screening carries ethical considerations. Although opportunistic preventive medicine is considered a part of good medical practice, is it always ethically justifiable? Consider a male smoker age 70 who consults for arthritis. Should the primary care clinician at the time of the consultation advise the patient to undergo screening for AAA? Should the primary care clinician advise a prostate specific antigen?

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. Every test carries a chance of a false-positive result leading to interventions that do not benefit the patient, and may cause harm.

I believe many primary care clinicians would limit screening for AAA to patients who consult for a specific indication—assessment of their general health status.

One or Two Drinks a Day May Decrease the Risk of Cognitive Decline.

1-12 EFFECTS OF MODERATE ALCOHOL CONSUMPTION ON COGNITIVE FUNCTION IN WOMEN.

This study asks—What is the effect of *moderate* consumption of alcohol on cognition? A benefit is plausible considering the strong link between moderate alcohol and decreased risk of cardiovascular disease. Cognitive impairment and cardiovascular disease share common risk factors.

Compared with abstainers, moderate drinkers (less than 15 g alcohol per day; one drink) had better mean cognitive scores. (Relative risk of impairment = 0.81 based on a global cognitive score.) Also, compared with abstainers, moderate drinkers (15 to 30 g per day) had a reduced relative risk of cognitive impairment (although slightly less favorable, with wider confidence intervals).

In older women consumption of one alcoholic drink per day did not impair cognitive function, and may actually decrease risk of cognitive decline.

Benefits of moderate alcohol consumption have been reported with remarkable consistency over the past 10 years. Indeed, some epidemiologists consider abstinence to be a risk factor for cardiovascular disease.

As always, we should be cautious about generalizing the conclusions of observational studies.

Statins Reduce C-Reactive Protein Levels and Improve Outcomes Independently of LDL-Cholesterol

1-13 STATINS FOR ATHEROSCLEROSIS—Autoimmunity, Inflammation, and C-reactive Protein.

Statin drugs, in addition to inhibiting synthesis of cholesterol, now appear to directly inhibit inflammation.

Two articles in this issue of NEJM confirm that reducing the inflammatory component of cardiovascular disease with statin therapy improves clinical outcomes independently of the reduction in cholesterol. Both studies found that the statin-induced decrease in C-reactive protein (**CRP**), a marker of inflammation, is only weakly correlated with changes in lipid levels.

The LDL-c lowering effect of statins and their effect on lowering CRP are largely independent of each other. Patients achieving the lowest CRP levels through statin therapy had a higher event-free survival at all levels of LDL-cholesterol.

Only by assaying both C-reactive protein and cholesterol can the full effect of statins be identified.

Statins are the "penicillin" of the last of the 20th century

This is not a practical point at this time. Although it is still "far out", I included the abstract because of its potential. We need a more specific agent to reduce C-reactive protein levels.

CRP is formed in the liver in response to acute inflammation. It is a non-specific marker. C(capsule)-reactive protein has an interesting history. It was first described in 1930 as an indicator of pneumococcal infection because it reacts with the polysaccharide in the capsule of the pneumococcus.

Development May be Delayed by Good Glycemic Control and Modification of Cardiovascular Risk Factors.

1-14 VASCULAR RISK FACTORS AND DIABETIC NEUROPATHY

The Diabetes Control and Complications Trial reported a 60% reduction in DN in the intensively treated group at 5 years. But the incidence still remained substantial. This suggests that DN can develop despite intensive control of glucose levels. Risk factors other than glucose are involved.

This study assessed potentially modifiable risk factors for development of distal, symmetric DN.

Dyslipidemia, elevated BMI, smoking, and hypertension were associated with development of DN.

Cardiovascular disease at baseline was associated with double the risk of neuropathy.

What can be done prospectively to try to prevent DN?

Control glycemia as best it can be controlled

Stop smoking

Control BP

Control weight, obtain lower body mass index

Reduce other cardiovascular risk factors.

(*Ie, essentially standard diabetes management*.)

I enjoyed reviewing the diagnosis of neuropathy.

The mean age at baseline was about 30. Of an initial cohort, 28% already had DN. Prospectively, over 7 years 23% developed DN. Thus at age about 40, over half had DN. I would expect almost all patients with type 1 diabetes will eventually develop DN.

Fasting Serum Glucose Level and Diabetes were Associated with Cancer Risk

1-15 FASTING SERUM GLUCOSE LEVEL AND CANCER RISK IN KOREAN MEN AND WOMEN

Is there any connection between diabetes and cancer? Some observational studies have suggested there is. This prospective cohort study investigated this possibility.

A ten-year prospective study enrolled over 829 000 men and over 468 000 women age 30 to 95 at baseline. (Mean = 46; mean body mass index = 23)

After adjusting for smoking and alcohol use, the stratum with the highest fasting glucose (> 140) had higher death rates from all cancers compared with the stratum with the lowest level (< 90). Hazard ratio = 1.25

Age-adjusted cancer deaths per 100 000 men rose linearly from about 600 in the groups with fasting glucose < 90 to about 1400 per 100 000 in the group with glucose levels above 140. (*Although absolute numbers are low, the linear relationship depicted on page 196 and 200 is impressive. RTJ*). Similar linear increases were recorded in women, although not as high in absolute terms. Incidence of cancer was similar to mortality.

The association was strongest for pancreatic cancer. (Hazard ratio = 2 comparing the highest glucose stratum with the lowest.) Significant associations were also found in other cancers (esophagus, colo-rectal, liver, cervix).

”We have shown that fasting serum glucose level and diabetes are associated with cancer risk in a population far leaner than the Western populations.”

This is my first encounter with the relation between glucose intolerance and cancer. It is not a clinically important point now. I felt it was interesting enough to abstract. I will watch for follow-up studies.

ABSTRACTS JANUARY 2005

Treat the Patient, Not the Blood Pressure—Not the Cholesterol.

1-1 TREATMENT WITH DRUGS TO LOWER BLOOD PRESSURE AND BLOOD CHOLESTEROL BASED ON AN INDIVIDUAL'S ABSOLUTE CARDIOVASCULAR RISK.

Fifty years ago it was thought that people either had hypertension, or not, in the same way that a woman was pregnant or not. Now we realize that BP is *continuously* related to cardiovascular risk. Hypertension is now being defined as the BP level above which there would be clinically significant benefits from lowering BP.

The same applies to dyslipidemia.

Cardiovascular risk factors cannot be divided into present or absent (yes or no) categories.

This review focuses on the clinical implications of these definitions. This is relevant because almost every adult in the USA would be eligible for individualized treatment to lower risk of cardiovascular disease (**CVD**) (*I would argue that every adult in the USA could benefit from lowering modifiable risk factors. RTJ)* This has broad public-health implications.

The authors state that treatment decisions should be based on *absolute* estimates on cardiovascular risk. As a result, some patients with average or below average levels of BP and cholesterol should be treated in preference to other patients who have higher levels.

Relative risks of cardiovascular disease:

Meta-analyses show the same general pattern of the associations between BP and cholesterol and relative risk **(RR)** of cardiovascular disease**.** When large groups of patients are considered, for each change in BP there is a constant relative change in CVD risk. This applies to the BP range of about 110/70 to 170/105. As systolic BP is lowered from 170 to 160 to 150 to 140 to 130 to 120 to 110, there is a relative risk reduction of coronary heart disease and stroke at each step. Considering 130 as having a RR of 1.00, a large group of patients with a systolic of 110 has a RR of about 0.75. The RR progressively increases up to about 2.5 in those with a systolic of 170. (*Figure 1 p 435*). The same applies for diastolic BP and total cholesterol. This does *not* mean, however, that every man with a systolic of 170 would have his relative risk reduced from 2.5 to 1.00 if his systolic was reduced to 130.

Absolute risk of cardiovascular disease:

Absolute risk of a cardiovascular disease is the probability that an *individual* patient will have an event over a defined period. It is determined by a synergistic effect of *all* CVD risk factors present in the individual. It may be true that, for a large group of individuals with a systolic BP of 160, the CVD risk is higher than a large group with a systolic of 110 (relative risk). In an individual, however, absolute risk depends on much more than a single risk factor. Indeed, absolute differences in risk can vary more than 20-fold in patients with the same BP (eg, systolic 160). The difference is due to the additive effect of other risk factors present in an individual. Powerful risk predictors such as age, sedentary lifestyle, obesity, previous symptomatic CVD, left ventricular hypertrophy, renal impairment, increasing BP, lipid levels, male sex, smoking, (and others) interact to determine *absolute* risk of an individual. Single risk factors (eg, BP, lipids) have a minor effect on an individual patient's absolute risk if they exist alone. They can have a major effect when added to other risk factors.

"Cardiovascular treatment benefit is directly proportional to the pre-treatment absolute risk."

The article presents several figures (pp 436 & 437) to illustrate this point:

Figure 5 (*p 437*) shows the effect on absolute cardiovascular risk of successively adding other risk factors in individuals with the same total cholesterol levels:

> Consider a 50-year old women with a total cholesterol of 150. If she is non-smoking, non-diabetic, has a HDL-cholesterol of 60, and a systolic BP of 130 she has an absolute 5-year risk of CVD of less than 1%.
>
> Consider another woman with the same total cholesterol (150). She smokes, has a systolic BP of 170, and a HDL-cholesterol of 38. Her absolute 5-year risk is 10%
>
> Consider a 50-year old man with the same total cholesterol (150). He is a smoker, has a systolic BP of 170, and a HDL-cholesterol of 38. His absolute 5-year risk is 15%.
>
> In all three examples, adding risks associated with diabetes and increasing age would greatly increase absolute risk even if the total cholesterol remained at 150.

As a result of the synergistic effect of risk factors, individuals who have achieved the "target level" BP or cholesterol might have much higher absolute risk than an individual with higher BP and cholesterol. This depends on the associated risk factors in each individual. It is true, when considering a *large group*, that reducing cholesterol from 250 to 150 the risk of a CVD event over 5 years will be lowered on *average* by a certain percentage. This does not apply, however, to individual patients since each has different risk factors and a different absolute risk. Suppose we push therapy in an individual to achieve a cholesterol of 150 and a systolic BP of 130. The patient smokes, is obese, and sedentary. His absolute risk will remain high. In estimating absolute risk, multiple risk factors must be considered. "These observations emphasize the clinical limitations of terms such as hypertension and hypercholesterolemia."

Short-term absolute risk (eg, 5-year risk of a cardiovascular event) increases exponentially with age. Therefore there is greater short-term absolute benefit from eliminating risk factors. This would favor treatment of older patients. It has been argued that younger individuals have the more to gain because of their greater life expectancy. But, younger persons value time in the distant future less than in the near future. Case-fatality after a cardiovascular event is much higher in older than in younger people.

The authors go on to comment on consideration of the substantial merits of the "Polypill", a combination of 6 drugs (aspirin, a statin, folic acid, and 3 antihypertension drugs) given in low dose. A pill given to everyone over age 55 would be consistent with the absolute risk-based treatment strategy that lessens the importance of lowering individual risk factors to "target level" in favor of less drastic treatment of multiple risk factors. This would more effectively lower risk. "Less emphasis should be placed on reaching treatment targets for specific risk factors, and more on identifying high-risk patients and targeting multiple risk factors." Because cardiovascular risk factors act synergistically, the most effective strategy for lowering cardiovascular risk might be one that targets *moderate* reductions in *multiple* risk factors rather than large reductions in single factors. (Beneficial lifestyle changes are the most productive, and they have no adverse effects.)

Conclusion

Individualized management of cardiovascular risk should be based on the probable size of absolute treatment benefits.

Attention should be moved from knowing one's blood pressure and cholesterol concentrations to knowing one's absolute cardiovascular risk and its determinants.

A *quantitative* cardiovascular risk/benefit assessment should be a routine component of quality clinical practice. "It is time for terms such as hypertension and hypercholesterolemia to be removed from our clinical vocabulary." The next generation of primary care clinicians should treat risk, not risk factors.

Moderate reductions of several risk factors can be more effective in prevention than major reductions in one. Treat the patient, not the blood pressure—not the cholesterol.

Lancet January 29, 2005; 365: 434-41 "Treating individuals", commentary, first author Rod Jackson, University of Auckland, New Zealand.

I believe, with the necessary aid of computers, primary care is moving closer to judging individual patient's absolute risk of disease, and acting on multiple risk factors, not emphasizing only one or two. (For a beginning effort to assess multiple risks see www.yourdiseaserisk.harvard.edu.)

We should eventually be able to tell a patient—"Mr Jones, according to the latest scientific data, your chance of having a heart attack or stroke in the next 5 years is one in W. You can reduce this risk to one out of X by lifestyle changes and drug therapy. Over 5 years you will run the risk of having a serious adverse event due to the drugs of one in Y. Over 5-years this will cost you $Z. Is this worth it to you?

We cannot, and should not, tell a patient on the basis of relative risk studies--"Mr. Jones, your risk of having a heart attack will be lowered by 30% if you lower your cholesterol to 150".

There is a corrrelary regarding risks of adverse drug effects. Consider the recent Cox-2 turmoil. There may be, in large groups of patients, a small increase in relative risk of stroke and myocardial infarction in those taking *Vioxx*. But, the risk does not apply equally to all. It will be higher in those with more CVD risk factors. Some will be at very low risk.

In addition to lowering multiple modifiable risk factors, there are other applications which will lower risk. Adding external protective factors such as exercising more; drinking a glass of wine daily; and eating nuts, fish, and fruit and vegetables regularly will lower risk still farther. (See "The Polymeal" *Practical Pointers* December 2004 [12-4].

The approach focusing on reduction of multiple risk factors is not new. This is the most convincing paper on the subject I have read. I believe this concept points to the future.

Guidelines continue to treat BP and lipid levels, *not* individual patients with varying risk factors.

==========

Why do we Underuse Treatments That are Beneficial in Trials?

1-2 EXTERNAL VALIDITY OF RANDOMIZED CONTROLLED TRIALS: To Whom do the Results of this Trial Apply?

(*This is the first of a series of 5 articles concerning application of trial data to individual patients.)*

Randomized controlled trials **(RCTs)** and systematic reviews must be *internally* validated. (Ie, the design and conduct of RCTs must keep the possibility of bias to a minimum. To be clinically useful, however, the results must be relevant to a definable group of patients in a particular clinical setting. This is termed *external validity*, applicability, or generalizability. How should the results best be used in practice? There are no accepted guidelines on how external validity of RCTs should be assessed.

The most frequent criticism by clinicians of RCTs, systematic reviews, and guidelines is the lack of external validity. This explains the widespread underuse in routine practice of treatments that are beneficial in trials and recommended by guidelines. The external validity of an RTC depends on whether the outcomes are *clinically* relevant. Indeed, RCTs often do lack external validity. The aim of RCTs is not to measure the benefit that will be derived from treatment in clinical practice. Assessment of external validity requires clinical rather than statistical expertise.

RCTs should be designed and reported in a way that allows clinicians to judge to whom they can reasonably be applied.

The response to, and compliance with, treatment can be influenced strongly by the doctor-patient relationship, placebo effects, and patient preferences. The importance of these factors outside of trials should not be underestimated. Note the popularity of “alternative” therapies in which such factors are the only active ingredients.

RCTs and systematic reviews cannot be expected to produce results that are directly relevant to all patients in all settings. To be externally valid they should at least be designed and reported in a way that allows patients and clinicians to judge to whom they can reasonably be applied.

Lancet January 1, 2005; 365: 82-93Commentary by Peter M Rothwell, Radcliffe Infirmary, Oxford, UK

==========

Is the Evidence “Generalizable” to my Patient?

1-3 EVIDENCE-BASED PRACTICE AND THE INDIVIDUAL

(*This essay comments on the 5-part series in the Lancet which concerns applying trial data to individual patients.*)

Focus on the individual is central to the development of evidence-based practice.

It can be tempting to consider the application of trial data in rigid terms. “Could my patient have been randomized in this trial?” If so, the results of the trial may be applicable; if not they may not be applicable.

A more matter-of-fact approach to clinical complexity may be to ask—Is my patient so different from those in the trial that its results cannot help me make my treatment decision? The more family practitioners feel they know their patient, the less likely they are to apply external evidence to guide management. How can the clinician be guided through this dilemma and be assisted in applying personal experience, patient’s preferences, local resources, and valid evidence to make the best recommendations for care?

Trialists and journals should embrace clinically significant outcomes that are meaningful to patients, their attendants, and care organizations. Disingenuous surrogate markers and misleading composite outcomes may create good advertising material, but should not obscure data and hinder genuine patient-centered care.

Let us not neglect the central role of individual patients as decision-makers in their own care. “It is the responsibility of healthcare workers to communicate objective evidence in a manner which allows recipients to make an informed choice, and then to respect that choice.”

“Now and then, clinicians will have to accept and explain that uncertainty is an inherent facet of the uniqueness of human nature. Evidence helps to quantify that uncertainty, but cannot remove it.”

Lancet January 1, 2005; 365: 13-14 Comment by William Summerskill, The Lancet, London, UK

==========

If Confirmed, This Represents An Enormous Public Health Benefit.

1-4 FOLATE INTAKE AND THE RISK OF HYPERTENSION AMONG U.S. WOMEN

Oral folic acid supplementation improves endothelial function. Folate may have beneficial effects on blood pressure by increasing nitric oxide synthesis in endothelial cells, and by reducing plasma homocysteine levels. (Homocysteine by itself can cause endothelial cell injury.)

This study assessed the association of folate intake with incident hypertension in 2 large groups of women.

Conclusion: Higher total folate intake was associated with decreased risk of *incident* hypertension.

STUDY

1. The Nurses’ Health Study prospectively followed 2 cohorts of women: 1) over 93 000 younger women (age 27 to 44 at baseline), and 2) over 62 000 older women (age 43 to 70 at baseline).
2. None had a history of hypertension.
3. A food frequency questionnaire obtained information on dietary and supplemental folate intake. This allowed calculation of total folate intake.
4. Main outcome measure = relative risk of incident self-reported hypertension during 8 years of follow-up related to folate intake.

RESULTS

1. Younger women (mean age 36 at baseline):
   Identified 7373 incident cases of hypertension (8%) over 8 years.
   Subjects whose daily consumption was at least 1000 ug of total folate (diet + supplement) had a relative risk (**RR)** of developing hypertension of 0.54 compared with women who consumed less than 200 ug daily.
   Absolute risk reduction of incident hypertension was about 8 cases per 1000 person-years.
2. Older women (mean age 55 at baseline):
   Identified 12347 incident cases of hypertension (19%) over 8 years.
   Relative risk of hypertension (1000 ug folate daily *vs* less than 200 ug) = 0.82.
   Absolute risk reduction of incident hypertension was about 6 per 1000 person-years.
3. The recommended folate intake in the USA is 400 ug per day. When those taking 1000 ug or more per day were compared with those taking up to 400 ug, subjects taking 1000 ug had a significant reduction in risk of

incident hypertension. (RR = 0.60 for younger women and 0.87 for older). (*Ie, there may be benefit in raising daily intake above the RDA of 400 ug. RTJ*)

4. In the group of women whose dietary folate was low (less than 200 ug), those who took supplements to raise intake to 800 ug had a RR of hypertension of 0.55 (in younger women) and 0.61 (in older women).
5. In the women who took no supplements and whose daily food folate was at least 400 ug, the RR of developing hypertension was 0.87 compared with those ingesting 200 ug or less.
   (*Ie, the present food fortification program may be beneficial. RTJ*)

DISCUSSION

1. After controlling for a large number of covariates, this prospective study found that higher folate intake was significantly associated with a reduced risk of developing hypertension over an 8-year period.
2. The inverse relationship was robust even after changing the upper limit of the reference group from 200 ug to 400 ug. (*Ie, the present recommended daily allowance may be too low to obtain maximum benefits. RTJ*)
3. The most significant relationship was associated with supplemental (not dietary) folate intake. (Bioavailability of supplemental folate is twice that of food folate.)
4. Younger women achieved the most benefit. Younger women whose intake was at least 1000 ug experienced 1/3 the risk of developing hypertension over 8 years. (*Ie, start supplementation early. RTJ*)

CONCLUSION

1. Higher intake of folate was associated with a decreased risk of incident hypertension, especially in younger women. Supplemental folate was independently beneficial.

JAMA January 19, 2005; 293: 320-29 Original investigation, first author John P Forman, Harvard Medical School, Boston Mass.

==========

Aromatase Inhibitor Safer and More Effective Than Tamoxifen

1-5 RESULTS OF THE ATAC (ARMIDEX, TAMOXIFEN, ALONE OR IN COMBINATION) TRIAL OF 5 YEARS' ADJUVANT TREATMENT FOR BREAST CANCER

The standard adjuvant endocrine treatment for post-menopausal women with hormone-receptor-positive localized breast cancer **(BC)** is 5 years of tamoxifen. Recurrence of BC and adverse effects restrict its usefulness.

This study compared the aromatase inhibitor anastrozole with tamoxifen over 5 years. (*This is a preliminary fast-tracked report.*)

Conclusion: Compared with tamoxifen, anastrozole was associated with greater benefits and fewer adverse effects.

STUDY

1. Double-blind, randomized trial compared tamoxifen alone with anastrozole alone. (*It also presented a subset of tamoxifen* + anastrozole *vs tamoxifen alone. I omit this data because there was no advantage over anastrozol alone.)*
2. Randomized over 6000 women to either 1) tamoxifen or 2) anastrozole. All were postmenopausal. All had localized BC.
3. Followed for a median of 68 months.

RESULTS

1. Anastrozole led to significant improvements compared with tamoxifen for disease-free survival, and time-to recurrence, especially in women whose BC was hormone-receptor-positive. Benefits were also demonstrated in hormone-receptor-negative patients.
2. Benefits were therefore *in addition* to the risk reduction previously shown in tamoxifen *vs* placebo trials. (*Ie, anastrozole vs placebo would have shown greater absolute benefits compared with tamoxifen vs placebo*)
3. Benefits of anastrozole were seen at all times after the first year.
4. The incidence of contralateral BC was substantially reduced by anastrozole as compared with tamoxifen. (This was also an improvement over the benefit of tamoxifen alone vs placebo as demonstrated in previous studies.)
5. A slight decrease in death from BC was present in the anastrozole group. (*Not statistically significant possiblydue to the short period of observation*.)
6. Since almost all patients had completed the scheduled course of 5 years, safety and tolerability can be deemed final:

    Withdrawals were significantly fewer in the anastrozole group (11% vs 14%).

    Drug-elated serious adverse events were also fewer (5% vs 9%)
7. Compared with tamoxifen, anastrozole was associated with significant reductions in endometrial cancer, thromboembolic events, ischemic cerebrovascular events, vaginal bleeding, and hot flushes.
8. Arthralgias and fractures were more frequent in the anastrozole group. (*The authors suggest concomitant bisphosphonate therapy because of this finding*.)

DISCUSSION

1. “This analysis…confirms the efficacy and tolerability of anastrozole as *initial* adjuvant treatment for postmenopausal women with localized breast cancer.”

2. Results of other studies evaluating anastrozole or exemestane (another aromatase inhibitor) after 2 to 3 years of adjuvant tamoxifen, suggest it is reasonable to switch patients currently on tamoxifen to an aromatase inhibitor. It is not appropriate to wait until after a 5-year period of treatment with tamoxifen. The most effective and well-tolerated therapy should be offered at the earliest opportunity.

CONCLUSION

Anastrozole should be considered the preferred initial adjuvant endocrine therapy for post-menopausal women with hormone-receptor positive localized BC.

Lancet January 1, 2005; 365: 60-62 "Research Letter", peer-reviewed, fast-tracked for early publication by the ATAC Trialists' Group, Anthony Howell, chairman of the steering committee, Christie Hospital, Manchester UK

==========

Proposing an ABCDE Memory Device to Simplify Adherence to Guidelines

1-6 A SIMPLIFIED APPROACH TO THE MANAGEMENT OF NON-ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROMES

Implementation of guidelines for treatment of non-ST-elevation acute coronary syndromes (**NSTE-ACS**) remains suboptimal. This article attempts to simplify guidelines by proposing a modification of the "ABC" approach that incorporates risk reduction, lifestyle changes, and medical therapies that can be easily used by primary care clinicians.

Many physicians consider guidelines too lengthy and complex.

Conclusion: An "ABCDE" approach is presented based on a systematic-review evidence of efficacy.

STUDY

1. NSTE-ACS is a comprehensive term that combines two entities: 1) unstable angina and 2) non-ST-elevation myocardial infarction. It is part of a continuum of disease processes resulting from reduced coronary blood flow due to plaque disruption and subsequent thrombus formation.
2. It should be differentiated from ST-segment-elevation myocardial infarction (**STE-MI**). The treatment differs. STE-MI is typically characterized by complete thrombotic occlusion and is generally treated with immediate reperfusion therapy. NSTE-ACS usually results from a transiently or nearly occluded vessel and may or may not require revascularization. Anti-ischemic and anti-thrombotic therapy is recommended for all with NSTE-ACS
3. The study assembled a comprehensive plan through an "ABCDE" approach. The intention was to provide an overview of therapies and lifestyle changes that are clinically useful for patients with NSTE-ACS.

RESULTS

1. Elements of the plan:
   - A Antiplatelet; Anticoagulation; ACE inhibitors; Angiotensin II blockers.
   - B Beta-blockers; Blood pressure control
   - C Cholesterol management; Cigarette cessation
   - D Diet; Diabetes management
   - E Exercise.
2. Antiplatelet:

   Aspirin given immediately and continued indefinitely

   "Most patients with NSTE-ACS who are at low bleeding risk should have clopidogrel (*Plavix*) added to aspirin at hospitalization with continuation for up to 12 months."

3. Anticoagulation:

Patients managed with an early conservative strategy should receive anticoagulation.

Low-molecular-weight heparin (LMWH; specifically enoxaparin) should be preferred.

4. ACE-inhibition:

All with left ventricular systolic dysfunction, heart failure, hypertension, or other high-risk factors. No preferred agent

5. Angiotensin II blockers:

All who are intolerant to ACE-inhibitors.

6. Beta-blockade:

All patients. No preferred agent.

7. BP control:

ACE-inhibitors and beta-blockers first line drugs. Goal < 130/85; lower if diabetes or renal disease.

8. Cholesterol treatment:

All patients. Start immediately with high-dose statin. Goal LDL-c under 70.

9. Cigarette cessation:

Long-term behavioral support. Buproprion (*Wellbutrin*; *Zyban; generic*) + nicotine replacement

10. Diet:

Weight reduction. Modification to control lipids. Salt restriction.

11. Diabetes management:

HbA1c under 7% at a minimum.

12. Exercise:

Aerobic and weight bearing 4-5 times weekly for > 30 minutes, preferably within a cardiac rehabilitation program.

CONCLUSION

This practical approach to NSTE-ACS allows physicians to more effectively create disease management protocols, define roles and responsibilities for different medical personnel, and ensure implementation of evidence-based short- and long-term medical and risk-reducing strategies.

JAMA January 19, 2005; 293: 349-57 "Clinical Review". First author Ty J Gluckman, Johns Hopkins Hospital, Baltimore MD

==========

Adherence was Poor. Those Who Adhered for One Year Lost Weight

1-7 COMPARISON OF THE ATKINS, ORNISH, WEIGHT WATCHERS, AND ZONE DIETS FOR WEIGHT LOSS AND HEART DISEASE RISK REDUCTION

Popular diets are becoming more controversial. More than 1000 diet books are now available. Many popular diets depart substantially from mainstream medical advice.

Some (eg, Weight Watchers) are based on long-standing medical advice which recommends restriction of portion sizes and calories. The Atkins diet minimizes carbohydrate intake. Ornish recommends fat restriction. Zone recommends modulation of macronutrients and glycemic load.

This study assessed adherence rates and effectiveness of the 4 diets in producing weight loss and reducing cardiac risk factors.

Conclusion: Over 1 year, overall adherence rates were low for all 4 diets. For adherents, all diets resulted in weight loss and reduction in cardiovascular risk factors.

STUDY

1. Recruited and followed 160 subjects (mean age 49) to an intention-to-treat analysis. Almost all were obese. (Mean BMI 35)
2. Randomized equally to each of the 4 diets:

Atkins	Low carbohydrate—20 g carbohydrate daily
Zone	High protein, low glycemic load
Weight Watchers	Balanced diet—total daily ”points” in a range determined by current weight (Aimed for 24 to 32 points daily.)
Ornish	Low fat, vegetarian diet containing 10% of calories as fat.

3. Subjects received diet-specific instruction 4 times during the first 2 months. Thereafter they were on their own.
4. The study addressed only the dietary component, not any other specific components of the program.
5. Followed for 1 year.

RESULTS

1. About half of the subjects in each group failed to complete the 1-year course. The most common reasons were “too hard to follow” and “not yielding enough weight loss”. Adherence was particularly low for Atkins and Ornish.
2. Overall, the *mean* weight loss at one year varied from 2.1 kg (Atkins) to 4.9 kg (Weight Watchers) [This assumed no change from baseline among those who discontinued.]
3. Completers lost more at 1 year. (-3. 9 kg for Atkins and -6.6 kg for Ornish)
4. Each diet significantly reduced LDL/HDL-cholesterol ratio by about 10%. The Atkins diet did not lower LDL-cholesterol significantly. The Ornish diet did not increase the HDL-cholesterol. No diet significantly altered triglyceride levels.
5. No significant effect on glucose levels or on BP.
6. Reductions of total cholesterol, C-reactive protein, and insulin levels were significantly associated with the degree of weight loss.

DISCUSSION

1. A variety of popular diets can reduce weight and several cardiac risk factors under realistic conditions. But only about half of the subjects in this study sustained a high adherence level.

2. The authors suggest that one way to improve dietary adherence in clinical practice may be to use a broad spectrum of diet options to better match individual patient's food preferences, lifestyles, and cardiovascular risk factors. They suspect adherence would have been better if subjects had been given the option to choose their diet.
3. Low carbohydrate diet was no better than other diets.
4. In the long run, sustained adherence rather than the diet type was the key predictor of weight loss and risk reduction.

CONCLUSION

Poor adherence rates were evident for all 4 diets. In adherent subjects all diets resulted in modest weight loss and reduction in cardiovascular risk factors.

JAMA January 5, 2005; 293: 43-53 Original investigation, first author Michael L Dansinger, Tufts New England Medical Center, Boston, Mass.

An editorial in this issue of JAMA by Robert Eckel, University of Denver, Colo. comments:

There is insufficient knowledge about mechanisms for recidivism in obesity. One factor may be that, once weight loss of more than several kilograms occurs, a substantial step-up in the amount of physical activity is required to maintain the loss and to continue losing. In addition, continuing and more conscientious attention to the weight-loss program is required.

What is truly needed now is evidence that weight loss by diet (and exercise and behavioral modification) along with risk factor improvement can be achieved and maintained for 10 years, and hard outcomes such as risks of death, myocardial infarction, cancer, and stroke can be improved.

Meanwhile, the best evidence points toward a modest persistent restriction in calories with higher intake of fruits, vegetable, fish, and whole grains along with modest increase in physical activity.

==========

A Particularly Ominous Public Health Issue

1-8 FAST-FOOD HABITS, WEIGHT GAIN, AND INSULIN RESISTANCE

About two out of every three US adults were overweight or obese in the year 2000. Rates were even higher in minority groups.

The associated rising prevalence of glucose intolerance and type 2 diabetes is a particularly ominous public health issue.

One potentially important associated dietary factor is consumption of fast-foods (defined as convenience food purchased in self-service or carry out eating places.) (*Name your own. RTJ*) Consumption of fast food by children has risen from 2% of total energy intake in 1970 to 10% in the 1990s. Several factors inherent to fast food could promote a positive energy balance: excessive portion size (single meals often approach individual daily energy requirements); palatability; emphasis on primordial taste preferences for sugar, salt, and fat; high energy density; and high glycemic load.

Trans fat and glycemic load might also enhance risk of type 2 diabetes through energy-independent mechanisms.

This study investigated the association between fast-food habits and changes in body weight and insulin resistance over a 15-year period.

Conclusion: Fast-food consumption was positively associated with weight gain and insulin resistance.

STUDY

1. Multicenter prospective study included over 3000 young adults (age 18-30; mean = 25 at baseline) in 1985-86.
2. Questionnaires assessed the frequency of fast-food restaurant visits at baseline and follow-up.
3. Correlated fast-food visits with changes in weight and insulin resistance. Insulin resistance was measured by a product of glucose concentration (mmol/L) times insulin levels (mU/L).
4. Also assessed total physical activity and TV watching.
5. Follow-up = 15 years.

RESULTS

1. At baseline:
   - Weekly visits to fast-food restaurants = 2.4 for men and 1.7 for women. Younger subjects made more visits.
   - There was a direct and independent monotonic association between fast-food frequency and weight and insulin resistance. Subjects who visited three times a week had a mean weight about 2 kg higher than those who visited less than once a week.
2. Over 15 years:
   - Fast-food visits increased over 15 years in those with high frequency of visits at baseline.
   - Frequent visitors gained more weight compared with those who visited less than once a week.
   - Insulin resistance was directly associated with visits of 3 times a week.
   - Compared with subjects whose fast-food visits were less than once a week, those who visited over 2 times weekly gained an extra 4.5 kg and had a 104% greater increase in insulin resistance.
3. This association was especially strong among the least physically active subjects.

DISCUSSION

1. At baseline, there was a direct and independent monotonic association between fast-food frequency and weight and insulin resistance.
2. Over 15 years, in young adults living in the USA, there were strong positive associations between frequency of visits to fast-food restaurants and increases in bodyweight and insulin resistance, two major risk factors for type 2 diabetes.
3. The large portion size is the most obvious aspect of fast food that might lead to weight gain.
4. Fast food also contains large amounts of partially hydrogenated oils which are associated with insulin resistance. They also contain large amounts of highly refined starchy food and added sugar, carbohydrates that have a high glycemic index.

CONCLUSION

Fast-food habits have strong, positive and independent association with weight gain and insulin resistance in young adults. This suggests an increased risk of type 2 diabetes and obesity.

Lancet January 1, 2005; 365: 36-42 Original investigation by the Coronary Artery Risk Development in Young Adults (CARDIA) study, first author Mark A Pereira, University of Minnesota, Minneapolis.

==========

Stool Antigen Test is Recommended

1-9 TEST AND TREAT FOR DYSPEPSIA: But Which Test?

The National Institute for Clinical Excellence **(NICE)** of the UK recommends that patients with *persistent or recurrent uncomplicated dyspepsia* should have a non-invasive test for *Helicobacter pylori*. If the test is positive they should receive eradication (triple antibiotic) therapy.

With a policy requiring non-invasive testing and treatment we need the use of an accurate test so that the patients receive the correct treatment. The urea breath test and serology were the first non-invasive tests available. The specificity and sensitivity of the breath test are high, but the test is time consuming and requires two breath samples taken 20 minutes apart. Serology is less accurate.

Now the stool antigen test is available. It detects *H pylori* antigens passed in feces. A commercial monoclonal antibody test is available. It is reported to be as accurate as the urea breath rest. It can be introduced with ease into routine laboratory practice. It is less expensive and less time consuming than the urea breath test. It is useful also in confirming eradication of the infection.

In developed countries, where typically 25% of dyspeptic patients are *H pylori* positive, only 3% will be false positive on the stool antigen test and receive unnecessary antibiotics. (The serologic test is associated with many more false positives.)

"We need to have an easy, accurate diagnostic test and the stool antigen test is just that."

BMJ January 15, 2005; 330: 105-06 Editorial, first author Cliodna McNulty, Gloucestershire Royal Hospital, Gloucester, UK

The editorial cites a helpful web site for guidelines for dyspepsia: www.sign.ac.uk/pdf. This refreshed my memory regarding some clinical points for dyspepsia:

Definition: Dyspepsia is a symptom, not a disease—pain or discomfort centered in the upper abdomen. (Ie, in or around the midline.) Pain in the right or left hypochondrium is not considered. "Discomfort" refers to subjective symptoms the patient does not consider painful: fullness, early satiety, belching, nausea, retching, and/or vomiting.

Functional dyspepsia is defined in patients in whom no organic disease can be demonstrated.

Uncomplicated dyspepsia refers to dyspepsia not accompanied by alarm features or NSAID use.

Management for patients under age 55 who have disturbing, persistent, and recurring functional dyspepsia:

The strategy of "test and treat" is recommended - ie, treat without endoscopy. If *H pylori* positive by a non-invasive test, treat with a course of antibiotics.

Advantages:

Will treat an unsuspected peptic ulcer. And reduce risk of subsequent ulcer disease.

Will reduce or eliminate symptoms in some patients (~ 10%). Eradication will remove symptoms in only a small percentage of patients with dyspepsia.

Remove a risk factor for gastric cancer.

Other therapy:

Diet. No evidence in favor of special diets. Recommend the usual healthy, balanced diet.

Stop smoking. Take only moderate amounts of caffeine and alcohol.

Drug therapy. There is a substantial placebo response. A trial of acid suppression may be considered. Response is variable. For antacids and prokinetics there is no evidence of efficacy.

Inform patients:

When no disease or abnormality has been found.

Functional dyspepsia is not by itself serious, although the symptoms are real and may be disturbing.

It is not caused by gastric hypersecretion of acid. Acid secretion is usually normal.

It is not caused by food allergy or sensitivity. No specific diet or restriction is required. Nevertheless, avoid foods you that upset you.

These applications differ for older patients. Look more carefully for organic disease.

I would not dissuade use of antacids, acid-suppressing drugs or changes in food intake according to individual patients' judgment.

==========

Physician's Power Can be Enhanced, Diminished, Used Well or Ill, but It Cannot be Disowned.

1-10 CONSENT OR OBEDIENCE? Power and Authority in Medicine

This essay considers the role of inappropriate obedience as a source of abuse in the teaching hospital and the effect of obedience on patients' autonomy and consent.

Patients provide consent not only about big issues, but, in the course of an illness, sick patients consent innumerable times to interventions that they would rather not undergo.

Serious illness is marked by losses of normal function in many dimensions of existence, including the ability to reason and to act (without which "autonomy" loses meaning). Sick patients do not reason their way to decisions based on their appraisals of the relevant information, but because an authority helps them to decide.

A power comes from the hospital setting and the trappings of medical authority. "Such power can be enhanced, diminished, used well or ill, but it cannot be disowned."

Bearing in mind the effect of sickness on function, we should accept the propensity of sick patients to seek our approbation, celebrate our expertise, and acknowledge the legitimacy of our authority by doing as they think we wish. These tendencies present us with difficult responsibilities.

"The biggest thief of autonomy is sickness."

I enjoyed this thoughtful essay.

We live in a world in which authority leads multitudes to follow blindly and commit unspeakable atrocities. The resistance of one man is a badge of courage.

I believe physicians apply their power to some extent in every patient encounter. Physicians, wield your power carefully and always with the aim of benefit to the patients.

==========

The USPSTF Now Recommends One-Time Screening in Select Subsets of Men

1-11 SCREENING FOR ABDOMINAL ANEURYSM

The U.S. Preventive Services Task Force **(USPSTF)** now recommends one-time ultrasonographic screening for abdominal aortic aneurysm **(AAA)** for men ages 65 to 75 who presently smoke or who have smoked in the past.

The task force found good evidence that screening and surgical repair of large AAAs (5.5 cm an over) leads to decreased AAA-specific mortality.

One-time screening is sufficient.

The task force makes no recommendation for or against screening men who have never smoked. It recommends *against* routine screening for women. In general, women and men under age 65 and adults who have never smoked are at low risk. The increased presence of co-morbid conditions for people over age 75 decreases the likelihood that they will benefit from screening.

There is only a modest association between risk factors for atherosclerotic disease and AAA.

In men age 65-75 who have smoked or continue to smoke, an estimated 500 would need-to-be-screened to prevent one AAA-related death over the next 5 years.

Clinical judgment guides screening in other individuals.

For AAAs 4.0 to 5.4 cm, periodic surveillance offers comparable mortality benefits compared with elective surgery, with the benefit of fewer operations. Most authorities also recommend periodic surveillance for those with AAAs 3.0 to 3.9 cm.

Annals Int Med February 1, 2005; 142: 198-202 “Clinical Guidelines” by the U.S. Preventive Services Task Force. www.preventiveservices.ahrq.gov

==========

One or Two Drinks a Day May Decrease the Risk of Cognitive Decline.

1-12 EFFECTS OF MODERATE ALCOHOL CONSUMPTION ON COGNITIVE FUNCTION IN WOMEN.

Habitual excess alcohol consumption impairs the brain.

This study asks—What is the effect of *moderate* consumption of alcohol on cognition? A benefit is plausible considering the strong link between moderate alcohol and decreased risk of cardiovascular disease. Cognitive impairment and cardiovascular disease share common risk factors.

Moderate alcohol consumption has been related to a decreased risk of both vascular and non-vascular dementia.

Conclusion: In women, one or two drinks a day may decrease the risk of cognitive decline.

STUDY

1. The Nurses' Health Study evaluated cognitive function in over 12 000 women age 70-81 (mean = 74) at baseline. Followed over 11 000 for two years. Participants were community dwellers without a history of stroke.
2. Determined the level of alcohol consumption at baseline.
3. At baseline, calculated mean global cognitive scores by a cognitive status score based on the Mini-Mental State Examination and memory tests of immediate and delayed recall.
4. Correlated degree of cognitive impairment related to level of alcohol consumption.
5. Also calculated the mean decline in cognitive function over 2 years related to alcohol consumption.

RESULTS

1. Compared with abstainers, moderate drinkers (less than 15 g alcohol per day; one drink) had better mean cognitive scores. (Relative risk of impairment = 0.81 based on a global cognitive score.)
2. Also, compared with abstainers, moderate drinkers (15 to 30 g per day) had a reduced relative risk of cognitive impairment (although slightly less favorable, with wider confidence intervals).
3. Over a 2-year period, relative risk of decline in cognition was 0.85 in moderate drinkers compared with abstainers.
4. No significant differences according to the type of alcoholic beverage consumed.

DISCUSSION

1. "We found that older women who consumed up to one drink per day had consistently better cognitive performance than non-drinkers."
2. Women who drank up to 15 g alcohol per day (one drink) had a decrease in risk of cognitive impairment of 20% compared with abstainers. They were also less likely to experience a decline in cognitive function over a 2-year period.
3. The relationship was similar for all types of alcohol.
4. Several mechanisms for the benefit have been proposed. The most plausible relates to the consistently lower rates of cardiovascular disease among moderate drinkers. This has been attributed to a higher HDL-cholesterol and reductions in fibrinogen and other thrombotic factors. This helps preserve brain vasculature.
5. Another study reported that older persons without cerebrovascular disease who drank moderately had fewer white-matter infarcts on MRI.

CONCLUSION

In older women consumption of one alcoholic drink per day did not impair cognitive function, and may actually decrease risk of cognitive decline.

NEJM January 20, 2005; 352: 245-53 Original investigation, first author Meir J Stamfer, Harvard Medical School, Boston, Mass.

==========

Statins Reduce C-Reactive Protein Levels Independently of LDL-Cholesterol

1-13 STATINS FOR ATHEROSCLEROSIS—Autoimmunity, Inflammation, and C-reactive Protein.

Inflammation is a notable component of the atherosclerotic process.

Statin drugs, in addition to inhibiting synthesis of cholesterol, now appear to directly inhibit inflammation. The list of disorders for which statins might prove beneficial is growing and now extends from multiple sclerosis and neurodegenerative disorders to rheumatoid arthritis and systemic lupus.

Recent studies have revealed the multiple immunologic actions of statins. The immune modulator interferon gamma is now generally accepted as directly promoting atherosclerosis. Statins inhibit its action.

The immunomodulatory effects of statins apply to cardiovascular disease, in which immune dysregulation is observed. “Indeed, the inflammatory component of atherosclerosis, characterized by increased production of interferon-gamma by T cells has led immunologists to suggest that atherosclerosis should be added to the list of organ-specific autoimmune diseases.”

Two articles in this issue of NEJM [1,2] confirm that reducing the inflammatory component of cardiovascular disease with statin therapy improves clinical outcomes independently of the reduction in cholesterol. Both studies found that the statin-induced decrease in C-reactive protein (**CRP**), a marker of inflammation, is only weakly correlated with changes in lipid levels.

Only by assaying both C-reactive protein and cholesterol can the full effect of statins be identified.

NEJM January 6, 2005; 352: 73-74 Editorial, first author Michael R Ehrenstein, University College, London, UK

1 “C-reactive Protein Levels and Outcomes after Statin Therapy” NEJM January 6, 2005; 352: 20-28 original investigation, first author Paul M Ridker, Harvard Medical School, Boston Mass

Statins have a remarkable ability to lower CRP levels. Patients with acute coronary syndromes who achieve low CRP levels from statin therapy had better clinical outcomes than those with higher levels.

The LDL-c lowering effect of statins and their effect on lowering CRP are largely independent of each other. Patients achieving the lowest CRP levels through statin therapy had a higher event-free survival at all levels of LDL cholesterol.

The authors suggest that CRP should be monitored when stain therapy is employed.

2 “Statin Therapy, LDL-Cholesterol, C-Reactive Protein, and Coronary Artery Disease” NEJM January 6, 2005; 352: 29-38 Original investigation, first author Steven E Nissen, Cleveland Clinic Foundation, Cleveland Ohio

This study reports a reduced rate of progression of coronary atherosclerosis associated with intensive statin therapy. This was related to reductions in levels of CRP as well as LDL-cholesterol.

==========

Development May be Delayed by Good Glycemic Control and Modification of Cardiovascular Risk Factors.

1-14 VASCULAR RISK FACTORS AND DIABETIC NEUROPATHY

Diabetic neuropathy (**DN**) is a common cause of morbidity and death among patient with diabetes. Other than glycemic control, there are no treatments for DN. Thus, identifying potentially modifiable risk factors for neuropathy is critical.

The duration and level of hyperglycemia are important determinants of micro-vascular complications, including DN.

The Diabetes Control and Complications Trial reported a 60% reduction in DN in the intensively treated group at 5 years. But the incidence still remained substantial. This suggests that DN can develop despite intensive control of glucose levels. Risk factors other than glucose are involved. The relative effects of cardiovascular risk factors (hypertension, dyslipidemia, overweight and obesity, and smoking) are not fully understood.

This study assessed potentially modifiable risk factors for development of distal, symmetric DN.

Conclusion: Dyslipidemia, elevated BMI, smoking, and hypertension were associated with development of DN.

STUDY

1. Prospectively followed over 1100 patients with type 1 diabetes for 7 years. Mean age of subjects was about 30; mean duration of DM = 13 years. None had DN at baseline.
2. Used a standard protocol for diagnosis: clinical evaluation, quantitative sensory testing, and autonomic function tests.
3. Clinical evaluation included symptoms of "asleep, numbness or "dead feeling" in the feet, prickling sensation in the feet, deep aching or burning pains in the legs, unusual difficulty in climbing stairs, difficulty with bladder control, and nocturnal diarrhea.
4. Vibration perception was tested by a special "biothesiometer".
5. Autonomic function assessed by cardiovascular reflex responses. (Eg, change in heart rate and BP on standing)
6. Neuropathy was diagnosed in patients with two or more of these factors:
   - Two or more symptoms
   - Absence of two or more reflexes of ankle and knee tendons
   - Abnormal vibration-perception threshold. (A common manifestation)
   - Abnormal autonomic function.

RESULTS

1. Over 7 years, DN developed in 23% of the subjects who were without DN at baseline.
2. Cumulative incidence was related to higher glycosylated hemoglobin values and longer duration of diabetes.
3. After adjustment for the preceding, other factors were significantly associated with cumulative incidence of DN:
   - Higher levels of LDL-cholesterol
   - Higher levels of triglycerides
   - Higher BMI
   - Hypertension
   - Smoking
4. Cardiovascular disease at baseline was associated with double the risk of neuropathy.

DISCUSSION

1. Over 7 years, about ¼ of patients in their early 30s with type 1 diabetes developed DN.
2. DN more likely developed in those with longer duration of diabetes.

3. DN more likely developed in patients with higher HbA1c levels at baseline and in those whose HbA1c rose during the observation period.
4. Cardiovascular disease presence at baseline was related to a much higher risk of DN.
5. Cardiovascular risk factors (hypertension, smoking, obesity, and dyslipidemia) also related to increased incidence of DN.
6. Mortality in patients with DN is high. The cause is often cardiovascular.
7. What can be done prospectively to try to prevent DN?
   Control glycemia as best it can be controlled
   Stop smoking
   Control BP
   Control weight, obtain lower body mass index
   Reduce other cardiovascular risk factors.
   (*Ie, essentially standard diabetes management*.)

CONCLUSION

Incidence of DN is associated with potentially modifiable cardiovascular risk factors

NEJM January 27, 2005; 341-50 Origin investigation from the EURODIAB Prospective Complications Study Group, first author Solomon Tesfaye, Royal Hallamshire Hospital, Sheffield, UK.

I enjoyed reviewing the diagnosis of neuropathy.

The mean age at baseline was about 30. Of an initial cohort, 28% already had DN. Prospectively, over 7 23% developed DN. Thus, at age 40, over 50% had DN. I would expect almost all patients with type 1 diabetes will eventually develop DN.

==========

Fasting Serum Glucose Level and Diabetes were Associated with Cancer Risk

1-15 FASTING SERUM GLUCOSE LEVEL AND CANCER RISK IN KOREAN MEN AND WOMEN

Is there any connection between diabetes and cancer? Some observational studies have suggested there is. This prospective cohort study investigated this possibility.

Conclusion: In Korea, elevated serum glucose levels and a diagnosis of diabetes were independent risk factors for cancer incidence and cancer deaths.

STUDY

1. A ten-year prospective study enrolled over 829 000 men and over 468 000 women age 30 to 95 at baseline. (Mean = 46; mean body mass index = 23) All had received health care from a national insurance company.
2. Their biannual health examinations included a fasting serum glucose.
3. Obtained records every 2 years for 10 years regarding cancer incidence and cancer deaths.

RESULTS

1. Over 10 years there were 20 556 cancer deaths in men (2.5% of cohort) and 5907 cancer deaths in women (1.2% of cohort). And over 37 000 incident cancers in men (4.5%) and over 16 000 in women (3.4%).
2. After adjusting for smoking and alcohol use, the stratum with the highest fasting glucose (> 140) had higher death rates from all cancers compared with the stratum with the lowest level (< 90). Hazard ratio = 1.25
3 Age-adjusted cancer deaths per 100 000 men rose linearly from about 600 in the groups with fasting glucose < 90 to about 1400 per 100 000 in the group with glucose levels above 140. (*Although absolute numbers are low, the linear relationship depicted on page 196 and 200 is impressive. RTJ*). Similar linear increases were recorded in women, although not as high in absolute terms. Incidence of cancer was similar to mortality.
4. The association was strongest for pancreatic cancer. (Hazard ratio = 2 comparing the highest glucose stratum with the lowest.)
5. Significant associations were also found in other cancers (esophagus, colo-rectal, liver, cervix).
6. For persons with a diagnosis of diabetes, or a fasting blood glucose over 125, risks for incidence and mortality from cancer were elevated compared with those without diabetes.

DISCUSSION

1. In Korea, the frequency of obesity is much lower than in the USA. The average BMI of subjects in this study was 23. Only ¼ of these subjects had a BMI over 25.
2."We have shown that fasting serum glucose level and diabetes are associated with cancer risk in a population far leaner than the Western populations."
3. The authors suggest that the mechanism of increased cancer risk is a consequences of hyperinsulinism.

CONCLUSION

In Korea, elevated fasting glucose and a diagnosis of diabetes were independent risk factors for cancer incidence and cancer death. Risk increased linearly as serum glucose rose.

JAMA January 12, 2005; 293: 194-202 Original investigation, first author Sun Ha Jee, Yousei University, Seoul, Korea

==========