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This document is divided into two parts

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

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

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

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

   I hope you will find Practical Pointers interesting and helpful. The complete content of all issues for the past 6 years can be accessed at www.practicalpointers.org

Richard T. James Jr. M.D.

Editor/Publisher.

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9-1  COMBINED IMPACT OF LIFESTYLE FACTORS ON MORTALITY

Diet, physical activity, adiposity, cigarette smoking, and alcohol *abstinence* (and over use) have been associated with risk of chronic diseases. Identifying priorities for clinical and public health efforts, and understanding the magnitude of effects of these risk factors on overall health is fundamental.

The prospective Nurses’ Health Study followed over 77 000 women aged 34 to 59, beginning in 1980. All were free from cardiovascular disease and cancer at baseline.

Periodically assessed:
- A. Diet assessed by a 61-item food frequency questionnaire. Nutrient intakes were calculated.
- B. Cigarette smoking
- C. Physical activity
- D. Alcohol consumption
- E. BMI (calculated at baseline)

Classified as low risk:
- A. Healthy diet on a scale of 0 to 10 (0 = least healthy; 10 = recommended intake). Considered the highest 40% to be at low risk
- B. Never smoking
- C. Average of 30 minutes per day of moderate physical activity
- D. Alcohol consumption less than 15 g per day. (Up to approximately one drink daily.)
- E. BMI 18.5 to 25

Determined mortality over 24 years.

Comparing the high risk with the low risk category of lifestyle factors, the estimated population attributable risk of mortality:
- A. Cigarette smoking 28%
- B. Overweight 14%
- C. Lack of physical activity 17%
- D. Low diet quality 13%
- E. Not having light to moderate alcohol intake 7%

Never smoking, engaging in regular physical activity, eating a healthy diet, and avoiding overweight were each associated with a markedly lower mortality over 24 years. “We estimated the 55% of all-cause mortality, 44% of cancer mortality, and 72% of cardiovascular mortality could have been avoided
by adherence to these four lifestyle guidelines. Light to moderate alcohol consumption (up to one drink a day) was also associated with a lower risk of all cause mortality.”

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If the investigators were to repeat the study, I think they would include vitamin D intake and levels as another risk factor.

All of us have heard this message repeatedly over the years. It deserves repetition. I believe educating patients about healthy lifestyles and following their compliance is one of the most important tasks of primary care clinicians. Patients would likely benefit from a hand-out listing the lifestyle risk factors.

As a prerequisite, clinicians should follow the healthy lifestyle themselves.

A Commitment To Lifelong Learning Must Be Integral To Ethical Professional Practice

9-2 Evidence-Based Medicine (EBM) and the Medical Curriculum: The Search Engine Is Now As Essential As The Stethoscope

Today, health professionals cannot rely on what they were first taught if they want the best for their patients. Clinical performance deteriorates over time. A commitment to lifelong learning must be integral to ethical professional practice.

The skills needed to find potentially relevant studies quickly and reliably, to separate the wheat from the chaff, and to apply sound research findings to patient care, have today become as essential as skills with the stethoscope.

Individual practitioners need to be able to find and use the evidence themselves. A 21st century clinician who cannot critically read a study is as unprepared as one who cannot take a blood pressure or examine the cardiovascular system. The medical curriculum should reflect the importance of changing information for today’s practitioner—the necessary skills must be taught and assessed with the same rigour as the physical examination.

We should teach students the anatomy of research and the basic knowledge and skills for evidence-based practice. These basic skills of using (not doing) research—searching, appraising, and applying research evidence to individual patients—should be taught early and applied as an integral part of learning in all years of the curriculum. But, to be integrated with clinical skills, they must also be regularly applied in the clinical setting.

If today’s practitioners are to retain their professionalism, information and appraisal skills need to be improved urgently.

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“Keeping up” is a continuing and major challenge for primary care physicians (PCPs). The question is—how to do it?

I agree with the editorialists’ comments regarding training medical students and residents to find and appraise the evidence themselves, and to decide if the conclusions presented are firmly evidence-based.

I do not believe this extends to primary care. The editorialists place too great a burden on primary care clinicians. We are already time-constrained. PCPs must rely on independent experts who have the time and skill to interpret and condense the evidence without bias. The local medical librarian and informal consultations with local specialists can be helpful. Trying to access the evidence through a search engine (eg, through GOOGLE) may lead to overwhelming confusion. There are periodicals and digests available to help us to keep current. Some scan the literature frequently, and assess the evidence rigorously and reliably.

PCPs’ responsibility is to interpret the evidence as it applies to their individual patient. Their job is to develop an empathetic relationship with the patient, determine the patient’s goals and willingness to comply with a medical program, fully inform the patient about benefits, harms and costs of an intervention, and to negotiate his acceptance or rejection. There is no guarantee an individual patient will benefit from application of the best of EBM. Indeed it may cause harm.

Whatever the evidence, value and preference judgments are implicit in every clinical decision. Clinical decisions must not only attend to the best available evidence, but also to the values, and preferences of the informed patient that refer to patients’ perspectives, beliefs, expectations, and goals. “Patient participation in decision-making is a patient’s right.”

There may be 100 reasons why an individual patient does not fit the pattern of a randomized, controlled trial (RTC). PCPs should not place too much faith on the ever-changing and sometimes conflicting evidence of the best of EBM. EBM is a work in progress. It can be a fickle mistress.

There may be good reasons why the best evidence cannot be applied to an individual patient.

1) Costs of the intervention may be too high. The patient may be uninsured.
2) The patient may be medically illiterate. He may not understand.
3) There may be a language barrier.
4) The patient may be non-compliant. The application may be considered too burdensome and inconvenient.
5) Risks may outweigh benefits for an individual. If the number needed to treat to benefit one patient = 24, 23 patients will be exposed to the harms and costs of the intervention without benefit. Patients should understand this.
6) Guidelines, based RCTs may quickly become obsolete. (Some say, on average, they change every 5 years.)

7) The results of a trial may not be generalizable. The individual patient may be included in the many exclusions all RCTs contain.

8) The evidence from different trials may be conflicting.

9) Many trials report surrogate outcomes. They may not determine clinical outcomes.

10) Many trials are biased. Relative to not-for-profit funding, researchers funded by industry may interpret results differently and in favor of the industry product. (When abstracting an article on drug effects, I always look for the funding source. If it is a drug company, I automatically, perhaps unfairly at times, look for bias. Sometimes “spin” is painfully evident.

11) RCTs may downplay adverse effects.

12) RCTs may stress statistical outcomes when clinical outcomes are dubious.

13) RCTs may emphasize relative risk reductions and downplay absolute risk reductions.

14) RCTs may be based on a small sample size with limited power.

15) RCTs may emphasize the new and neglect the old.

16) All trials have exclusion criteria. If the individual patient fits one of the exclusions, how does the PCP proceed?

17) RCTs may present a nebulous and complex treatment in the intervention or control group. What is cognitive behavioral therapy; a graded exercise program; salt restriction; a stroke unit; low fat diet; telephone counseling? Many authors are willing to supply more detailed information on request. (Drug trials are usually more specific.)

Some of these comments are based on PROGRESS IN EVIDENCE-BASED MEDICINE JAMA October 15, 2008; 300: 1814-16 first author Victor M Montori, College of Medicine, Mayo Clinic, Rochester, MINN

9-3 ADHERENCE TO MEDITERRANEAN DIET AND HEALTH STATUS: A Meta-analysis

This meta-analysis included 12 prospective studies (over 1 500 000 subjects) which reported the association between adherence to the MD and incidence of diseases.

Defined MD by scores that estimated conformity of the dietary pattern with the traditional MD. Values of 0 or 1 were assigned to each dietary component: vegetables, meat, nuts, seeds, legumes, fruits, milk and dairy products. Total adherence scores varied from a minimum of 0 to a maximum of 9 points.

Overall mortality: Each 2-point increase in adherence score was associated with a significant
reduction. (Relative risk = 0.91)

Cardiovascular mortality: Each 2-point increase in the MD score was associated with a significant reduction. (RR = 0.91)

Cancer incidence and mortality: Each 2-point increase in the MD score was associated with a significant reduction. (RR = 0.94)

Parkinson’s disease and Alzheimer’s disease: Each 2-point increase in the MD score was associated with a significant reduction (RR = 0.87)

A 2-point increase in the MD score determined a 9% reduction in overall mortality, a 9% reduction in mortality from cardiovascular disease, a 6% reduction in incidence and mortality from neoplasms, and a 13% reduction in the incidence of Parkinson’s disease and Alzheimer’s disease.

Conclusion: Adherence to a MD can significantly decrease the risk of overall mortality, mortality from cardiovascular disease, incidence of and mortality from cancer, and incidence of Parkinson’s disease and Alzheimer’s disease.

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I have not understood what food factors are related to increased or decreased risk of cancers, and why.

The sunny Mediterranean latitude may also be a factor in the original observation of benefit for persons residing in this area. Vitamin D levels are higher among persons who enjoy the sun and are more exposed to it.

The study included little about fish, olive oil, and modest alcohol consumption. All of us know roughly what the MD is. We should be more compliant with the diet. We should add the MD to our continuing recommendations to patients regarding healthy lifestyles.

**Extends The Time-To-Treatment Window**

**9-4 THROMBOLYSIS WITH ALTEPLASE 3 TO 4.5 HOURS AFTER ACUTE ISCHEMIC STROKE**

Thrombolytic treatment with alteplase initiated within 3 hours after onset of symptoms is the only medical therapy currently available for acute ischemic stroke. Patients so treated were reported to be at least 30% more likely to have minimal or no disability at 3 months than those who received placebo.

This phase 3 trial was designed to test the hypothesis that alteplase can be safe and effective when given 3 to 4.5 hours after onset of symptoms of ischemic stroke.
The trial entered 821 patients (mean age = 60) with acute ischemic stroke. All had onset of stroke symptoms 3 to 4.5 hours before initiation of treatment. All received a CT brain scan before and within 36 hours after treatment. At baseline, none had brain hemorrhage or a major infarction.

Randomized to:

1) Intravenous alteplase (*Actilyse*; Boehringer Ingelheim) 0.9 mg per kg body weight, given 10% as a bolus intravenously, and the remainder over 1 hour, or

2) Placebo

Primary endpoint = disability at 90 days, dichotomized as a favorable outcome (score 0 to 1 on the modified Rankin scale), or an unfavorable outcome (score 3, 4, 5, or 6).

Secondary outcome = global outcome analysis of 4 neurologic and disability scores combined.

Percentage of patients grouped according to time intervals of receiving treatment after onset:

- 3 – 3.5 h  10%
- 3.5 - 4.0 h  47%
- 4.0 – 4.5 h  39%

(Median time for administration of alteplase was 4 hours. Time not available in 12 patients)

**Efficacy:**

<table>
<thead>
<tr>
<th></th>
<th>Alteplase</th>
<th>Placebo</th>
<th>Absolute difference</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Primary end point.</td>
<td>52%</td>
<td>45%</td>
<td>7%</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>(Patients with Rankin scores 0 and 1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. Secondary outcome—global odds ratio (favoring alteplase)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intention to treat</td>
<td>1.28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per protocol</td>
<td>1.39</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Safety:**

Deaths (8%) were equal in both groups and occurred at about the same time intervals.

Incidence of symptomatic intracranial hemorrhage: alteplase 2.4%; placebo 0.3%. All occurred within the first 36 hours

The initial severity of a stroke is a strong predictor of the functional and neurological outcome and the risk of death. Patients with severe stroke were excluded from this trial. It is likely that the milder initial severity of stroke overall among patients enrolled in the trial explains the improved outcomes as compared with other trials.

**Conclusion:** Intravenous alteplase given within 3 to 4.5 hours after onset of stroke symptoms was associated with a modest, but significant, improvement in clinical outcomes.

There was a higher rate of symptomatic intracranial hemorrhage.
Questions for primary care:

1) How accurately is the time of onset determined? Do patients really know the exact time in most cases? The study excluded patients for whom the time of onset was not known.

2) Is there any attempt to negotiate a treatment plan with the patient or family? Would time limits negate any attempt to explain risks and benefits, allowing the patient to choose?

3) Could primary care clinicians accurately determine severity of the stroke? Would the patient recover just as well without thrombolysis?

4) Would primary care clinicians consider all exclusion criteria? There are 15 listed on page 1320. I believe this application would be extremely difficult for primary care clinicians to apply in their communities. Stroke specialists should be available at local hospitals round the clock, just as cardiologists are available for treatment of acute myocardial infarction.

Large Polyps Occur In About One In 14 Asymptomatic Patients Over Age 50. Most Are Precancerous.

9-5 PREVALENCE OF COLON POLYPS DETECTED BY COLONOSCOPY SCREENING IN ASYMPTOMATIC BLACK AND WHITE PATIENTS

This study prospectively collected from over 80,000 whites and over 5,000 blacks receiving an initial screening colonoscopy. All were asymptomatic.

Main outcome measures = prevalence and location of polyps 10 mm and over, adjusted for age, sex, and family history of colon cancer.

About 84% of polyps of this size were advanced adenomas: tubular adenoma, serrated adenoma, adenoma with villous histology, high grade dysplasia, or invasive cancer. (Only 10% to 20% of polyps ≥10 mm are not neoplastic.)

Prevalence of one or more polyps ≥10 mm:

<table>
<thead>
<tr>
<th></th>
<th>White (%)</th>
<th>Black (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>6.2</td>
<td>7.7</td>
</tr>
<tr>
<td>Male</td>
<td>7.7</td>
<td>8.4</td>
</tr>
<tr>
<td>Female</td>
<td>4.7</td>
<td>7.2</td>
</tr>
</tbody>
</table>

Prevalence of one or more polyps ≥10 mm according to age:

<table>
<thead>
<tr>
<th></th>
<th>White (%)</th>
<th>Black (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>4.2</td>
<td>6.2</td>
</tr>
<tr>
<td>50-59</td>
<td>5.3</td>
<td>6.1</td>
</tr>
<tr>
<td>60-69</td>
<td>7.1</td>
<td>10.5</td>
</tr>
<tr>
<td>70-79</td>
<td>7.7</td>
<td>10.8</td>
</tr>
</tbody>
</table>
Conclusion: Asymptomatic black patients were more likely than whites to have polyps ≥10 mm.
   Polyps ≥10 mm were more common after age 60.
   The great majority of polyps ≥10 mm were neoplastic (pre-cancer).

I abstracted this article, not because of the modest racial difference, but to inform that larger polyps occur in about one in 14 asymptomatic patients over age 50. Most are precancerous. Removing these polyps will reduce incidence of CRC and death from CRC.

These Findings Provide Support For Rescreening After An Interval Of 5 Years Or Longer

9-6 FIVE-YEAR RISK OF COLORECTAL NEOPLASIA AFTER NEGATIVE SCREENING COLONOSCOPY

This study determined the incidence of any neoplasia and advanced neoplasia at a 5-year rescreening interval among patients (2943) who had no neoplasia on the initial colonoscopy.

Forty two % (1243) returned for rescreening at 5 years. Of these, 199 had hyperplastic polyps at baseline. These were considered to have had negative colonoscopies.

At 5 years, categorized patients according to the most advanced lesion present: no polyp; hyperplastic polyp; tubular adenoma less than 1 cm; advanced adenomas (tubular adenoma one or more cm in diameter, a polyp with villous histological features or high grade dysplasia); or a colorectal cancer [CRC]).

No CRCs were detected on the rescreen.

Outcomes from a 5-year repeat colonoscopy:

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of subjects</th>
<th>Any adenoma (%)</th>
<th>Advanced adenoma (%)</th>
<th>NNS**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1256</td>
<td>16</td>
<td>1.3</td>
<td>79</td>
</tr>
<tr>
<td>Men***</td>
<td>712</td>
<td>20</td>
<td>1.8</td>
<td>55</td>
</tr>
<tr>
<td>Women</td>
<td>544</td>
<td>10</td>
<td>0.6</td>
<td>182</td>
</tr>
<tr>
<td>Hyperplastic ****</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>polyp a baseline</td>
<td>199</td>
<td>24</td>
<td>2.0</td>
<td>50</td>
</tr>
<tr>
<td>No polyps at baseline</td>
<td>1057</td>
<td>15</td>
<td>1.1</td>
<td>88</td>
</tr>
</tbody>
</table>

(* Almost all were villous.)

(** Number needed to screen at 5 years to detect one advanced adenoma.)

(*** Adenomas and advanced adenomas were more common in men.)
Hyperplastic polyps may be an independent risk factor for adenoma and advanced adenoma.

The natural history of advanced adenomas is not known. There is uncertainty about the clinical importance of “advanced adenoma” and its appropriateness as a target for programs of screening and surveillance.

“Given the low risk of advanced neoplasia, we believe that 5 years is probably the minimum duration of protection for nearly all persons who do not have a family history of colorectal cancer.”

Conclusion: Among persons previously screened with colonoscopy who have no neoplasia, the 5-year risk of CRC is extremely low. The risk of advanced neoplasia is also low. It is lower for women than for men. These findings suggest that among persons at average risk for CRC, rescreening colonoscopy need not be performed sooner than 5 years after an initial negative colonoscopy.

I believe this has practical implications for advice given to patients by primary care clinicians.

Colonoscopies may be performed too frequently. Costs and inconvenience are high. Complications occur in up to 2 in 1000 patients. But, there is no doubt that colonoscopy saves lives.

The study does not try to answer remaining questions:

1) How frequently to rescreen those with a polyp at the initial screen?
2) At what interval should we advise an individual patient with a negative screen to be rescreened?
3) Should patients with a hyperplastic polyp be screened more frequently? Should men be screened more frequently than women?
4) How to factor in costs, inconvenience, and possible adverse effects of colonoscopy?
5) How often to screen patients with a positive family history?

This is a good example of the value of negotiations between physicians and individual patients based on informed consent. Some will wish early rescreen; some will be comfortable to extend the period. Some will never return.

To Prevent Further Bone Loss And To Reduce The Risk For Initial And Subsequent Fracture

9-7 PHARMACOLOGICAL TREATMENT OF LOW BONE DENSITY OR OSTEOPOROSIS

TO PREVENT FRACTURES: A Guideline from the American College of Physicians.

Recommendation 1: ACP recommends that clinicians offer pharmacological treatment to men as well as women who have known osteoporosis, and to those who have experienced fragility fractures. (Strong recommendation; high quality evidence)
Recommendation 2: ACP recommends that clinicians consider pharmacologic treatment for men and women who are at risk for developing osteoporosis. (Weak recommendation; moderate quality evidence.)

Recommendation 3 ACP recommends that clinicians choose among pharmacologic treatment options for osteoporosis in men and women on the basis of an assessment of risks and benefits in individual patients. (Strong recommendation; moderate quality evidence.)

Good evidence supports the treatment of patients with known osteoporosis to prevent further bone loss and to reduce the risk for initial and subsequent fracture.

Bisphosphonates are FDA approved for prevention and treatment. Bisphosphonates reduce risk of vertebral, non-vertebral, and hip fractures. They are reasonable options as first-line therapy especially for patients who have high risk for hip fracture. Estrogen also reduces risk of these fractures, but is associated with serious risks.

There is strong evidence of a modest effect of calcium and vitamin D. Most trials of other drugs included their use. ACP recommends adding them.

Further study is needed on prevention strategies in both men and women and the appropriate duration of treatment for osteoporosis.

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Practical Pointers has favored articles on osteoporosis and osteopenia. I believe prevention (contrasted to treatment) is a major opportunity for primary care. The chief risk factor is age. As patients age, bone loss continues, finally affecting everyone. Thus, prevention (as for cardiovascular disease) is a major public health opportunity.

I believe that, if bisphosphonates were started in low dose at an early age and continued, much of the osteoporosis problem would disappear. Why not prescribe a “polypill” for prevention of osteoporosis which would be taken universally beginning at age 60? The pill would contain 800 IU vitamin D3, 1000 mg calcium, and a very low dose of a bisphosphonate.

This would have to be given empirically. It would take years to conduct a trial to prove or disprove effectiveness.

The article notes that bisphosphonate trials have not lasted longer than 5 years.

Certainly, vitamin D and calcium supplements should be started at an early age.
Observational studies suggest that older people who are free of dementia, but report memory decline or show objective evidence of cognition impairment, are more likely to develop Alzheimer disease over time. Numerous observational studies have found that people who are physically active seem less likely than sedentary persons to experience cognitive decline and dementia later in life.

This trial was designed to test whether a 24-week home-based physical activity intervention would reduce the rate of cognitive decline among older adults at increased risk of dementia.

Randomized, controlled trial of 6-months of physical activity recruited volunteers (n = 170; mean age = 69) who reported memory problems, but did not meet criteria for dementia. 138 completed the trial.

Randomized to: 1) an education and usual care group (about memory loss, stress management, healthful diet, alcohol consumption, and smoking, but not physical activity), or 2) home-based program of physical activity.

Participants were encouraged to perform at least 150 minutes of moderate-intensity physical activity per week. (Three sessions of 50 minutes.)

Main outcome measure = change in Alzheimer Disease Assessment Scale (ADAS-cog) score over 18 months. Possible range = 0 to 70.

Intention-to-treat analysis:

A. End of 6-month intervention:
   Exercise group: ADAS-cog score improved by 0.26 points
   Control group: ADAS-cog score deteriorated by 1.04 points.

B. At 18 months:
   Exercise group: ADAS-cog score improved by 0.73 points.
   Control group: ADAS-cog score improved by 0.04 points.

   (Differences between participants in the ADAS-cog score were statistically significant.)

“Unlike medication, which was found to have no significant effect on mild cognitive impairment at 36 months, physical activity has the advantage of health benefits that are not confined to cognitive function alone.” (Physical activity has been associated with lessening physical disability, depression, and incidence of falls, increased quality of life, and improvement in cardiovascular function.)
Importantly, the beneficial effects of physical activity were sustained during the 18 month follow-up period.

Conclusion: In adults with subjective memory impairment, a 6-month program of physical activity provided a modest improvement in cognition over an 18-month follow-up.

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I doubt the improvement is clinically significant. However, there was no deterioration in the exercise group at 18 months. The intervention may delay deterioration thus decreasing the end-of-life dependence on others. It would be advisable to begin a program of exercise before aging prevents it.

Physical activity undoubtedly has many other advantages in the elderly. It has few adverse effects—much fewer than medications. Primary care clinicians should prescribe an exercise program for all patients, and adopt one themselves as a role model.
ABSTRACTS SEPTEMBER 2008

Associated With Markedly Lower Mortality

9-1 COMBINED IMPACT OF LIFESTYLE FACTORS ON MORTALITY

Diet, physical activity, adiposity, cigarette smoking, and alcohol abstinence (and over use) have been associated with risk of chronic diseases. Identifying priorities for clinical and public health efforts, and understanding the magnitude of effects of these risk factors on overall health are fundamental.

This study examined combinations of lifestyle factors in relation to cancer, cardiovascular disease, and all cause mortality during a 24-year follow-up of middle-aged women.

Conclusion: Adherence to lifestyle guidelines was associated with markedly lower mortality.

STUDY

1. The prospective Nurses’ Health Study followed over 77 000 women aged 34 to 59 at baseline, beginning in 1980. All were free from cardiovascular disease and cancer at baseline.

2. All completed periodic questionnaires on known and suspected risk factors for chronic diseases.

   Periodically assessed:
   A. Diet by a 61-item food frequency questionnaire. Nutrient intakes were calculated.
   B. Cigarette smoking
   C. Physical activity
   D. Alcohol consumption
   E. BMI (calculated at baseline)

3. Classified as low risk:
   A. Healthy diet on a scale of 0 to 10 (0 = least healthy; 10 = recommended intake). Considered the highest 40% to be at low risk
   B. Never smoking
   C. Average of 30 minutes per day of moderate physical activity
   D. Alcohol consumption less than 15 g per day. (Up to approximately one drink daily.)
   E. BMI 18.5 to 25

4. Determined mortality over 24 years.

RESULTS

1. During follow-up of over 1 700 000 person-years, documented 8882 all-cause deaths; 1790 from cardiovascular disease; 4527 from cancer
2. Cigarette smoking, higher BMI, less physical activity, and a lower healthy diet score were associated with increased cardiovascular, cancer, and all-cause mortality. Modest alcohol consumption was associated with a lower risk of cardiovascular disease than alcohol abstinence. Heavy alcohol consumption was associated with an increased risk of cancer. Light to moderate alcohol consumption was associated with the lowest all-cause mortality.

3. Comparing the high risk with the low risk category of lifestyle factors, the estimated population attributable risk of mortality:

A. Cigarette smoking 28%
B. Overweight 14%
C. Lack of physical activity 17%
D. Low diet quality 13%
E. Not having light to moderate alcohol intake 7%

4. Relative risk of mortality associated with 5 risk factors compared with no risk factors.

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Death from any cause</th>
<th>Cardiovascular death</th>
<th>Cancer death</th>
</tr>
</thead>
<tbody>
<tr>
<td>No risk factors (2.4%)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>One risk factor (12%)</td>
<td>1.34</td>
<td>1.13</td>
<td>1.55</td>
</tr>
<tr>
<td>Two risk factors (27%)</td>
<td>1.70</td>
<td>1.88</td>
<td>1.71</td>
</tr>
<tr>
<td>Three risk factors (34%)</td>
<td>2.25</td>
<td>2.80</td>
<td>2.07</td>
</tr>
<tr>
<td>Four risk factors (21%)</td>
<td>3.27</td>
<td>4.77</td>
<td>2.79</td>
</tr>
<tr>
<td>Five risk factors (4.2%)</td>
<td>4.31</td>
<td>8.17</td>
<td>3.26</td>
</tr>
</tbody>
</table>

DISCUSSION
1. Never smoking, engaging in regular physical activity, eating a healthy diet, and avoiding overweight were each associated with a markedly lower mortality over 24 years. Light to moderate alcohol consumption (up to one drink a day) was also associated with a lower risk of all cause mortality.

2. “We estimated the 55% of all-cause mortality, 44% of cancer mortality, and 72% of cardiovascular mortality could have been avoided by adherence to these lifestyle guidelines”.

3. Randomized, controlled trials (RCT) support the protective effect of a prudent Mediterranean style diet. And the combination of physical activity, a healthy diet, moderate weight loss and smoking cessation for protection against premature mortality.

4. RCTs have also shown beneficial effects of moderate alcohol consumption, reduced trans fat intake, high fruit and vegetable intake, and whole grain intake on biological markers of cardiovascular risk.
Heavy alcohol consumption is associated with higher cancer mortality, and low alcohol consumption is associated with lower cardiovascular mortality.

CONCLUSION

Adherence to lifestyle guidelines is associated with markedly lower mortality in middle aged women.

BMJ September 27, 2008; 337: 742-45 Original investigation, first author Rob M vanDam, Harvard School of Public Health, Boston, Mass.

A Commitment To Lifelong Learning Must Be Integral To Ethical Professional Practice.

9-2 EVIDENCE-BASED MEDICINE AND THE MEDICAL CURRICULUM: The Search Engine Is Now As Essential As The Stethoscope

Today health professionals cannot rely on what they were first taught if they want the best for their patients. Clinical performance deteriorates over time. A commitment to lifelong learning must be integral to ethical professional practice.

However, the speed of the increase in knowledge—more than 2000 new research papers are added to Medline each day—presents a challenge.

The skills needed to find potentially relevant studies quickly and reliably, to separate the wheat from the chaff, and to apply sound research findings to patient care, have today become as essential as skills with the stethoscope.

Although evidence-based guidelines may help clinicians in selected areas, they cannot cover the range of questions, or have the timeliness that clinical practice needs. Individual practitioners need to be able to find and use evidence themselves. A 21st century clinician who cannot critically read a study is as unprepared as one who cannot take a blood pressure or examine the cardiovascular system.

The medical curriculum should reflect the importance of changing information for today’s practice. These necessary skills must be taught and assessed with the same rigour as the physical examination. We should teach students the anatomy of research and the basic knowledge and skills for evidence-based practice. These basic skills of using (not doing) research—searching, appraising, and applying research evidence to individual patients should be taught early and applied as an integral part of learning in all years of the curriculum. They must also be regularly applied in the clinical setting.
Doctors should regularly log and discuss clinical questions, produce critically appraised topics, and lead evidence-based journal clubs.

Workplace learning is urgently needed if we are to make best use of medical research. A relatively small expenditure on developing the skills of the users of these resources will help translate evidence-based guidelines not changes in practice thereby improving the quality of health care. If today’s practitioners are to retain their professionalism, information and appraisal skills need to be improved urgently.

BMJ September 27, 2008; 337: 704-05 Editorial, first author Paul Glasziou, University of Oxford, UK.

Associated With Significant Improvements In Health Status

9-3 ADHERENCE TO MEDITERRANEAN DIET AND HEALTH STATUS: A Meta-analysis

The Mediterranean diet (MD) has been widely reported to be a model of healthy eating. MD has a beneficial effect on cardiovascular disease and chronic degenerative diseases.

This study aimed to systematically review all available prospective studies in order to establish the role of adherence to a MD in primary prevention.

Conclusion: General adherence to the MD is associated with significant improvements in health status.

STUDY

1. This meta-analysis included 12 prospective studies (over 1 500 000 subjects) which reported the association between adherence to the MD and incidence of diseases.
2. Defined MD by scores that estimated conformity of the dietary pattern with the traditional MD.
   Values of 0 or 1 were assigned to each dietary component: vegetables, meat, nuts, seeds, legumes, fruits, milk and dairy products. Total adherence scores varied from a minimum of 0 to a maximum of 9 points.

RESULTS

1. Overall mortality: Each 2-point increase in adherence score was associated with a significant reduction. (Relative risk = 0.91)
2. Cardiovascular mortality: Each 2-point increase in the MD score was associated with a 
significant reduction. (RR = 0.91)

3. Cancer incidence and mortality: Each 2-point increase in the MD score was associated with a 
significant reduction. (RR = 0.94)

4. Parkinson’s disease and Alzheimer’s disease: Each 2-point increase in the MD score was 
associated with a significant reduction (RR = 0.87)

DISCUSSION

1. “This meta-analysis comprising more than 1.5 million healthy subjects and 40 000 fatal and 
non-fatal events shows that greater adherence to a Mediterranean diet is significantly associated with 
a reduced risk of overall mortality, cardiovascular mortality, cancer incidence and mortality, and 
incidence of Parkinson’s disease and Alzheimer’s disease.”

2. A 2-point increase in the MD score determined a 9% reduction in overall mortality, a 9%
reduction in mortality from cardiovascular disease, a 6% reduction in incidence and mortality from 
neoplasms, and a 13% reduction in the incidence of Parkinson’s disease and Alzheimer’s disease.

3. The MD is not a homogeneous pattern of eating. Heterogeneity on the score items exists. How to 
group some food categories such as legumes, nuts, and milk and dairy products; the real importance 
of different types of meat; and the establishment of moderate amounts of alcohol intake are still 
matters of debate. However, the key characteristics of a MD were present in all studies, and the 
overall analysis seemed not to be significantly influenced by differences in specific food categories 
between studies.

4. A MD has been shown to have a beneficial effect on the occurrence of disease in industrialized and 
non-industrialized countries. Unfortunately, despite the worldwide promotion of the MD, a 
progressive shift to a non-MD dietary pattern has developed.

5. These results strongly encourage a MD pattern for the primary and secondary prevention of 
major chronic diseases.

CONCLUSION

Adherence to a MD can significantly decrease the risk of overall mortality, mortality from 
cardiovascular disease, incidence of and mortality from cancer, and incidence of Parkinson’s disease and 
Alzheimer’s disease.
Extends The Time-To-Treatment Window

9-4 THROMBOLYSIS WITH ALTEPLASE 3 TO 4.5 HOURS AFTER ACUTE ISCHEMIC STROKE

Thrombolytic treatment with alteplase initiated within 3 hours after onset of symptoms is the only medical therapy currently available for acute ischemic stroke. Patients so treated were reported to be at least 30% more likely to have minimal or no disability at 3 months than those who received placebo.

Subsequent trials reported no efficacy when treatment was given up to 6 hours after start of symptoms.

Other analyses showed a clear association between treatment efficacy and favorable outcomes even when the treatment was given between 3 and 4.5 hours. (Odds ratio = 1.4 compared with placebo.) The analyses also suggested that the longer time window was not associated with higher rates of intracranial hemorrhage and death.

International guidelines recommend alteplase as first line treatment for eligible patients within 3 hours. It is as safe and effective in routine clinical practice as it is in randomized trials.

Despite these recommendations, alteplase is underused. It is estimated that fewer than 2% receive the treatment, primarily because of delayed admission to a stroke center.

This phase 3 trial was designed to test the hypothesis that alteplase can be safe and effective when given 3 to 4.5 hours after onset of symptoms of ischemic stroke.

Conclusion: It was effective, but was more frequently associated with symptomatic intracranial hemorrhage.

STUDY
1. This trial entered 821 patients (mean age = 60) with acute ischemic stroke. All had onset of stroke symptoms 3 to 4.5 hours before initiation of treatment.
2. All received a CT brain scan before and within 36 hours after treatment. At baseline, none had brain hemorrhage or a major infarction.¹
3. Randomized to:
   1) Intravenous alteplase (Actilyse; Boehringer Ingelheim) 0.9 mg per kg body weight, given 10% as a bolus intravenously, and the remainder over 1 hour, or
2) Placebo

4. Primary endpoint = disability at 90 days, dichotomized as a favorable outcome (score 0 to 1 on the modified Rankin scale\textsuperscript{2}), or an unfavorable outcome (score 3, 4, 5, or 6).

5. Secondary outcome = global outcome analysis of 4 neurologic and disability scores combined.

6. Safety end points included death, symptomatic intracranial hemorrhage, and other serious events.

RESULTS

1. Percentage of patients grouped according to time intervals of receiving treatment after onset:

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 – 3.5 h</td>
<td>10%</td>
</tr>
<tr>
<td>3.5 - 4.0 h</td>
<td>47%</td>
</tr>
<tr>
<td>4.0 – 4.5 h</td>
<td>39%</td>
</tr>
</tbody>
</table>

   (Median time for administration of alteplase was 4 hours. Time not available in 12 patients)

2. Efficacy:

<table>
<thead>
<tr>
<th></th>
<th>Alteplase</th>
<th>Placebo</th>
<th>Absolute difference</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Primary end point.</td>
<td>52%</td>
<td>45%</td>
<td>7%</td>
<td>14</td>
</tr>
</tbody>
</table>
   (Patients with Rankin scores 0 and 1)

   B. Secondary outcome—global odds ratio (favoring alteplase)

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention to treat</td>
<td>1.28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per protocol</td>
<td>1.39</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. Safety:

   A. Deaths (8%) were equal in both groups and occurred at about the same time intervals.

   B. There were more cases of intracranial hemorrhage in the alteplase group: 27% vs 18%.

   C. Incidence of symptomatic intracranial hemorrhage: alteplase 2.4%; placebo 0.3%. All occurred within the first 36 hours. (This was not a higher rate of symptomatic intracranial hemorrhage than that reported previously among patients treated within 3 hours.)

DISCUSSION

1. Patients with acute ischemic stroke benefited from alteplase given between 3 and 4.5 hours after symptom onset.

2. The overall rate of symptomatic intracranial hemorrhage was increased with alteplase.

   Mortality was not affected.

3. The initial severity of a stroke is a strong predictor of the functional and neurological outcome
and the risk of death. Patients with severe stroke were excluded from this trial. It is likely that the milder initial severity of stroke overall among patients enrolled in the trial explains the improved outcomes as compared with other trials.

4. There has been a gradual decline in the overall initial severity of stroke and the mortality rates among patients enrolled in major randomized trial of acute ischemic stroke over the past two decades.

5. Early treatment remains essential. The effect size of thrombolysis is time-dependent.

   Treatment with alteplase is twice as efficacious when administered within the first 1.5 hours as when given within 1.5 to 3 hours. The “door to needle” time remains paramount. “Having more time does not mean we should be allowed to take more time.”

6. The effect size of this trial is clinically significant (NNT = 14), and extends the treatment window for patients who do not arrive at the hospital early.

CONCLUSION

Intravenous alteplase given within 3 to 4.5 hours after onset of stroke symptoms was associated with a modest, but significant, improvement in clinical outcomes.

There was a higher rate of symptomatic intracranial hemorrhage.

NEJM September 25, 2008; 359: 1317-29 Original investigation by the European Cooperative Acute Stroke Study (ECASS), first author Werner Hacke, University of Heidelberg, Germany.
The trial was supported by Boehringer Ingleheim

1 Defined as involving more than 1/3 of the middle cerebral artery territory. No patient had a severe stroke defined as a score of > 25 on the National Institutes of Health Stroke Scale. This scale contains 15 items. The scores range up to 42. For other exclusion criteria see table 1 page 1320.

2 The modified scale has a range of 0 to 6. Zero = no symptoms; 6 = death.

9-5 PREVALENCE OF COLON POLYPS DETECTED BY COLONOSCOPY SCREENING IN ASYMPTOMATIC BLACK AND WHITE PATIENTS
Colorectal cancer (CRC) incidence and mortality are higher in black patients compared with whites. Factors such as poor access to care and lower rates of screening could delay diagnosis, resulting in more advanced stage disease at diagnosis.

There is considerable evidence that tumor biology and genetics play a role in some of the racial differences.

The American College of Gastroenterology has recommended CRC screening beginning at age 45 in blacks.

This study hypothesized that, in patients undergoing screening colonoscopy, black patients are more likely to have polyps sized ≥10 mm than white patients.

Conclusion: Compared with whites, black men and women had higher risk of larger polyps.

**STUDY**

1. Prospectively collected, from multiple sites, of over 80,000 whites and over 5000 blacks who received an initial screening colonoscopy. Ages: 50-59 46%; 60-69 30%. All were asymptomatic.

2. Main outcome measures = prevalence and location of polyps 10 mm and over, adjusted for age, sex, and family history of colon cancer.

3. About 84% of polyps of this size were advanced adenomas: tubular adenoma, serrated adenoma, adenoma with villous histology, high grade dysplasia, or invasive cancer. (Only 10% to 20% of polyps ≥10 mm are not neoplastic.)

**RESULTS**

1. Prevalence of one or more polyps ≥10 mm:

<table>
<thead>
<tr>
<th></th>
<th>White (%)</th>
<th>Black (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>6.2</td>
<td>7.7</td>
</tr>
<tr>
<td>Male</td>
<td>7.7</td>
<td>8.4</td>
</tr>
<tr>
<td>Female</td>
<td>4.7</td>
<td>7.2</td>
</tr>
</tbody>
</table>

2. Prevalence of one or more polyps ≥10 mm according to age:

<table>
<thead>
<tr>
<th>Age Group</th>
<th>White (%)</th>
<th>Black (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>4.2</td>
<td>6.2</td>
</tr>
<tr>
<td>50-59</td>
<td>5.3</td>
<td>6.1</td>
</tr>
<tr>
<td>60-69</td>
<td>7.1</td>
<td>10.5</td>
</tr>
<tr>
<td>70-79</td>
<td>7.7</td>
<td>10.8</td>
</tr>
</tbody>
</table>

3. There was no statistically significant increase in risk of polyps ≥10 mm in subjects of either race with a family history of CRC.
4. There was a higher prevalence of proximal (right side) polyps ≥10 mm in blacks compared with whites.

DISCUSSION
1. In an asymptomatic population, cancer precursor lesions are common, more so in black patients than in white. This strongly emphasizes the importance of timely screening in blacks.
2. In this analysis, individuals over age 60, female sex, and patients with a family history were more likely to have proximal lesion.

CONCLUSION
Asymptomatic black patients were more likely than whites to have polyps >10 mm.

Polyps ≥10 mm were more common after age 60.

The great majority of polyps ≥10 mm were neoplastic (pre-cancer).

JAMA September 24, 2008; 300: 1417-22 Original investigation, first author David A Lieberman, Portland VA Medical Center, Oregon.

These Findings Provide Support For Rescreening After An Interval Of 5 Years Or Longer
9-6 FIVE-YEAR RISK OF COLORECTAL NEOPLASIA AFTER NEGATIVE SCREENING COLONOSCOPY

The appropriate interval for endoscopic rescreening after a negative colonoscopic examination is uncertain. There is concern about whether adequate resources exist to satisfy the demand for colonoscopy. Some data suggest that colonoscopy may be performed too frequently and for inappropriate indications. Determination of the appropriate frequency of rescreening for persons with a normal initial colonoscopy could have a substantial effect on costs and the capacity to provide it.

Guidelines differ.

This study determined the incidence of any neoplasia and advanced neoplasia at a 5-year rescreening interval among patients who had no neoplasia on the initial colonoscopy.

Conclusion: The 5-year risk of cancer was extremely low. The risk of advanced adenoma was also low.

STUDY
1. Retrospectively identified 2943 persons (mean age 57) who had a negative screening colonoscopy at baseline.

2. Of these 1256 (42%) returned for rescreening at 5 years. Of these, 199 had hyperplastic polyps at baseline. These were considered to have had negative colonoscopies.

3. At 5 years, categorized patients according to the most advanced lesion present: no polyp; hyperplastic polyp; tubular adenoma less than 1 cm; advanced adenomas (tubular adenoma one or more cm in diameter, a polyp with villous histological features or high grade dysplasia); or a colorectal cancer [CRC].

RESULTS

1. No CRCs were detected on the rescreen.

2. Outcomes from a 5-year repeat colonoscopy:

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of subjects</th>
<th>Any adenoma (%)</th>
<th>Advanced adenoma (%)</th>
<th>NNS**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1256</td>
<td>16</td>
<td>1.3</td>
<td>79</td>
</tr>
<tr>
<td>Men***</td>
<td>712</td>
<td>20</td>
<td>1.8</td>
<td>55</td>
</tr>
<tr>
<td>Women</td>
<td>544</td>
<td>10</td>
<td>0.6</td>
<td>182</td>
</tr>
<tr>
<td>Hyperplastic ****</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>polyp a baseline</td>
<td>199</td>
<td>24</td>
<td>2.0</td>
<td>50</td>
</tr>
<tr>
<td>No polyps at baseline</td>
<td>1057</td>
<td>15</td>
<td>1.1</td>
<td>88</td>
</tr>
</tbody>
</table>

(* Almost all were villous.)

(** Number needed to screen at 5 years to detect one advanced adenoma.)

(*** Adenomas and advanced adenomas were more common in men.)

(**** Hyperplastic polyps may be an independent risk factor for adenoma and advanced adenoma.)

DISCUSSION

1. No CRCs were detected in persons at average risk who were rescreened 5 years after a first negative colonoscopy.

2. At 5-year rescreen, at least one adenomatous polyp was found in nearly 16% of subjects.

3. Advanced adenomas were present in 1.3%—more prevalent in men.

4. These findings provide support for rescreening after an interval of 5 years or longer.

5. The study did not assess a 10-year rescreening interval, which some guidelines recommend.
There are no data from prospective studies of sufficient size and duration to permit a direct assessment of the 10-year recommendation. At least two studies permit some assessment of this recommendation:

1) A retrospective cohort study of over 32,000 persons with no neoplasia on colonoscopy calculated the ratio of incidence of CRC in the screened group as compared with incidence in the general unscreened population. The incidence ratios for CRC between groups were 0.66 at one year; 0.55 at 5 years; and 0.28 at 10 years. (Ie, incidence of CRC was much lower in those with a negative colonoscopy than in the general population. In the screened group, incidence declined with age compared with those who received no screen.)

2) A population-based case-control study in which cases had CRC and controls were subjects without CRC. (Controls were three times as likely to have had a normal previous colonoscopy as were cases.) The odds ratio of controls/cases was 0.26 for development of CRC. (Ie, CRC was much less common in those who had a colonoscopy than in those who did not have a colonoscopy.) A previous colonoscopy indicated some protection against CRC for up to 20 years.

6. Another study reported that large polyps (>10 mm) that were left intact progressed to CRC at a rate of 1% per year.

7. For lesions smaller than 10 mm, it is unclear whether polyps with villous features progress to cancer, and, if so, at what rate. Progression of advanced adenomas to CRC has been reported to be much higher as age increases.

8. However, the natural history of advanced adenomas is not known. There is uncertainty about the clinical importance of “advanced adenoma” and its appropriateness as a target for programs of screening and surveillance.

9. “Given the low risk of advanced neoplasia, we believe that 5 years is probably the minimum duration of protection for nearly all persons who do not have a family history of colorectal cancer.”

10. The investigators of the present study caution that the generalizability of the findings may be limited because the numbers of subjects was small and included chiefly compliant middle-class whites.

CONCLUSION

Among persons previously screened with colonoscopy who have no neoplasia, the 5-year risk of CRC is extremely low.

The risk of advanced neoplasia is also low. It is lower for women than for men.
These findings suggest that, among persons at average risk for CRC, rescreening colonoscopy need not be performed sooner than 5 years after an initial negative colonoscopy.

NEJM September 18, 2008; 359: 1218-24 Original investigation, first author Thomas F Imperiale, Indiana University School of Medicine, Indianapolis.

To Prevent Further Bone Loss And To Reduce The Risk For Initial And Subsequent Fracture

9-7 PHARMACOLOGICAL TREATMENT OF LOW BONE DENSITY OR OSTEOPOROSIS TO PREVENT FRACTURES: A Guideline from the American College of Physicians.

This guideline, based on an extensive literature search (1966-2006), presents recommendations on various pharmacologic treatments to prevent fracture.

Recommendation 1:

ACP recommends that clinicians offer pharmacological treatment to men as well as women who have known osteoporosis, and to those who have experienced fragility fractures. (Strong recommendation; high quality evidence)

Good evidence supports the treatment of these patients to prevent further bone loss and to reduce the risk for initial and subsequent fracture.

Summary of evidence: Vertebral fracture Non-vertebral fracture Hip fracture

Agent:

Bisphosphonates

Alendronate\(^1\) Strong evidence that these 2 drugs decrease risk of all 3 fractures

Risedronate\(^2\) Bisphosphonates are FDA approved for prevention and treatment

Zoledronic acid For prevention

Estrogen For prevention

Calcium and vitamin D: There is strong evidence of a modest effect. Because most trials of other drugs included their use, ACP recommends adding them. Evidence is insufficient to determine the appropriate duration of therapy\(^3\)

Adverse effects:

Bisphosphonates: upper GI events. The association with osteonecrosis of the jaw needs further study.
Estrogen: thromboembolic events; stroke; endometrial bleeding; breast pain and tenderness, and breast cancer (when combined with progestin⁴). Combined estrogen-progestin is also associated with greater risk of stroke.

Zoledronic acid: muscular and joint pain. Evidence linking it to atrial fibrillation is contradictory.

Recommendation 2:
ACP recommends that clinicians consider pharmacologic treatment for men and women who are at risk for developing osteoporosis. (Weak recommendation; moderate quality evidence.)

“Evidence supports the treatment of selected patients who are at risk for osteoporosis but do not have a T-score on DXA less than -2.5. Evidence supporting preventive treatment is stronger for patients who are at moderate risk for osteoporosis, which includes patients who have a T-score from -1.5 to -2.5, are receiving glucocorticoids, or are older than 62 years of age.”⁵

Factors that increase the risk of osteoporosis in men include: age > 70; low body weight; weight loss; physical inactivity; and androgen deprivation therapy.

Factors that increase risk of osteoporosis in women include: low body weight; smoking; weight loss; family history; decreased physical activity; alcohol and caffeine use; and low calcium and vitamin D intake.

The WHO tool (www.shef.ac.uk/FRAX/) predicts risk for osteoporosis fracture. It is a helpful guide.

Recommendation 3:
ACP recommends that clinicians choose among pharmacologic treatment options for osteoporosis in men and women on the basis of an assessment of risks and benefits in individual patients. (Strong recommendation; moderate quality evidence.)
Bisphosphonates reduce risk of vertebral, non-vertebral, and hip fractures. They are reasonable options as first-line therapy especially for patients who have high risk for hip fracture. Estrogen also reduces risk of these fractures, but is associated with serious risks.

Further study is needed on prevention strategies in both men and women and the appropriate duration of treatment for osteoporosis.

Annals Internal Medicine September 16, 2008; 149: 404-15 “Clinical Guideline” by the Clinical Efficiency Assessment Subcommittee of the ACP, first author Amir Qaseem, American College of Physicians, Philadelphia, PA

Bisphosphonate trials ranged from 3 months to 5 years.
1 Fosamax; Merck (A generic is now available at about half the price of Fosamax)
2 Actonel: Proctor and Gamble
3 I believe calcium and vitamin D supplements should be started at an early age and continued indefinitely.
4 Progestin is the chief culprit.
5 “If a patient has the risk factors that increase the risk of developing osteoporosis, we are recommending that clinicians consider preventive treatment. Evidence supports preventive treatment to patients over age 62.” (Personal communication Amir Qaseem MD PhD)

Comparably Favorable With The Improvement Reported With The Use Of Donepezil.

9-8 EFFECT OF PHYSICAL ACTIVITY ON COGNITIVE FUNCTION IN OLDER ADULTS AT RISK FOR ALZHEIMER DISEASE

Observational studies suggest that older people who are free of dementia, but report memory decline or show objective evidence of cognition impairment, are more likely to develop Alzheimer disease over time.

Several clinical trials have investigated whether cholinesterase inhibitors (eg, donepezil; [Aricept; Eisai]) prevent cognitive decline. In one trial of 769 patients with mild cognitive impairment randomized to donepezil vs placebo, progression to dementia and change in cognition did not differ between groups. A trial of rivastigmine (Exelon; Novartis) to prevent conversion of mild cognitive to dementia over 4 years was similarly negative.

Numerous observational studies have found that people who are physically active seem less likely than sedentary persons to experience cognitive decline and dementia later in life.

Confirmatory evidence from randomized trial is lacking.

This trial was designed to test whether a 24-week home-based physical activity intervention would reduce the rate of cognitive decline among older adults at increased risk of dementia.

Conclusion: In adults with subjective memory impairment, a 6-month program of physical activity provided a slight improvement in cognition.

STUDY

1. Randomized, controlled trial of 6-months of physical activity recruited volunteers (n = 170; mean age = 69) who reported memory problems, but did not meet criteria for dementia.—138 completed the trial.
2. Randomized to: 1) an education and usual care group (about memory loss, stress management, healthful diet, alcohol consumption, and smoking, but not physical activity, or 2) home-based program of physical activity.

3. Participants were encouraged to perform at least 150 minutes of moderate-intensity physical activity per week. (Three sessions of 50 minutes.) Those who were already achieving the recommended target at baseline were encouraged to add another 50 minutes per week. The most frequently recommended activity was walking. All participants were asked to use a simplified diary to record their physical activity.

4. Subjects were followed at 6, 12, and 18 months after baseline.

5. Main outcome measure = change in Alzheimer Disease Assessment Scale (ADAS-cog) score over 18 months. Possible range = 0 to 70.

RESULTS

1. Intention-to-treat analysis:
   A. End of 6-month intervention:
      Exercise group: ADAS-cog score improved by 0.26 points.
      Control group: ADAS-cog score deteriorated by 1.04 points.
   B. At 18 months:
      Exercise group: ADAS-cog score improved by 0.73 points.
      Control group: ADAS-cog score improved by 0.04 points.
      (Differences between participants in the ADAS-cog score were statistically significant.)
   C. Word list delayed recall and Clinical Dementia Rating improved modestly in the exercise group.
   D. Other mental and physical component summaries did not change significantly.

DISCUSSION

1. “This trial is the first to demonstrate that exercise improves cognitive function in older adults with subjective and objective mild cognitive impairment.”

2. The study intervention resulted in 142 minutes more physical activity per week than usual care.

3. “Unlike medication, which was found to have no significant effect on mild cognitive impairment at 36 months, physical activity has the advantage of health benefits that are not confined to cognitive function alone.” (Physical activity has been associated with lessening disability, depression, and incidence of falls, increased quality of life, and improvement in cardiovascular function.)
4. The 1.3 point relative improvement in the ADAS-cog scale at 6 months compares favorably with the reported improvement of 0.5 points associated with the use of donepezil.

5. Importantly, the beneficial effects of physical activity were sustained during the 18 month follow-up period.

6. One possible mechanism for the improvement is an alteration in cerebral vascular functioning and brain perfusion. And it may be possible that environmental enrichment associated with increased physical activity enhances brain plasticity.

7. However, the study sample was relatively young and may not represent the population at highest risk of cognitive decline. Furthermore, the effect size was small.

8. “The results of this trial cannot be used to infer that physical activity reduces the risk of dementia among at-risk older adults.”

CONCLUSION

In adults with subjective memory impairment, a 6-month program of physical activity provided a modest improvement in cognition over an 18-month follow-up.

JAMA September 3, 2008; 300: 1027-37  Original investigation  by The Fitness for the Aging Brain Study (FABS), first author Nicola T Lautenschlager, University on Melbourne, Australia

9-9 A RETRACTION:  Autologous Myoblasts and Fibroblasts for Treatment of Stress Urinary Incontinence: A Randomized Controlled Trial   Lancet 2007; 369: 2179-86

Lancet has received information about the conduct of this study. An Austrian Government Agency has concluded that the study was conducted neither according to Austrian law nor according to the standards of International Conference on Harmonization of Good Clinical Practice.

There were critical deficiencies in the way patients’ consent was obtained and the source data were documented. The study did not have the required ethics committee approval. Almost all documents presented to the inspectors were copies. Many existed in different unsigned and undated versions. In one case the document was alleged to be forged.

The inspectors raised doubts as to whether a trial as described ever existed.

Lancet September 6, 2008; 372: 789-80  Comment, first author Sabine Kleinert, Lancet Staff.

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Practical Pointers abstracted this article in June 2007 [6-11], not as a practical point, but because it was so dramatic and a possible breakthrough. I was fooled, as was Lancet.

Retractions occur rarely in the major journal, but they do occur. Fortunately deception is usually caught.

I recall another egregious error in an article I abstracted, the results of which I accepted uncritically. It was one of the first trials of rofecoxib (Vioxx; Merck). It compared Vioxx with another drug. Adverse cardiovascular effects were more common in the Vioxx group. In the discussion, the authors attributed this to a protective effect of the other drug, not to any adverse effect of Vioxx. The trial was underwritten by Merck.