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HIGHLIGHTS JUNE 2002

6-1 PHYSICIANS' AND PATIENTS' CHOICES IN EVIDENCE BASED MEDICINE

Clinical decisions must include consideration of: the patient's clinical and physical circumstances to establish what is wrong and what treatment options are available; 2) research evidence concerning the efficacy (as reported in systematic reviews); effectiveness (as applied in the real world of clinical practice) and efficiency (the benefit/harm-cost ratio) of the options; and 3) consideration of the patient's preferences and likely actions (in terms of what interventions she or he is ready and able to accept).

Finally, clinical expertise is needed to bring these considerations together and recommend the treatment that the patient is agreeable to accepting.

The term "evidence based medicine" was developed to encourage practitioners and patients to pay due respect – no more, no less – to current best evidence in making decisions.

Practical point: Best research evidence does not apply to the great majority of individual patients presenting to primary care. Primary care clinicians must deal with a large group of patients as best they can without firm evidence on which to base decisions. The clinician will extrapolate from the evidence, and rely on best clinical judgment, expert doctor-patient communication, and patient preferences.

6-2 PUTTING THE PATIENT IN PATIENT-SAFETY

Medical error has been addressed primarily through malpractice litigation. When in courts, patients rarely speak. They are spoken for.

A study in this issue of JAMA invites physicians to take a step away from the "community of experts" approach to patient safety and move a step closer to the patient. It categorizes complaints as relating to communication, humaneness, care and treatment access and availability, or billing. It finds no category of complaint more likely than any other to predict litigation.

Health care organizations need to elicit patients' stories, capture information relevant to safety, and feed that information back to the professionals who organize and deliver care.

Medical practice can be improved by providing earlier and more reliable warning of problems rather than waiting for suits to be filed. Hospitals must be enabled to learn about *valid* claims from patients whether or not the rarer and more chilling event of formal litigation ensues. "Uncaring medicine is itself bad medicine, something that tends to be overlooked in the rush to achieve technical perfection."

"A small number of physicians experience a disproportionate share of malpractice claims. If malpractice risk is related to factors such as patient dissatisfaction with interpersonal behaviors, care and treatment, and access, it might be possible to monitor physicians' risk of being sued."

Practical point: Establish rapport, provide access, administer care consistent with expectations, and communicate effectively.

6-3 WHEN INCREASED THERAPEUTIC BENEFIT COMES AT INCREASED COST

A study in this issue of NEJM [1] compared cost effectiveness in reducing recurrent cardiovascular events using 1) aspirin alone, 2) clopidogrel alone, and 3) aspirin + clopidogrel. (A secondary prevention study)

The investigators estimated cost effectiveness of the strategies. Given the extraordinarily low cost of aspirin, the estimated cost of each quality-adjusted year of life gained using aspirin alone was $11 000. Clopidogrel alone or in combination would cost $130 000 for each quality-adjusted year of life gained. (*Present cost of one 75 mg tablet of clopidogrel [Plavix] is over $3)* Is the benefit worth the harms and cost?

Practical point: Primary care clinicians must increasingly consider the cost factor in the benefit/harm-cost ratio.

6-4 THERAPY WITH HYDROXYMETHYLGLUTARYL COENZYME-A REDUCTASE INHIBITORS (STATINS) AND ASSOCIATED RISK OF INCIDENT CARDIOVASCULAR EVENTS IN OLDER ADULTS

Use of statins was associated with decreased risk of incident cardiovascular events among elderly adults

Practical point: Age per se in not a contraindication.

6-5 STATIN THERAPY IN OLDER PERSONS: Pertinent Issues

There is growing evidence that LDL-lowering therapy is effective in reducing risk for CHD in older persons. Practical point: statins are recommended for select elderly individuals.

6-6 WHAT WE NEED TO KNOW ABOUT AGE-RELATED MEMORY LOSS

Strategies for maintaining brain health.

Stress reduction

Physical activity

Healthy diet: (Include a daily multivitamin supplement).

Mental activity

Social involvement

Adopt lifestyle measures to reduce risk of atherosclerotic disease in order to protect the cerebrovascular circulation. This includes moderate amounts of alcohol and smoking cessation.

Putative protective factors: NSAIDs, postmenopausal estrogen, statin drugs, and aerobic conditioning.

6-7 GLUCOSE METABOLISM IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION AND NO PREVIOUS DIAGNOSIS OF DIABETES MELLITUS.

Previously undiagnosed diabetes and impaired glucose tolerance are common in patients with AMI. These abnormalities can be detected early. They could be used as early markers of high-risk.

Practical point: Surveillance and treatment of glucose intolerance may improve prognosis in patients with acute myocardial infarction.

6-8 ACARBOSE FOR PREVENTION OF TYPE 2 DIABETES MELLITUS

Acarbose, by reducing glycemic load, delays development of type 2 diabetes in patients with impaired glucose tolerance.

Practical point: Reduce glycemic load to lessen progression of glucose intolerance and risk of diabetes.

6-9 VITAMINS FOR CHRONIC DISEASE PREVENTION IN ADULTS

"Most people do not consume an optimal amount of vitamins by diet alone. Pending strong evidence of effectiveness from randomized trials, it appears prudent for all adults to take vitamin supplements." It is reasonable to consider a dose of two ordinary multivitamins daily for the elderly, especially since there is a high prevalence of suboptimal vitamin D and B12 intake.

Practical point: "We recommend that *all* adults take one multivitamin daily." They are safe and inexpensive. "We recommend multivitamins, rather than individual vitamins, because they are cheaper and simpler to take, and because a large proportion of the population needs supplementation of more than one."

6-10 FOLIC ACID, AGEING, DEPRESSION, AND DEMENTIA

Folates are important for the nervous system at all ages. There is growing evidence of their involvement in the aging brain, especially in mood and cognitive function. Low folate concentrations in serum, red cells, and cerebrospinal fluid, and the associated rise in plasma homocysteine, are associated with depression and dementia. "Some of the deficiency may be related to ageing, some may be secondary to mental illness, and some primary. But, whether it is primary or secondary, open and controlled treatment studies confirm an aetological link with specific effects of the vitamin on mood, drive, initiative, alertness, concentration, psychomotor speed, and social activity."

"Clearly, further clinical trials in precisely defined clinical categories are needed."

Practical point: Daily multivitamin supplement contains RDA amount of folic acid.

6-11 DECISION MAKING WITH CARDIAC TROPONIN TESTS

"Cardiac troponin assays offer clinicians a valuable tool for diagnosing myocardial infarction even at the level of microinfarction."

Cardiac-specific troponins come close to fulfilling many of the criteria for an ideal biologic marker. They convey prognostic information useful in making therapeutic decisions regarding patients with acute coronary syndromes.

Microinfarction can produce elevations of cardiac troponins. Levels can increase without any elevation of creatine kinase MB fraction (CK-MB). Troponins are much more sensitive to damage to small areas of myocardium. Given the nearly absolute specificity of cardiac troponins, they are now considered the preferred biologic markers for diagnosing myocardial infarction

Measurement may be useful for distinguishing unstable angina from MI without ST elevation. About 30% of patients previously considered to have unstable angina on the basis of CK-MB levels are now given a diagnosis of MI without ST elevation on the basis of troponin levels. Troponins also help to establish prognosis, select therapy, and diagnose reinfarction.

Patients with an acute coronary syndrome who are troponin-positive are more likely to have coronary thrombi, to have intermittent showers of emboli in the coronary microvasculature, and to have depressed ventricular function. The benefits of glycoprotein IIb/IIIa inhibitors, low molecular weight heparin, and an early invasive strategy are far greater in troponin-positive patients.

Practical point: Cardiac troponin screening by primary care clinicians may aid diagnosis, triage, and treatment of patients with symptoms suggesting unstable angina and acute myocardial infarction.

6-12 TROPONIN T LEVELS IN PATIENTS WITH ACUTE CORONARY SYNDROMES, WITH AND WITHOUT RENAL DYSFUNCTION

Given that renal dysfunction is common in patients with coronary disease, the ability of cardiac troponin levels to predict outcomes irrespective of creatinine clearance expands their clinical usefulness.

Practical point: cardiac troponin T predicted short-term prognosis in patients with ACS regardless of their level of creatinine clearance.

6-13 SIROLIMUS-ELUTING CORONARY STENTS

A sirolimus-eluting stent, as compared with a standard stent, shows considerable promise for prevention of neointimal restenosis. The gradual elution occurs over a period of 30 days. Only a small quantity of the drug is required. This avoids systematic adverse effects.

Practical point: Primary care clinicians follow developments along with their cardiologist consultants.

6-14 ALVEOLAR AND POSTCRANIAL BONE DENSITY IN POSTMENOPAUSAL WOMEN RECEIVING HORMONE/ESTROGEN REPLACEMENT THERAPY

HRT combined with supplemental calcium and vitamin D, produced significant improvement in oral bone mass.

Practical point: Informing postmenopausal women of this risk may increase compliance with anti-osteoporotic therapy.

6-15 ORAL CONTRACEPTIVES AND THE RISK OF BREAST CANCER

Among women age 35-64, current or former use of OC was *not* associated with a significantly increased risk of BC.

Practical point: Primary care clinicians may reassure patients taking birth control pills.

6-16 LANSOPRAZOLE FOR THE PREVENTION OF RECURRENCES OF ULCER COMPLICATIONS FROM LONG-TERM LOW-DOSE ASPIRIN USE

In patients with *H pylori* infection who had gastric or duodenal ulcer bleeding related to long-term use of low-dose aspirin, treatment with the proton-pump inhibitor, lansoprazole, in addition to eradication of the infection, reduced the rate of recurrence of bleeding despite continuation of aspirin.

Practical point: proton pump inhibitors protect against NSAID-induced ulcers.

6-17 NUT CONSUMPTION AND DECREASED RISK OF SUDDEN CARDIAC DEATH IN THE PHYSICIAN'S HEALTH STUDY

This study suggests that the inverse association between nut consumption and total coronary heart disease death is primarily due to a reduction in risk of sudden cardiac death.

Practical point: nuts are part of the healthy diet.

6-18 RESULTS OF SCREENING COLONOSCOPY AMONG PERSONS 40 TO 49 YEARS OF AGE

Up to 1000 persons this age would have to be screened with colonoscopy to detect one cancer. Sigmoidoscopy would detect about 50% of these.

Practical point: the current recommendations to begin screening at age 50 are unchanged.

6-19 SPIRITUAL BELIEFS MAY AFFECT OUTCOME OF BEREAVEMENT

Absence of spiritual belief may be a risk factor for delayed or complicated grief. People who profess stronger spiritual beliefs seem to resolve their grief more rapidly and completely after the death of a close person.

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The limited applicability of evidence based medicine in primary care

6-1 PHYSICIANS' AND PATIENTS' CHOICES IN EVIDENCE BASED MEDICINE

A criticism directed at evidence based medicine is that it ties the hands of practitioners and robs patients of their personal choices in reaching a decision about optimal care. "There are many barriers to implementing health research in practice, but tying clinical hands and robbing patients of their choices are not among them." Patients' preferences were incorporated into the first model of evidence based medicine.

Clinical decisions must include consideration of: 1) the patient's clinical and physical circumstances to establish what is wrong and what treatment options are available; 2) research evidence concerning the efficacy (as reported in systematic reviews) , effectiveness (as applied in the real world of clinical practice) , and efficiency (the benefit/harm-cost ratio) of the options; and 3) consideration of the patient's preferences and likely actions (in terms of what interventions she or he is ready and able to accept).

Finally, clinical expertise is needed to bring these considerations together and recommend the treatment that the patient is agreeable to accepting.

Decisions may vary from circumstance to circumstance, and from patient to patient with the same circumstances. Achieving the right balance among factors that can affect a decision is not easy. Providing evidence to patients in a way that allows them to make an informed choice is challenging. In many cases it is beyond our current knowledge of doctor-patient communication.

The term "evidence based medicine" was developed to encourage practitioners and patients to pay due respect – no more, no less – to current best evidence in making decisions.

BMJ June 8, 2002; 324: 1350: 1350 Editorial, first author R Brian Haynes, McMaster University Faculty of Health Sciences, Hamilton, Ontario, Canada. **www.bmj.com/cgi/content/full/324/7350/1350**

Comment:

Primary care clinicians face many obstacles when trying to fit an individual patient into the best of evidence based medicine. Consider patients presenting to primary care with a specific problem for which the clinician seeks guidance from evidence based medicine:

Begin with 1000 patients:

> Many will not fit the inclusion criteria; some may be medically illiterate and unable to comply; some will not understand because of language barriers; many who fit the criteria will choose not to participate in the specific treatment advised or will withdraw prematurely; more will withdraw because of adverse effects; some will be unable to continue because of social barriers. (age, infirmity, transport, finances, lack of family support); some will not comply for a variety of other reasons.

Finally, after receiving the treatment recommended by best evidence, the number needed to treat to benefit one patient will be such that the majority will not benefit. (A NNT of 10 to benefit one patient is favorable.) This exposes 9 out of 10 patients to adverse effects and costs of medications without any benefit.

How many patients of the 1000 remain? Very few. The primary care clinician must deal with a large group of individuals for whom recommendations of evidence based medicine cannot be applied. The clinician will then extrapolate from the evidence -- and rely on best clinical judgment, expert doctor-patient communication, and patient preferences. RTJ

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"Establish rapport, provide access, administer care consistent with expectations, and communicate effectively."

6-2 PUTTING THE PATIENT IN PATIENT-SAFETY

For decades, medical error has been addressed primarily through malpractice litigation. When in the courts, patients rarely speak. They are spoken for.

Now, it has become fashionable to think of error prevention as a cooperative, system-based pursuit of improvement rather than identification and discipline of individual bad apples. This process is typically framed as an exclusively professional one. The patient is often the object of discussion, but seldom the discussant.

How does one involve the patient in patient safety? It would help to forge stronger links between the "customer satisfaction" side of health care and the "clinical safety" side. Health care organizations need to elicit patients' stories, capture information relevant to safety, and feed that information back to the professionals who organize and deliver care.

A study in this issue of JAMA [1] invites physicians to take a step away from the "community of experts" approach to patient safety and move a step closer to the patient.

The study found:

> Female physicians are less likely than male physicians to generate complaints, or provoke lawsuits.
>
> Surgeons are more likely than non-surgeons to prompt these events.
>
> The number of complaints by patients predicts likelihood of being sued.

The study makes no attempt to ascertain whether care that generates complaints meets professional standards of safety and quality. Rather than technical competence, the authors emphasize ability to establish rapport, provide access, administer care and treatment consistent with expectations, and communicate effectively. These qualities protect against litigation.

The study categorizes complaints as relating to communication, humaneness, care and treatment access and availability, or billing. It finds no category of complaint more likely than any other to predict litigation.

Lawsuits may be triggered by uncaring attitudes rather than by clinically inappropriate decisions. The two are unconnected. Complaints reflect patients' subjective impressions. Lawsuits are similarly subjective, although they filter patients' beliefs through a screen of lawyer self-interest and eliminate any cases unlikely to generate significant monetary settlements (but not necessarily cases without underlying negligence).

Nevertheless, reducing lawsuits does require prevention of errors and not just placating patients.

Medical practice can be improved by providing earlier and more reliable warning of problems rather than waiting for suits to be filed. Hospitals must be enabled to learn about *valid* claims from patients whether or not the rarer and more chilling event of formal litigation ensues. "Uncaring medicine is itself bad medicine, something that tends to be overlooked in the rush to achieve technical perfection."

Neither self-regulatory organizations (eg, medical societies) nor formal government bodies (eg, state medical boards) are well positioned to receive and respond to patient complaints. Error detection and correction will be effective only if complaint-related safety systems are integrated into provider organizations such as hospitals, medical groups, or medical care organizations.

More must be done to improve patient perspectives into organizational quality-improvement. It would be enlightening to examine zero-complaint physicians as intensively as the high-complaint physicians. It never hurts to figure out what people are doing *right*.

"In the meantime, we can at least admit that the patient is usually right."

JAMA June 12, 2002; 287: 3003- 05 Editorial by William M Sage, Columbia Law School, New York.
www.jama.com

1 "Patient Complaints and Malpractice Risk" JAMA June 12, 2002; 287: 2951-57 first author Gerald B Hickson, Vanderbilt University School of Medicine, Nashville Tenn.

"A small number of physicians experience a disproportionate share of malpractice claims. If malpractice risk is related to factors such as patient dissatisfaction with interpersonal behaviors, care and treatment, and access, it might be possible to monitor physicians' risk of being sued."

Comment:

If you practice primary care medicine long enough, it is likely that some complaint will be brought against you, if not an actual lawsuit. Lawsuits are extremely upsetting. Physicians being sued constantly reflect on the circumstances. Their practice suffers. I remember, years ago, being sued (along with the hospital) because a patient received an intramuscular injection which damaged the sciatic nerve. Foot drop followed (obvious

malpractice). After a month or two of my preoccupying concern, the patient returned to the office and said he was going to drop the suit. “You and your partner have been so kind to me over the years. I cannot pursue the suit.” He remained our patient until he died. RTJ

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Consider the cost factor in the benefit/harm-cost ratio

6-3 WHEN INCREASED THERAPEUTIC BENEFIT COMES AT INCREASED COST

Antiplatelet therapy is effective in *secondary* prevention of vascular morbidity in patients who have experienced a cardiovascular event.

Aspirin is the first and most widely studied agent. It produces impressive reductions in cardiovascular morbidity in patients who have experienced a broad range of antecedent risk factors.

Clopidogrel (*Plavix*) is another anti-platelet drug. It reduces aggregation of platelets in response to adenosine diphosphate. It reduces the incidence of recurrent cardiovascular events more than aspirin alone, and produces additional benefits when combined with aspirin.

A study in this issue of NEJM [1] compared cost effectiveness in reducing recurrent cardiovascular events using 1) aspirin alone, 2) clopidogrel alone, and 3) aspirin + clopidogrel. (A secondary prevention study).The risk of death was lowest in the combination group. Single-agent therapy was less effective, although clopidogrel alone was more effective than aspirin alone.

The investigators estimated cost effectiveness of the strategies. Given the extraordinarily low cost of aspirin, the estimated cost of each quality-adjusted year of life gained using aspirin alone was $11 000. Clopidogrel alone or in combination would cost $130 000 for each quality-adjusted year of life gained. (*Present cost of one 75 mg tablet of clopidogrel is over $3.*)

NEJM June 6, 2002; 346: 1819-21 Editorial by Alastair J J Wood, Vanderbilt University School of Medicine, Nashville, Tenn. **www.nejm.org**

Comment:

1 “Cost Effectiveness of Aspirin, Clopidogrel, or Both for Secondary Prevention of Coronary Heart Disease” NEJM June 6, 2002; 346: 1800-06 Their conclusion: “Because clopidogrel is costly, its incremental cost effectiveness is currently unattractive, unless its use is restricted to patients who are ineligible for aspirin.”

From table 2 p 1803, I calculated the absolute benefits of clopidogrel + aspirin *vs* aspirin alone.

The investigators estimated benefits and harms over a 25 year period. For secondary prevention from years 2003 to 2027:

Reduction in rate of cardiovascular events: aspirin alone = 31%; clopidogrel + aspirin = 37.2%

(NNT for 25 years to benefit one patient = 14)

Other trials also estimate the number to treat to benefit one patient is secondary prevention:

1) Clopidogrel vs placebo – NNT to benefit one patient over 12 months = 50.

2) Clopidogrel vs aspirin – NNT = 200 over one year.

3) Clopidogrel vs placebo = NNT over one year to *harm* one patient (major bleeding) = 100.

Using other secondary prevention measures (beta-blockers, statins, ACE inhibitors would blunt any advantage of clopidogrel over aspirin.

This is a good example of how primary care clinicians could present patients with information about the benefit/harm-cost ratio of drug therapy. I believe more primary care clinicians will enter the cost of drugs along with the number needed to treat. This will give patients some idea of the costs of benefits and the likelihood of harm. . Costs of drugs are critical for patients seen in primary care, especially long-term use drugs. Compliance with expensive drugs will fall off over time.

For clopidogrel, benefits over aspirin alone are small and harms may be greater. (At the present, long-term harms of clopidogrel are far less certain than harms of aspirin.) Costs are vastly greater, considering that clopidogrel is long-term therapy.

A hypothetical example: Would you be willing to pay $1200 a year for 25 years to reduce the chance of a stroke, heart attack, or death by 1 in 14 while accepting a chance of 1 in 7 of major bleeding?

This gives patients some information on which to base a personal preference. RTJ

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More evidence of benefit in the elderly.

6-4 THERAPY WITH HYDROXYMETHYLGLUTARYL COENZYME-A REDUCTASE INHIBITORS (STATINS) AND ASSOCIATED RISK OF INCIDENT CARDIOVASCULAR EVENTS IN OLDER ADULTS

Should older adults be treated with statins for *primary* prevention of coronary heart disease?

Conclusion: Yes, for many, if not most.

STUDY

1. This observational study investigated the association of statin use with incidence of cardiovascular disease in over 1800 individuals. All were over age 65 (mean = 72). All free of known cardiovascular disease. (A primary prevention study.) According to National Cholesterol Education Program guidelines reduction in cholesterol was recommended for all
2. Some received statin + dietary therapy; some dietary therapy alone.

3. At baseline:	Drug therapy recommended (n = 717)	Dietary treatment alone (n = 946)
Total cholesterol	259	229
LDL cholesterol	177	147
HDL cholesterol	51	53

4. End point = incident cardiovascular events. Follow-up = 7 years.

RESULTS

1. Cardiovascular events:	Person years	No. of cardiovascular events	Outcomes per 1000 patient-years
No drug	9453	347	37

Statin	1129	17	15

2. Cardiovascular deaths:

No drug	10 131	141	14
Statin	1250	9	7

(*By my calculation NNT for 7 years to benefit one = 45*.)

3. Compared with no use, adjusted hazard ratio of statin use for cardiovascular events = 0.44; for all cause mortality = 0.56. Cardiovascular mortality was similar.
4. Benefits were observed in subjects over age 74 at baseline as well as younger subjects.

DISCUSSION

1. This study observed a 50% reduction in risk of cardiovascular events and all-cause mortality in patients for whom cholesterol-lowering was recommended and who were at average age of 72 years at baseline.
2. "For primary prevention among older persons, drug therapy should be considered for those at high risk, including persons with diabetes, multiple risk factors, or subclinical disease."
3. "In this study 80% of subjects would be considered at high risk by the definitions used by 2001 guidelines."

CONCLUSION

Use of statins was associated with decreased risk of incident cardiovascular events among elderly adults

Archives Int Med June 24, 2002; 162: 1395-1400 Original investigation by the Cardiovascular Health Study, first author Rozenn N Lemaitre, University of Washington, Seattle. **www.archinternmed.com**

Comment:

The authors report that the power of the study was limited by the small number of subjects. This was not a controlled clinical trial. It was a subgroup analysis in which residual confounding could not be removed.

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Recommendations for therapy are extending more and more into elderly patients.

6-5 STATIN THERAPY IN OLDER PERSONS: Pertinent Issues

(*This editorial comments and expands on the preceding study*.)

Statins have been shown to lower risk for CHD in all subgroups – people with and without established CHD, men and women, persons with and without risk factors including diabetes and people with lower as well as higher cholesterol levels. There is evidence of benefit of LDL-lowering with statins therapy regardless of patients' baseline LDL levels.

An important question is whether statins will reduce risk of major coronary syndromes in persons over age 65. Most coronary morbidity occurs after age 65. Even when CHD has onset after age 65, the majority of affected persons survive the initial clinical event and live to an older age. However, absolute risk of coronary mortality and morbidity is greater in the elderly.

Most of published trials of statin therapy have not specifically targeted older persons. Nonetheless, most studies have included persons over age 65. Subgroup analysis strongly suggests statin therapy significantly reduces risk in this age group. The National Cholesterol Education Program Treatment Panel recommends the same management for older persons as for younger. Although the preceding trial was not definitive, it was consistent with results of other trials. The absolute (attributable) benefit of LDL-lowering could be even greater in older persons even if the relative risk reduction is lower in this age range. Older patients with established CHD are doubly at risk.

The issue of LDL-lowering in older persons without established CHD is more problematic. The critical issues for primary prevention in older persons are risk assessment and patient selection. "Some investigators have suggested, perhaps tongue in cheek, that all persons should automatically begin statin therapy at age 65 years." The majority of the elderly population does indeed eventually develop coronary heart disease.

How best to assess the risk of future cardiovascular events in the elderly?

Patients with non-coronary forms of clinical atherosclerotic disease calls for intensive therapy: peripheral artery disease, abdominal aortic aneurysm, carotid artery disease, and a 10-year risk for CHD greater than 20% by the Framingham risk scoring. [1]

The goal of LDL-cholesterol for patients with diabetes is set at 100mg/dL.

As patients age, the accuracy of the Framingham risk predictions declines. Advancing age becomes the predominant risk factor.

In deciding about primary prevention in older patients, a distinction between *young* old (65-74) and *old* old (> 75) may be useful. Many in the 65-74 group are at high risk for CHD even if they are otherwise healthy. And use of statins for primary prevention is justifiable. In older patients, statins should be used more cautiously for primary prevention. This group often contains individuals with impaired drug metabolism, many taking multiple drugs, many with multisystem disease, more women with low body weight, and more frequent surgical procedures. Clinical judgment must be used on whether to use statins in the first place. A more conservative approach seems appropriate even though some efficacy in reducing CHD risk almost certainly exists. "Undoubtedly, some patients in this age range will benefit from statin therapy and should be treated."

If the patient has a high triglyceride and low HDL-cholesterol, a fibrate or nicotinic acid can be used as an alternative to statin.

Summary:

There is growing evidence that LDL-lowering therapy is effective in reducing risk for CHD in older persons. It is recommended for older patients with established cardiovascular disease, regardless of age. Recommendations for treatment extend to older persons with CHD risk equivalents, especially non-coronary forms of atherosclerotic disease and type 2 diabetes.

Archives Int Med June 24, 2002; 162: 1329-33 Editorial by Scott M Grundy, University of Texas Southwestern Medical Center at Dallas. **www.archinternmed.com**

Comment:

1 Would not hypertension, especially systolic hypertension, also be regarded as a risk factor for cardiovascular complications? Patients with hypertension + elevated cholesterol are more at risk than patients with hypertension without elevated cholesterol. Including this group would extend recommendation for statins in the elderly.

As one ages, risk factors increase, and application of recommendations for drug therapy become almost universal. The benefit/risk-cost ratio becomes more questionable. Good clinical judgment and patient's preferences after receiving best evidence-based information are required to decide about therapy. RTJ

Suggestions to maintain mental health.

6-6 WHAT WE NEED TO KNOW ABOUT AGE-RELATED MEMORY LOSS

Elderly patients are expressing greater concern about their frequent age-related memory changes. What can they do to preserve their memory abilities as they grow older?

This paper, based on clinical experience of the author and literature search, provides a practical strategy for assessing age-related memory loss, and discusses interventions that may or may not protect brain health.

Definitions:

Age associated memory impairment, the mildest form, is characterized by self-perception of memory loss and a standard memory test score showing a decline in memory performance as compared with younger adults. [*Also called benign forgetfulness of old age. RTJ*] About 40% of people over age 65 have age-related impairment. Only about 1% will progress to dementia each year.

Mild cognitive impairment represents a more severe form of memory loss. It is often defined by important memory defects without functional impairments. These individuals are able to live independently but they show objective memory impairments similar to those seen in persons with very mild Alzheimer's disease. About 10% of those over age 65 have mild cognitive impairment. Nearly 15% develop Alzheimer's each year.

Alzheimer's disease: As age increases, the risk of Alzheimer's increases dramatically. Vascular disease contributes to the occurrence of dementia. Not everyone is destined to develop Alzheimer's disease. Genetic predisposition (the apolipoprotein E-4 allele) explains only some of the risk. Severe head trauma and lower educational level seem to increase risk.

Assessment:

The first assessment step is to determine if the patients falls into one of the three main categories noted above. Risk factors should trigger a memory screen (diabetes; Parkinson's disease; stroke; family history of dementia).

A simple screening question asking about the patient's ability to remember is often informative.

The mini-mental state examination consists of 30 items rating memory, orientation, attention, calculation, language, and visual skills. The test is limited because it will not detect subtle memory losses, particularly among college graduates.

More detailed neuropsychological tests will provide a better idea of subtle memory loss.

Delayed memory recall is tested by a word list task, giving the patient a list of 10 unrelated words to memorize in one minute, and then asking him to repeat in 20 minutes. [*See illustrative list on p 1503.]* This will identify subtle memory deficits in educated people.

Positron emission tomography (PET scan) may help the diagnosis. It has a high diagnostic accuracy and sensitivity for detection of Alzheimer's early in its course.

Evaluation should rule out treatable conditions, including medication history, screening for depression, and laboratory tests to rule out thyroid disease, B12 deficiency, anemia, liver disease, and other metabolic disturbances which could cause memory change.

Treatment options:

If memory loss is severe enough to warrant a diagnosis of dementia, cholinesterase inhibition would be indicated. For milder forms of memory loss, drug therapy has not been approved. Unproved, but possible protective factors include: NSAIDs, postmenopausal estrogen, anti-oxidant vitamins, cholesterol-lowering statin drugs, and aerobic conditioning.

Strategies for maintaining brain health.

Stress reduction: Chronic stress may be detrimental to memory performance, perhaps due to effect of stress hormones (eg, cortisol) on the hippocampus. Chronic stress can contribute to anxiety and depression which often impair memory processing, especially in the elderly. Minimizing stress may have a beneficial impact on brain health.

Physical activity: Studies of persons age 20 to 60 reported that those who were physically active had a lower risk of Alzheimer's. A recent study of persons age 60 to 75 reported that mental tasks involved in executive control improved in a group taking aerobic exercise.

Healthy diet: Persons with excess body fat have greater risk of diabetes and hypertension. Obesity-related conditions increase risk of cerebrovascular disease, which often leads to memory loss and dementia. Lower fat diets in young and middle-aged adults may reduce risk of Alzheimer's. Some fats may be beneficial—eg, olive oil in the Mediterranean diet. Antioxidant vitamins E and C may protect the brain. Fruits and vegetables contain relatively high levels of antioxidants. Diets with a high glycemic index may increase risk.

Mental activity: Risk is lower in people who have been intellectually active. Reading, mentally stimulating jobs, and educational experiences may help maintain memory. "Continual life-long mental stimulation is healthy for human brains."

Other lifestyle choices: Smoking is a risk factor for memory loss. One study reported that smokers had double the risk of getting Alzheimer's as non-smokers. Cessation may reduce risk. Moderate alcohol consumption may *lower* risk as compared with abstainers and heavy drinkers. Staying in close contact with people and remaining involved in meaningful activities predict successful aging.

BMJ June 22, 2002; 324: 1502 – 05 "Clinical Review" by Gary W Small, University of California, Los Angeles, Neuropsychiatric Institute, Los Angeles CA. **www.bmj.com/cgi/content/full/324/7352/1502**

Comment:

The message is to live as healthy and vigorous a life as possible. Measures to preserve brain health include full physical, mental and social activities. Vascular disease is linked to Alzheimer's disease. Many of the measures to reduce atherosclerotic cardiovascular disease will reduce risk of dementia. Reducing risk includes prevention and treatment of hypertension, diabetes, and dyslipidemia. We should protect our brains as well as our hearts.

Two studies and an editorial appear in the June 26 issue of JAMA; Vol 287. They report that higher dietary intake of vitamins E and C lowers risk of Alzheimer's.

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Abnormal glucose metabolism common in patients with AMI

6-7 GLUCOSE METABOLISM IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION AND NO PREVIOUS DIAGNOSIS OF DIABETES MELLITUS.

People with impaired glucose tolerance have increased risk of cardiovascular disease. There is a relation between plasma glucose at time of admission for acute myocardial infarction (**AMI**) and risk of death.

The amount by which a patient's plasma glucose increases in the early phase of AMI is associated with the degree of left ventricular failure. (Ie, catecholamines and cortisol produced in response to infarct extension and myocardial dysfunction result in an increase in blood glucose.)

The glycometabolic state on admission, as indicated by blood glucose and HbA1c concentrations is a long-term risk marker in patients with diabetes and AMI. A similar relation has recently been suggested for patients without diabetes.

This study ascertained the prevalence of impaired glucose metabolism in patients without diabetes who sustained an AMI, and assessed whether such abnormalities can be identified in the early course of an AMI. This would permit early initiation of appropriate preventive measures.

Conclusion: Previously undiagnosed diabetes and impaired glucose tolerance were common in patients with an AMI during hospitalization and at 3 months.

STUDY

1. Prospective study enrolled over 180 patients (mean age = 64) admitted to the coronary care unit with AMI.
2. None had a previous diagnosis of diabetes. All had a blood glucose under 200 mg/dL (11.1 mmol/L) recorded as soon as possible after admission.
3. Measured HbA1c (their upper normal = 5.3%) the morning after admission.
4 Recorded fasting glucose concentrations daily during the hospital stay, and a standardized glucose tolerance test at discharge.
5. Three months after discharge obtained HbA1c and a new oral glucose tolerance test.
6. Classified patients as having diabetes and impaired glucose tolerance according to WHO and ADA criteria.

RESULTS

1.	At discharge (4 days)	At 3 months
Diabetes	31%	25%
Impaired glucose tolerance	35%	40%
Normal glucose tolerance	34%	35%

2. Elevated concentrations of HbA1c and a fasting glucose above normal independently predicted impaired glucose tolerance at 3 months.

DISCUSSION

1. There was a high prevalence of abnormal glucose metabolism in patients with AMI. There was a strong correlation between the 2-h glucose at discharge and at 3 months. Raised glucose early in the course of AMI is not only related to stress induced by the ischemic event [1] but due to underlying abnormal glucose tolerance in some individuals.
2. The abnormality can be detected before hospital discharge.
3. If individuals with AMI with known diabetes before admission are included, the prevalence of diabetes associated with AMI would be much higher.
4. In this study, fewer than 35% of patients had normal glucose tolerance at 3 months. By this time the effects of acute stress, left ventricular dysfunction, and inflammatory processes should have subsided.
4. Abnormal glucose metabolism on admission to hospital with AMI predicts long-term outlook. Metabolic intervention improves outcome.
5. Patients with impaired glucose tolerance have increased risk of developing diabetes and its microvascular complications as well as cardiovascular disease. Early detection of impaired glucose tolerance would permit initiation of preventive measures.
6. Patients admitted with AMI should be tested for glucose tolerance along with conventional risk factors.
7. Another possibility would be to expose these individuals to early administration of insulin-glucose.

CONCLUSION

Previously undiagnosed diabetes and impaired glucose tolerance are common in patients with AMI. These abnormalities can be detected early. They could be used as early markers of high-risk.

Lancet June 22, 2002; 359: 2140-44 Original investigation, first author Anna Norhammar, Karolinska Hospital, Stockholm, Sweden. **www.thelancet.com**

An editorial in this issue by Steven M Haffner, University of Texas, San Antonio, comments:

Individuals with type 2 diabetes have an increased risk of developing AMI at a rate similar to non-diabetic patients who have established coronary heart disease. Diabetic patients who sustain an AMI have an

increased risk of dying. Even mild degrees of glucose intolerance (including elevated fasting glucose in the non-diabetic range) are associated with increased risk of coronary heart disease.

The editorialist repeats the observation that the ADA fasting blood glucose criterion for diabetes is not a good indicator of diabetes as that defined by the 2-h post 75 g oral glucose tolerance test.

"It is reasonable to suggest an oral glucose tolerance test at discharge after an AMI."

Comment:

1 Old conventional wisdom advised delaying testing for glucose tolerance until after discharge from hospital for AMI because of likelihood of false positives due to acute metabolic stress. This study negates this advice.

Primary care clinicians should be aware of the AMI-diabetes-impaired glucose tolerance link. Intervention may improve prognosis. RTJ

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Reducing glycemic load with acarbose may reduce progression of glucose intolerance.

6-8 ACARBOSE FOR PREVENTION OF TYPE 2 DIABETES MELLITUS

People who develop type 2 diabetes (**DM-2)** pass through a phase of impaired glucose tolerance. Defects in the secretion and the action of insulin lead to glucose intolerance. Resistance to insulin progressively increases; secretion of insulin gradually decreases. Glucose tolerance is assumed to remain normal as long as the beta cells can compensate for insulin resistance. Impaired glucose tolerance develops when insulin fails to compensate.

Any intervention in the impaired glucose tolerance phase which reduces resistance to insulin, or protects the beta cells, should prevent or delay progression to DM-2.

Acarbose (*Precose*) delays digestion of carbohydrates by inhibiting pancreatic amylase and intestinal glucosidases. It retards glucose absorption, improves sensitivity to insulin, and decreases postprandial hyperglycemia -- thereby reducing the stress on beta cells.

This study assessed the effect of acarbose on conversion of glucose intolerance to DM-2

Conclusion: Acarbose delayed development of DM-2 in glucose intolerant patients.

STUDY

1. Double-blind, placebo-controlled, randomized trial entered over 1400 patients. (Mean age = 54; mean body mass index = 31; mean waist circumference = 102 cm; mean fasting glucose = 112 mg/dL; mean 2-h glucose = 166).
2. All had impaired glucose tolerance (2-h glucose levels 140 to 200 after a 75 g glucose load.) And a fasting glucose of 100 to 139 – "a value that is associated with a 3.4-fold increase in risk of progression to type 2 diabetes".[1]
3. Randomized to: 1) acarbose 100 mg three times daily taken with the first bite of each meal; or 2) placebo.
4. Primary end-point = development of DM-2 on the basis of a yearly glucose tolerance test. (Plasma glucose 200 or greater 2 hours after glucose load.)
5. Follow-up = a mean of 3 years.

RESULTS

1. Thirty two percent (32%) of those assigned to acarbose developed DM-2 vs 42% of placebo patients. (Absolute difference = 10%; NNT for 3 years to prevent one patient from developing DM-2 = 10)
2. Acarbose significantly increased *reversion* of impaired glucose tolerance to normal.[2]
3. Adverse effects of acarbose – flatulence and diarrhea; 31% of acarbose patients and 19% of placebo patients discontinued treatment early.

DISCUSSION

1. Pharmacological intervention with acarbose in patients with impaired glucose tolerance delayed progression to type 2 diabetes. This was irrespective of age, sex, and body mass index, and loss of weight.
2. Acarbose therapy may cause reversion of impaired glucose tolerance to normal.[2]
3. "The drug has no toxic effects."
4. The higher the 2-h glucose after a 75 g glucose load, the higher the rate of conversion to DM-2. Acarbose significantly reduces the postprandial rise in glucose.
5. Acarbose is effective preventive therapy in addition to life-style changes.

CONCLUSION

Acarbose could be used in addition to lifestyle changes to delay development of type 2 diabetes in patients with impaired glucose tolerance.

Lancet June 15, 2002; 359: 2072-77 Original investigation by the STOP-NIDDDM Trial Research Group, first author Jean-Louis Chiasson, University of Montreal, Quebec, Canada. **www.thelancet.com**

1 The range 100 to 139 is based on the old diagnostic criteria. The WHO now defines "diabetes" as fasting glucose of 126 or above.

2 Not only can treatment revert impaired glucose tolerance to normal, but it can revert "diabetes" to normal. Take care in labeling a patient as having diabetes based on the lower range of fasting glucose levels (eg, 126-140). After treatment, he may no longer have "diabetes", but for insurance and employment purposes he may carry the label forward to his detriment.

Comment:

Would not frequent (six times daily) small feedings, especially with low glycemic-load food, relieve some of the stress on the metabolic system, as does acarbose? Gouging (eating essentially once daily) stresses the system.

Intervention with acarbose as well as life-style changes would be much more efficacious in patients at higher risk of DM-2 – eg, family history, high BMI, and an inactive lifestyle, with or without impaired glucose tolerance.

Metformin (*Glucophage*) has been reported effective in reducing incidence of DM-2 in obese patients with elevated fasting plasma glucose and impaired glucose tolerance. Lifestyle interventions were more effective. (NEJM February 7, 2002; 346: 393-403 See *Practical Pointers* February 2002) See also "Prevention of Type 2

Diabetes by Changes in Lifestyle among Subjects with Impaired Glucose Tolerance" NEJM May 3, 2001; 344; 1343-50 -- *Practical Pointers* May 2001.)

COST – Precose 25 mg #30 = $20

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A Sea Change in Primary Care Supplemental vitamins for all.

6-9 VITAMINS FOR CHRONIC DISEASE PREVENTION IN ADULTS

The classical vitamin-deficiency diseases (eg, scurvy; beriberi) are rare in Western societies. However, suboptimal intake of some vitamins, well *above* levels causing the classical deficiencies, is a risk factor for chronic diseases. Such deficiencies are common in the general population, especially the elderly.

Suboptimal levels of a vitamin can be defined as those associated with abnormalities of metabolism that can be corrected by supplementation with that vitamin. For example:

Suboptimal folic acid, B6 and B12 levels are related to increased risk of cardiovascular disease, neural tube defects, and breast cancer. Many people in the general population have increased serum homocysteine levels which fall with vitamin supplementation.

Low levels of antioxidant vitamins (A, E, and C) may increase risk for several chronic diseases (coronary heart disease, prostate cancer).

Low levels of vitamin D contribute to osteopenia and fractures. Elevated levels of parathyroid hormone fall with vitamin D supplementation.

"Most people do not consume an optimal amount of vitamins by diet alone. Pending strong evidence of effectiveness from randomized trials, it appears prudent for all adults to take vitamin supplements." It is reasonable to consider a dose of two ordinary multivitamins daily for the elderly, especially since there is a high prevalence of suboptimal vitamin D and B12 intake.

"We recommend that *all* adults take one multivitamin daily." They are safe and inexpensive. "We recommend multivitamins, rather than individual vitamins, because they are cheaper and simpler to take, and because a large proportion of the population needs supplementation of more than one."

JAMA June 19, 2002; 282: 3127-29 "Clinical Applications" first author Robert J Fletcher, Harvard Medical School/Harvard Pilgrim Health Care, Boston Mass. **www.jama.com**

A more extensive review in this issue of JAMA accompanies this article. (pp 3116-26): The review considered 9 vitamins. The authors cite evidence that folate deficiency may contribute to increased risk of colon and breast cancer. Interestingly, there is no mention of a link between folate and dementia and depression.

The science of vitamin supplementation for chronic disease prevention is still not well developed. Much of the evidence comes from observational studies.

Comment:

Some years ago, my son-in-law mentioned that he was taking vitamins and believed they were helpful. He asked my opinion. I replied with the current state of the art advice that vitamins were not needed if the diet was adequate. I am waiting for him to say – "I told you so." RTJ

Provocative. Overly Enthusiastic?

6-10 FOLIC ACID, AGEING, DEPRESSION, AND DEMENTIA

Folic acid is important for function of the nervous system at all ages. In adult patients presenting with megaloblastic anemia due to folate deficiency, approximately two thirds have neuropsychiatric disorders which overlap considerably with those associated with anemia due to vitamin B12 deficiency. Depression is more common in patients with folate deficiency. If these anemias are left untreated nearly all patients will eventually develop neuropsychiatric complications.

Over years, numerous studies have shown a high incidence of folate deficiency correlated with mental symptoms, especially depression and cognitive decline. Recent studies in elderly people suggest a link between folic acid, homocysteine, ageing, depression, and dementia -- including Alzheimer's disease and vascular disease.

This paper reviews the evidence relating folate deficiency to depression and dementia, especially in the ageing nervous system

Neurological patients:

Several reports of neurological disease associated with folate deficiency emphasized the importance of dementia and depression which were reversed with vitamin therapy. The syndrome of folate-responsive dementia and depression, sometimes with additional cord or peripheral nerves signs, was reported to be much more common in geriatric units than is recognized.

Psychiatric patients:

"On the basis of serum or red cell assays, folate deficiency has been reported in up to one third of psychiatric outpatients or inpatients, more so in the former." Raised homocysteine levels and folate deficiency have been identified in subgroups of patients with depression. "The few controlled trials of vitamin therapy in addition to standard psychotropic medication have all reported positive effects on patient's mental state." [200 ug of folic acid (*low dose*) added to lithium therapy for one year; 500 ug added to fluoxitine (*Prozac*) for 10 weeks significantly improved antidepressant response.]

Geriatric and psychogeriatric patients:

The highest incidence of folate deficiency as measured by serum and red cell folate concentrations occurs in elderly populations, especially psychogeriatric patients. As patients age, homocysteine levels rise and folate levels fall. "A close association with dementia and depression, apathy, withdrawal, and lack of motivation has been noted." A recent report from the Framingham community confirmed that a raised plasma homocysteine concentration doubled the risk of developing Alzheimer's and non-Alzheimer's dementia. (*See Practical Pointers February 2002*)

Neuropsychological studies:

A placebo controlled trial reported that 15 mg daily (*high dose*) for 4 months in folate deficient, depressed patients with mild cognitive impairment provided significant improvement. A survey of nutritional state and cognitive function in 260 healthy elderly subjects living in the community reported a significant relation between lower folate levels and impaired abstract thinking ability and memory.

Neuropathological studies:

A case-control study of neuropathological diagnosis of Alzheimer's reported that higher homocysteine levels were associated with more rapid atrophy of the temporal lobes. Another study concerned elderly nuns who died at mean age of 91. Of 18 nutritional factors examined, only serum folate was significantly negatively correlated with atrophy of the neocortex, especially in those with Alzheimer's disease.

Conclusions:

Folates are important in the nervous system at all ages. There is growing evidence of their involvement in the aging brain, especially in mood and cognitive function. Low folate concentrations in serum, red cells, and cerebrospinal fluid, and raised plasma homocysteine are associated with depression and dementia. "Some of the deficiency may be related to ageing, some may be secondary to mental illness, and some primary. But, whether it is primary or secondary, open and controlled treatment studies confirm an aetological link with specific effects of the vitamin on mood, drive, initiative, alertness, concentration, psychomotor speed, and social activity."

"Clearly, further clinical trials in precisely defined clinical categories are needed."

BMJ June 22, 2002; 324: 1512-15 "Education and Debate", commentary by E H Reynolds, King's College, London. **www.bmj.com/cgi/content/full/324/7352/1512**

Comment:

The article cites 32 references.

I hesitated to abstract this article. I believe it is overly enthusiastic. But it is provocative. The evidence is mainly observational. We await stronger evidence regarding vitamin supplements in treatment and primary prevention. Meanwhile, take your one-a-day.

Close to an ideal biological marker

6-11 DECISION MAKING WITH CARDIAC TROPONIN TESTS

Cardiac-specific troponins come close to fulfilling many of the criteria for an ideal biologic marker. They convey prognostic information useful in making therapeutic decisions regarding patients with acute coronary syndromes.

The troponin complex regulates the contraction of striated muscle. It consists of several subunits, including troponin I and troponin T. They are present in both cardiac and skeletal muscle. I and T are encoded by different genes in the two types of muscle, yielding proteins that are immunologically distinct. Assays, based on high-affinity antibodies specific for cardiac I and T, are available.

Normally cardiac I and T are not detectable in the blood of healthy persons. They are released into the circulation when myocardium is damaged.

Microinfarction can produce elevations of cardiac troponins. Levels can increase without any elevation of creatine kinase MB fraction (CK-MB). Troponins are much more sensitive to damage to small areas of myocardium. Given the nearly absolute specificity of cardiac troponins, they are now considered the preferred biologic markers for diagnosing myocardial infarction. A single cutoff point is chosen such that a MI would be diagnosed if troponin I or T is detected at least once within 24 hours after the index clinical event at a level exceeding the 99th percentile of values measured in a normal control population.

Cardiac troponin T vs troponin I:

The antibodies used for detection of T are standardized and produced by a single manufacturer. T has relatively uniform cutoff concentrations and a high precision at the low end of the measuring range. In contrast, variability in the cutoff concentrations and interassay variability among many available immunoassays for troponin I may be due in part to different specificities of the antibodies used. Clinicians should refer to the cutoff values specific for the particular assay used.

The ECG enables clinicians to separate patients with ischemic discomfort into those with MI associated with ST elevation, and those with unstable angina or MI without ST elevation. For patients presenting with ST elevation, treatment should not be delayed waiting for troponin results. Measurement may be useful for distinguishing unstable angina from MI without ST elevation. About 30% of patients previously considered to have unstable angina on the basis of CK-MB levels are now given a diagnosis of MI without ST elevation on the basis of troponin levels. Troponins also help to establish prognosis, select therapy, and diagnose reinfarction.

A positive troponin test in patients with unstable angina or MI without ST elevation is associated with a risk of death or non-fatal MI four times higher than in patients with a negative troponin. With increasing levels, the risks increase. There is a significant gradient.

Patients with an acute coronary syndrome who are troponin-positive are more likely to have coronary thrombi, to have intermittent showers of emboli in the coronary microvasculature, and to have depressed ventricular function. The benefits of glycoprotein IIb/IIIa inhibitors, low molecular weight heparin, and an early invasive strategy are far greater in troponin-positive patients. Patients with the lowest levels of troponins have little benefit from therapy; those with intermediate levels have the greatest benefit; those with the highest levels receive less benefit because of the large amount of irreversible myocardial damage.

A controversial issue has been the importance of elevations of cardiac troponins in patients with renal dysfunction. The preceding study gives some reassurance that the latest generation of troponin T assay provides accurate prognostic information in patients with impaired renal function.

“Cardiac troponin assays offer clinicians a valuable tool for diagnosing myocardial infarction even at the level of microinfarction.”

NEJM June 27, 2002; 346: 2079-82 Editorial by Elliott M Antman, Brigham and Women’s Hospital, Boston, Mass. **www.nejm.org**

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Renal dysfunction does not lessen value of troponin screening

6-12 TROPONIN T LEVELS IN PATIENTS WITH ACUTE CORONARY SYNDROMES, WITH AND WITHOUT RENAL DYSFUNCTION

Among patients with acute coronary syndromes (**ACS**), cardiac troponin measurements are useful in establishing a diagnosis. This study asks: Does renal dysfunction impair this diagnostic value?

Conclusion: No

STUDY

1. Analyzed outcomes of over 7000 patients. All had one or more episodes of angina while at rest that lasted over 5 minutes and a new ST-segment depression of at least 0.5 mm, or an abnormal result on troponin T testing. (Abnormal = level of 0.1 ng/mL or higher. A lower cut point of 0.03ng/mL was also considered.)
2. Creatinine clearance was calculated in all. [1]
3. Primary endpoint = composite of death and myocardial infarction (**MI**) within 30 days.

RESULTS

1. Death or MI occurred in 581 (8%)
2. When creatinine clearance was considered as a continuous variable after accounting for other confounders, the troponin T level was independently predictive of risk across the entire spectrum of renal function.
3. Outcomes in 30 days: Myocardial infarction or death

Creatinine clearance	Troponin T > 0.1 ng/mL	Troponin T < 0.1 ng/mL
First quartile (< 54 mL/min)	20%	9%
Forth quartile (> 98 mL/min)	5%	2%

	Troponin T > 0.03 ng/mL	Troponin T < 0.03 ng/mL
First quartile	18%	8%
Forth quartile	5%	1%

4. Troponin T levels were higher than 0.1 in 52% or patients; over 0.03 in 64%. An abnormal troponin T at baseline was associated with an increased risk of death within 30 days.
5. A troponin T level above 0.1 combined with a low creatinine clearance was associated with an increased mortality and MI as compared with a level of 0.1 combined with normal creatinine clearance.

DISCUSSION

1. Among patients presenting with ACS, base-line measurement of cardiac troponin T was strongly predictive of risk of death or myocardial infarction, even when renal dysfunction was present.
2. Given that renal dysfunction is common in patients with coronary disease, the ability of cardiac troponin levels to predict outcomes irrespective of creatinine clearance expands their clinical usefulness.

CONCLUSION

Cardiac troponin T predicted short-term prognosis in patients with ACS regardless of their level of creatinine clearance.

NEJM June 27, 2002; 346: 2047-52 Original investigation, first author Ronnier J Aviles, Cleveland Clinic Foundation, Cleveland. Ohio. **www.nejm.org**

1 Creatinine clearance = $\frac{(140 - \text{age}) \times \text{weight in kilograms}}{72 \times \text{serum creatinine in mg/dL}}$

This is the equation of Cockcroft and Gualt. It is used widely in clinical practice, although it is only an approximation of the glomerular filtration rate. It is a practical method to give estimated GFR at the bedside.

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A major advance in coronary angioplasty?

6-13 SIROLIMUS-ELUTING CORONARY STENTS

In 1975, on Easter Island, an actinomycete (*Streptomyces hydroscopius*) was cultured from the soil. It produces a novel macrolide antibiotic which has potent antifungal, immunosuppressive, and antimitotic activities. The generic name of the resulting drug is "sirolimus". (Also known as rapamycin, after Rapa Nui, the name given to Easter Island by its inhabitants.)

After years of research, it is now approved as an anti-rejection drug in organ-transplant recipients. It blocks cytokine-stimulated proliferation of T lymphocytes as well as a variety of other cell types.

Coronary stenting has assumed a major role in coronary revascularization procedures. It has limitations. Up to 20% of stented arteries become restenotic. Restenosis results from neointimal proliferation of smooth muscle cells. They are stimulated to proliferate by inflammatory mediators released in response to vessel injury. Ingrowth of tissue through the struts of the stent eventually narrows the lumen. Coating the stent with sirolimus, through its immunosuppressive and anti-mitotic properties, might inhibit neointimal proliferation of the revascularized artery.

A report in this issue of NEJM **1** suggests that a sirolimus-eluting stent, as compared with a standard stent, shows considerable promise for prevention of neointimal restenosis. The gradual elution occurs over a period of 30 days. Only a small quantity of the drug is required, avoiding systematic adverse effects.

NEJM June 6, 2002; 346: 1770-71 "Perspective", commentary by Gregory D Curfman.

1 "A Randomized Comparison Of A Sirolimus-Eluting Stent With A Standard Stent For Coronary Revascularization" NEJM June 6, 2002; 346: 1773-80 **www.nejm.org**

Comment:

Primary care clinicians – keep in touch with your cardiologist friends about developments.

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Osteoporosis adversely affects teeth as well as hip and vertebra

6-14 ALVEOLAR AND POSTCRANIAL BONE DENSITY IN POSTMENOPAUSAL WOMEN RECEIVING HORMONE/ESTROGEN REPLACEMENT THERAPY

Osteoporosis is a risk factor for tooth loss and edentulism in the elderly. It is commonly believed that estrogen deficiency, use of corticosteroids, and other conditions leading to bone demineralization also cause oral bone loss. Epidemiological evidence supports the association of decreasing bone mineral density (**BMD**) with tooth loss. Observational studies indicate that estrogen deficiency is associated with a loss of the dental attachment apparatus (cementum, periodontal ligament, and alveolar bone).

This study assessed whether the positive effects of hormone replacement therapy (**HRT**) on BMD of peripheral bone would be similarly protective in sustaining oral BMD.

Conclusion: Oral bone mass was increased in postmenopausal women receiving HRT.

STUDY

1. Randomized, double-blind, placebo-controlled study entered 135 postmenopausal women. None had evidence of moderate or severe periodontal disease.
2. Randomized to: 1) oral conjugated estrogen (*Preparing* 0.625 mg) alone, or in combination with medroxyprogesterone (*Prempro;* [0.625 – 2.5 mg]) , or 2) placebo.
3. All received supplemental calcium and vitamin D.
4. Measured alveolar crest height by radiography, and alveolar bone density by digital subtraction radiography. Also measured BMD at the proximal femur and lumbar spine by dual-energy X-ray absorptiometry.
5. All received regular dental care. Follow-up = 3 years.

RESULTS

1. Compared with placebo, HRT significantly increased alveolar bone mass (+1.8%), and tended to improve alveolar crest height (+4.8%).
2. BMD in the proximal femur, neck, and trochanter also increased in the HRT group.
3. Changes in the alveolar bone mass correlated with BMD of the total femur and trochanter.

DISCUSSION

1. In this study of postmenopausal women, HRT produced a significant improvement in alveolar bone mass and strengthened the dental attachment apparatus in postmenopausal women.
2. Tooth loss may be a manifestation of osteoporosis. By extension, protection from alveolar bone loss or increases in oral bone mass should result in reduced tooth loss.
3. Edentulous women are more likely to have low BMD than dentate women. Three large retrospective cohort studies indicated that estrogen users have more teeth and a lower prevalence of edentulism.
4. This study was not powered to detect differences in tooth loss, which would be a relatively rare

event over 3 years in good oral health and no clinically significant periodontal disease.

5. In the presence of periodontal disease and poor oral hygiene, systemic bone loss plays a lesser role than oral disease in disrupting the attachment apparatus.

6. Actually the placebo group also experienced increase in alveolar crest height, possibly due to supplemental calcium and vitamin D. "Thus, dental care and dietary supplementation may be sufficient to prevent postmenopausal oral bone loss."

CONCLUSION

HRT combined with supplemental calcium and vitamin D, produced significant improvement in oral bone mass.

Archives Int Med June 24, 2002; 162: 1409-15 Original investigation, first author Roberto Civitelli, Washington University School of Medicine, St. Louis, MO. **www.archinternmed.com**

Comment:

I doubt protecting against alveolar bone loss would have much benefit unless the women also received regular dental hygiene to protect against periodontal disease.

In view of the recent furor over adverse effects of estrogen/progesterone (*Prempro*) in increasing cardiovascular risk, women might opt to take bisphosphonates to protect their bones and teeth.

Primary care clinicians do not often consider oral BMD when advising female patients about treatment or prevention of osteoporosis. I believe adding information regarding benefits on dental health would lead more women to accept prophylactic drug therapy.

Are males less edentulous than females? RTJ

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Best evidence shows no increased risk

6-15 ORAL CONTRACEPTIVES AND THE RISK OF BREAST CANCER

The Cancer and Steroid Hormone (**CASH**) study reported in 1986 did not show any association between oral contraception (**OC**) and breast cancer (**BC**). (Relative risk = 1.0)

Conversely, a large pooled analysis of 54 studies (1996) reported that women who currently used OC , or had used them in the past 10 years, had a slightly increased risk of BC (RR = 1.3). Women who have used contraceptives over 10 years prior did not have increased risk.

Now, many women who have taken OC early in their reproductive years are reaching the age at which risk of BC is highest.

This population-based study determined the risk of BC in former and current users of OC.

Conclusion: Among women age 35-64, current and former use was not associated with BC.

STUDY

1. Case control study interviewed over 9000 women age 35-64. Half had BC and half were controls.

RESULTS

1. The relative risk of BC in women currently using OC was 1.0 (confidence interval = 0.8 to 1.3).
2. The relative risk of BC was 0.9 in women who had previously used OC.
3. The relative risk did not increase consistently with longer periods of use or with higher doses of estrogen.
4. OC was not associated with increased risk among women with a family history of BC.
5. Initiation at an early age was not associated with increased risk.

DISCUSSION

1. In the pooled analysis referred to above, the relative risk of BC in women currently taking OC was 1.3 compared with never-users. The current study found no increase in risk (RR = 1.0).
2. The pooled analysis also reported a slight increased risk among women who had used OC within 10 years previously.
3. Note that the pooled analysis included some women under age 35 with BC. The current study did not include this age group.

CONCLUSION

Among women age 35-64, current or former use of OC was *not* associated with a significantly increased risk of BC.

NEJM June 27, 2002; 346: 2025-32 Original investigation, first author Polly A Marchbanks, Center for Disease Control and Prevention, Atlanta, Ga. **www.nwjm.org**

An editorial in this issue of NEJM comments: The CASH study reported that OC use reduces the risk of both endometrial and ovarian cancer. However adverse effects do occur – venous thromboembolism, ischemic stroke, and, among women over age 35 who smoke, myocardial infarction. Long term use may also increase risk of cervical cancer in women positive for the human papilloma virus.

Beneficial effects, other than pregnancy prevention, include greater regularity of periods, reduction in menstrual blood loss and iron-deficiency anemia, and amelioration of dysmenorrhea.

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Proton pump inhibitor protects against aspirin-induced ulcers.

6-16 LANSOPRAZOLE FOR THE PREVENTION OF RECURRENCES OF ULCER COMPLICATIONS FROM LONG-TERM LOW-DOSE ASPIRIN USE

Patients who take low-dose aspirin (< 325 mg daily) have increased risk of ulcer complications. One option for prevention is to reduce gastric acidity by use of proton pump inhibitors (**PPIs**). A recent study reported PPIs

substantially reduce risk of GI bleeding in patients taking low-dose aspirin. PPIs also prevent relapse of ulcers in patients taking long-term NSAIDs.

H Pylori is an important risk factor for ulcer bleeding. This study compared efficacy of 1) eradication of *H pylori* alone with 2) combined eradication/proton-pump inhibition in prevention of recurrence of ulcer complications in users of low-dose aspirin.

Conclusion: In patients who had ulcer complications related to long-term aspirin use, lansoprazole, in addition to eradication of *H pylori*, reduced rate of recurrence of ulcer complications.

STUDY

1. Enrolled over 120 patients (mean age 70) who had bleeding ulcer (gastric or duodenal) in the past after using low-dose aspirin. All had *H pylori* infection. All were treated to eradicate the infection. (Eradication failed in 4 patients despite 2 courses of therapy. These were eliminated from the study.)
2. Then randomized to: 1) lansoprazole (*Prevacid*) 30 mg daily, or 2) placebo. All continued to receive aspirin 100 mg daily.
3. Primary end-point = recurrence of ulcer bleeding.
4. Follow-up = 12 months.

RESULTS

1. Recurrence of bleeding:	Lansoprazole	Placebo
	1 of 62 (1.6%)	9 of 61 (15%)

2. NNT to benefit one patient = 7

DISCUSSION

1. In patients who had past bleeding ulcer, eradication of *H pylori* infection followed by PPI treatment significantly reduced rate of recurrent bleeding, as compared with eradication of *H pylori* alone.
2. Eradication of *H pylori* alone did not completely abolish the ulcerogenic effect of aspirin.
3. Epidemiological studies have reported a reduced risk of ulcer bleeding in patients taking a PPI with aspirin (primary prevention). Reduction in acid production is likely related to the benefit.

CONCLUSION

In patients with *H pylori* infection who had gastric or duodenal ulcer bleeding related to long-term use of low-dose aspirin, treatment with the proton-pump inhibitor, lansoprazole, in addition to eradication of the infection, reduced the rate of recurrence of bleeding despite continuation of aspirin.

NEJM June 27, 2002; 346: 2033-38 Original investigation, first author Kam Chuen Lai, University of Hong Kong. **www.nejm.org**

Comment:

This brings up the question – Does the presence of *H pylori* infection increase risk of peptic ulcer in patients taking NSAIDs, including aspirin? Although this point was not directly investigated in this study, I believe evidence suggests that the likelihood of ulcer inception or recurrence is lessened by eradication of the infection.

I congratulate the patients and investigators who participated in this study. I doubt it could have been done in the USA. RTJ

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Nuts are part of the healthy diet

6-17 NUT CONSUMPTION AND DECREASED RISK OF SUDDEN CARDIAC DEATH IN THE PHYSICIAN'S HEALTH STUDY

Recent trials have reported a reduced risk of recurrent events and cardiac death in patients assigned to the Mediterranean diet after an acute myocardial infarction. Increased concentrations of alpha-linolenic acid (an n-3 fatty acid) in patients on the Mediterranean diet may have been partially responsible. These acids have been reported to prevent sudden cardiac death in patients who have had a myocardial infarction.

Nuts are an important component of the Mediterranean diet. They contain moderate amounts of alpha-linolenic acid. Some components of nuts may have anti-arrhythmic properties.

Previous studies have reported a decrease in coronary heart disease mortality among persons who consume nuts more frequently.

This study examined associations between nut consumption and sudden cardiac death.

Conclusion: Nut consumption was related to lowering total cardiac death and sudden cardiac death.

STUDY

1. Prospective study assessed whether increased frequency of nut consumption was associated with lower risk of sudden death and coronary heart disease in over 21 000 male physicians.
2. Assessed nut consumption by food-frequency questionnaire.
3. Follow-up = average 17 years.

RESULTS

1. Nut consumption was associated with a *statistically* significant reduced risk of sudden death after controlling for known cardiac risk factors and other dietary habits.
2. Persons consuming nuts 2 or more times weekly had a relative risk of sudden cardiac death of 0.53 compared with men who rarely or never consumed nuts
3. Relative risk of total coronary heart disease deaths was also decreased. (Relative risk = 0.70) The effect appeared linear.
4. Nut intake was not associated with reduced risk of non-sudden coronary heart disease death or non-fatal myocardial infarction.

DISCUSSION

1. In this large prospective study, nut intake was associated with a significantly reduced risk of sudden cardiac death after controlling for other risk factors.
2. Risk for non-fatal myocardial infarction and other types of coronary heart disease death was not reduced
3. As for fatty acids in fish, the fatty acid in nuts may have anti-arrhythmic activity. Walnuts in particular contain high amounts of alpha-linolenic acid. Nuts are also rich in polyunsaturated and monounsaturated fatty acids which improve the lipoprotein profile when substituted for other fats in the diet.
4. Three large prospective studies have also reported inverse associations between nut consumption and fatal coronary disease.

CONCLUSION

This study suggests that the inverse association between nut consumption and total coronary heart disease death is primarily due to a reduction in risk of sudden cardiac death.

Archives Int. Med. June 24, 2002; 162: 1382-87 Original investigation, first author Christine M Albert, Channing Laboratory Boston Mass. **www.archinternmed.com**

Comment:

To put this into *clinical* significance (as opposed to *statistical* significance):

Sudden death	No. of cases	Person years	Cases per 10 000 person-years
Nuts less than once monthly	48	73 000	7
Over twice a week	29	73 000	4
Total CHD death			
Nuts less than once monthly	136	73 000	18
Over twice weekly	97	73 000	`13

Thus eating nuts twice weekly lessened risk of sudden coronary death by 3 in 10 000 every year. And reduced total CHD deaths by 5 in 10 000. The NNT would be very high, hardly clinically significant. RTJ

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Screening beginning at age 50 is still reasonable

6-18 RESULTS OF SCREENING COLONOSCOPY AMONG PERSONS 40 TO 49 YEARS OF AGE

About 7% of colorectal cancers are known to occur in persons under age 50. .

This retrospective analysis reviewed data on over 900 individuals age 40-49 who underwent their first colonoscopy.

About 80% had no detected lesions; 10% had hyperplastic polyps; 9% had tubular adenomas; 3% had advanced neoplasms [1] About half were located distally and potentially within reach of the sigmoidoscope.

None of the lesions were cancerous. It is not possible to estimate how many of the advanced neoplasms detected in the study might have progressed to incurable cancer before being detected by screening beginning at age 50.

An estimated 250 and 1000 persons this age would have to be screened with colonoscopy to detect one cancer. Sigmoidoscopy would detect about 50% of these.

The authors concur with the current recommendations to begin screening at age 50.

NEJM June 6, 2002; 346: 1781-85 Original investigation, first author Thomas F Imperiale, Indiana University School of Medicine, Indianapolis. **www.nejm.org**

1 The authors comment on the term "advanced neoplasia" – ie, neoplasms classified as advanced on the basis of size and histologic findings (adenoma at least 1 cm in diameter or with villous histologic features or severe dysplasia). There are virtually no data to confirm or refute the appropriateness of the label "advanced". Although a convenient proxy for colorectal cancer, its use as an outcome measure may be misleading. One study reported that polyps over 1 cm in diameter progress to colorectal cancer at a rate of about 1% a year. It is not clear whether the histologic features of advanced neoplasia have an ominous natural history.

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Stronger spiritual beliefs help resolve grief more rapidly and completely

6-19 SPIRITUAL BELIEFS MAY AFFECT OUTCOME OF BEREAVEMENT

Death of a loved-one can lead to prolonged grief. Do spiritual or religious beliefs alter the process of grieving? Some studies have suggested that they do. The research was often retrospective and hampered by lack of standardized measures.

This prospective study explored the relation between spiritual beliefs and resolution of bereavement.

Conclusion: People who professed stronger spiritual beliefs seemed to resolve grief more rapidly.

STUDY

1. Prospective cohort study followed 135 relatives and close friends of patients admitted to a center offering specialist care for terminal illnesses. Patients were admitted regardless of their religious affiliation.
2. Measured core bereavement items, a standardized measure of grief, at 1, 9, and 14 months.
3. The aim was to test the null hypothesis that spiritual belief has no effect on the grieving process. (Ie, the investigators at outset considered that religious beliefs would not have any effect on the grieving process.) And to study possible confounders which could be associated with spiritual beliefs and bereavement outcomes.

RESULTS

1. People reporting no spiritual belief (n = 21) had not resolved their grief by 14 months after the death. They had a slight and temporary lower level of grief at 9 months. The symptoms of grief intensified again by 14 months.
2. Participants with strong beliefs (n = 55) resolved their grief progressively, in a linear fashion, over 14 months.

3. Participants with low level beliefs (n = 53) showed little change in the first 9 months, but thereafter resolved their grief.
4. Strength of spiritual belief remained an important predictor after controlling for relevant confounding variables.
5. Age and sex of participants did not significantly affect the findings. Men had higher grief scores than women initially, but not by 9 months.
6. Mean scores on the hospital anxiety and depression scale before the death were significantly associated with initial levels of grief. But these scores were not related to any major effect on the strength of belief.
7. Closeness to the dying patient predicted higher grief scores.
8. After all of these possible confounders were entered into the model, the strength of spiritual belief retained its significance.

DISCUSSION

1. "Our main finding is that the strength of spiritual belief is an important predictor of bereavement outcome."
2. Spiritual beliefs may provide an existential framework in which grief is resolved more readily. Most spiritual beliefs, whether or not associated with religious practice, contain tenets about the course of human life and existence beyond it.
3. Strong beliefs may be a proxy for better adjustment and less psychological distress. But the analysis suggests that the strength of belief affected the course of bereavement independently of psychological status.
4. "We are not suggesting that an intervention concerning spiritual matters is appropriate for people with no professed beliefs. Rather it might help in identifying people who are having difficulty in readjusting to life, after their loss."

CONCLUSION

Absence of spiritual belief may be a risk factor for delayed or complicated grief.

People who profess stronger spiritual beliefs seem to resolve their grief more rapidly and completely after the death of a close person.

BMJ June 29, 2002; 324: 1551-54 Original investigation, first author Kiri Walsh, Royal Free and University College Medical School, London, UK **www.bmj.com/cgi/content/full/324/7353/1551**

Comment:

I could not think of any practical application of this article for primary care. I abstracted it because of general interest. It may be helpful to Hospice workers.