

PRACTICAL POINTERS FOR PRIMARY CARE

ABSTRACTED MONTHLY FROM THE JOURNALS

APRIL 2000

IS THE “FOOD PYRAMID” DIET REALLY IMPORTANT?

THE MOST IMPORTANT PREVENTIVE MEASURE AFTER A MYOCARDIAL INFARCTION

ROSIGLITAZONE ADDED TO METFORMIN AIDS GLYCEMIC CONTROL

ASPIRIN OR HEPARIN IN THE FIRST 2 WEEKS OF EMBOLIC STROKE?

IS LOW DOSE ASPIRIN REALLY HELPFUL IN PREVENTING VENOUS THROMBOEMBOLISM?

SHOULD THE HEALTHY DIET CONTAIN NUTS?

EVALUATION OF ABNORMAL LIVER ENZYMES REPORTED BY A ROUTINE SCREEN

PRETEST PROBABILITY ; POST-TEST PROBABILITY

BIOCHEMICAL DIAGNOSIS OF HEART FAILURE

TREATMENT OF HEART FAILURE GUIDED BY BIOCHEMICAL MARKERS

WHEN IS SURGERY FOR PRIMARY HYPERPARATHYROIDISM INDICATED?

ONE DRINK A DAY FOR PATIENTS WITH DIABETES?

DEATH OF SEDENTARY PATIENTS WITH DIABETES

FRIENDS, FAMILY, AND RISK OF DEMENTIA

ANTIHISTAMINES; WHICH IS THE LEAST SEDATING?

RENAL ARTERY STENOSIS

AMBULATORY BP MONITORING

ULCERATIVE COLITIS

EVALUATION OF PATIENTS WITH CHEST PAIN

ARTERIAL ANEURYSMS

TREATMENT FOR HEAT STROKE

RED CELL ABNORMALITIES

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HIGHLIGHTS APRIL 2000

4-1 A PROSPECTIVE STUDY OF DIET QUALITY AND MORTALITY IN WOMEN

Study supports the practical clinical value of adherence to the “Healthy diet” promoted by the well known food pyramid.

4-2 EFFECT OF SMOKING CESSATION ON MORTALITY AFTER MYOCARDIAL INFARCTION.

Smoking cessation is the most productive intervention to improve prognosis after a MI.

4-3 EFFECT OF METFORMIN AND ROSIGLITAZONE COMBINATION THERAPY IN PATIENTS WITH TYPE 2 DIABETES

Addition of rosiglitazone to high dose metformin improves glycemic control – a valid, practical clinical application.

4-4 LOW MOLECULAR WEIGHT HEPARIN VERSUS ASPIRIN IN PATIENTS WITH ACUTE ISCHEMIC STROKE AND ATRIAL FIBRILLATION

Another boost for regular use of aspirin immediately after AF-related embolic stroke and continued for 2 weeks. Just as beneficial as heparin and more acceptable, easier to use, and much cheaper.

4-5 PREVENTION OF PULMONARY EMBOLISM AND DEEP VEIN THROMBOSIS WITH LOW-DOSE ASPIRIN; The Pulmonary Embolism Prevention (PEP) Trial.

Another boost for use of aspirin post hip-surgery. “There is now good evidence for considering aspirin routinely in a wide range of surgical and medical patients at high risk of venous thromboembolism.”

4-6 SERUM LIPID EFFECTS OF HIGH-MONOUNSATURATED FAT DIET BASED ON MACADAMIA NUTS.

Nuts, used as a snack, would improve lipid patterns. Clinicians should emphasize the beneficial effects of nuts (in place of the usual sweets and pastries) for patients without weight problems.

4-7 EVALUATION OF ABNORMAL LIVER-ENZYME RESULTS IN ASYMPTOMATIC PATIENTS.

Reference article. Practical advice when elevated liver enzymes are reported on a screening panel.

4-8 PRE-TEST PROBABILITY; POST-TEST PROBABILITY

The third step in the analysis of the probability that a diagnostic test is valid. Understanding sensitivity, specificity, predictive values, and pre- and post-test probabilities clarifies many aspects of current studies, and makes journal reading more enjoyable.

4-9 BIOCHEMICAL DIAGNOSIS IN VENTRICULAR FUNCTION IN ELDERLY PATIENTS IN GENERAL PRACTICE

Plasma natriuretic peptide levels increase in patients with left ventricular dysfunction. Normal concentrations in elderly patients suspected of heart failure, effectively “rules out” heart failure. Elevated levels do not “rule in” heart failure. There are other causes of elevated levels.

4-10 TREATMENT OF HEART FAILURE GUIDED BY PLASMA AMINOTERMAL BRAIN NATRIURETIC PEPTIDE (N-BNP) CONCENTRATIONS.

Serial measurement of natriuretic peptides may lead to improved drug treatment of heart failure. Clinicians, keep alert for further developments.

4-11 A BRAIN NATRIURETIC PEPTIDE AS BRIDGE TO THERAPY FOR HEART FAILURE.

Not yet entered into primary care, but promising.

4-12 SURGERY FOR PRIMARY HYPERPARATHYROIDISM — SOONER RATHER THAN LATER.

Practical advice. Early surgery is advised.

4-13 ALCOHOL CONSUMPTION AND RISK OF TYPE 2 DIABETES AMONG U.S. MALE PHYSICIANS.

Another suggestion that one drink a day improves prognosis. Problem is – how to advise patients.

4-14 LOW CARDIORESPIRATORY FITNESS AND PHYSICAL INACTIVITY AS PREDICTORS OF MORTALITY IN MEN WITH TYPE 2 DIABETES

Another benefit of physical fitness. Primary care clinicians should constantly advise fitness as a cornerstone of treatment, not only for patients with diabetes, but for all.

4-15 INFLUENCE OF SOCIAL NETWORK ON OCCURRENCE OF DEMENTIA: A COMMUNITY-BASED LONGITUDINAL STUDY

Interesting observation. Satisfying social connections lessen likelihood of developing dementia. Another indication that you should “use it or lose it”.

4-16 WHICH INFLUENCES COGNITIVE FUNCTION: LIVING ALONE OR BEING ALONE?

“Being alone is what is risky, not living alone.

4-17 SEDATION WITH NON-SEDATING ANTIHISTAMINES: Four Prescription-Event Monitoring Studies In General Practice

Loratidine (*Claritin*) and fexofenadine (*Allegra*) are the least sedating.

4-18 RENAL ARTERY STENOSIS

A review article – clinical features, diagnosis, and treatment. Atheromatous RAS is *not* commonly associated with mild or moderate hypertension. It is present in up to 1/3 of patients with malignant or drug-resistant hypertension. Nevertheless, the hypertension can be controlled in most patients with drug therapy. Angioplasty using stents has been an advance. Surgery should probably be reserved for patients in whom stenting fails. But, the quality of evidence makes treatment recommendations difficult.

4-19 USE AND INTERPRETATION OF AMBULATORY BLOOD PRESSURE MONITORING: Recommendations of The British Hypertension Society.

A review article. "There is now firm evidence that ambulatory blood pressure monitoring is a more sensitive predictor of cardiovascular outcome than conventional measurement." Primary care practices should make ABPM available to their patients.

4-20 ULCERATIVE COLITIS

Review article. "Most patients can be managed wholly as outpatients." Oral 5-amino-salicylic acid will keep most relapses to a minimum. Most distal disease is amenable to topical 5-amino-salicylic acid and corticosteroid preparations.

4-21 EVALUATION OF THE PATIENT WITH ACUTE CHEST PAIN

Review article. Helpful tables from the American College of Emergency Physicians.

4-22 ARTERIAL ANEURYSMS

Review article – screening; indications for surgery.

4-23 COOLING METHODS FOR HEATSTROKE VICTIMS

Method used by the American Armed Forces. Over 200 treated without a fatality. File for reference.

4-24 RED CELLS I: Inherited Anaemias

Review article

4-25 RED CELLS II: Acquired Anaemias and Polycythemia

Review article.

REFERENCE ARTICLES

4-7 EVALUATION OF ABNORMAL LIVER-ENZYME RESULTS IN ASYMPTOMATIC PATIENTS.

4-18 RENAL ARTERY STENOSIS

4-19 USE AND INTERPRETATION OF AMBULATORY BLOOD PRESSURE MONITORING

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4-21 EVALUATION OF THE PATIENT WITH ACUTE CHEST PAIN

4-22 ARTERIAL ANEURYSMS

4-23 COOLING METHODS FOR HEATSTROKE VICTIMS

4-24 RED CELLS I: Inherited Anaemias

4-25 RED CELLS II: Acquired Anaemias and Polycythemia

4-1 A PROSPECTIVE STUDY OF DIET QUALITY AND MORTALITY IN WOMEN

Diets of free living individuals consist of a combination of foods containing multiple nutrients. What are the health effects of dietary patterns comprising multiple independent dietary factors? Interrelation of dietary variables makes it difficult to isolate effects of single nutrients. In vivo biological activities of nutrients are interdependent.

This study addressed health effects of different dietary habits which included complex mixtures of foods containing multiple nutrients. (Similar to the familiar food pyramid.)

Conclusion: Consumption of foods recommended by current dietary guidelines was associated with decreased mortality.

STUDY

1. Prospective cohort study begun in 1987-89 entered over 42 000 women (mean age 60) who completed a food frequency questionnaire. (*See p 2110 for details of foods included.*)
2. Divided subjects into quartiles according to a recommended food score — the sum of favorable foods recommended in current guidelines: fruits, vegetables, whole grains, low fat dairy, and lean meats and poultry. The highest quartile ingested the greatest quantity of favorable foods, and the lowest quartile the least quantity of favorable foods.
3. Determined all-cause mortality by quartile. Mean follow-up = 6 years.

RESULTS

1. Over 200 deaths occurred due to all causes.
2. The quality of the recommended food score was inversely related with all cause mortality.
3. The highest quartile consumed less fat as a percentage of energy intake compared with the lowest quartile, (32% vs 39%) The diet of the highest quartile contained more fiber, vitamin C, folate, vitamin E, and vitamin A. (*See table 2 p 2111*)
4. Compared with those in the lowest quartile of food quality, the upper quartile had a mortality risk of 0.69. (Quartiles 2 & 3 intermediate.) This was after multiple adjustments for possible confounding factors.

DISCUSSION

1. Women consuming the highest quality diet had a 30% lower mortality over 6 years compared with those consuming the lowest quality diet.
2. “Our results provide evidence in support of the prevailing food-based dietary guidelines.”

Compliance with current dietary guidelines results in improved health outcomes. “The potential public health implications of these findings are considerable.”

3. Despite increased public awareness, large gaps remain in food-based recommendations and actual dietary practices.
4. A previous study “Dietary Approaches to Stop Hypertension” (DASH)¹ reported a diet similar to the high quality diet reduced BP in both hypertensive and normotensive subjects.
5. Conceptions of diet quality have evolved over time. Earlier, nutrition scientists focused on preventing nutrient deficiencies. Diets that provided the recommended intake levels of known nutrients and energy were considered desirable. With the increasing recognition of the role of diet in prevention and promotion of chronic diseases, dietary characteristics associated with decreased risk have been promoted.²

CONCLUSION

A dietary pattern characterized by consumption of foods recommended in current dietary guidelines was associated with decreased risk of death in women over 6 years.

JAMA April 26, 2000; 283: 2109-15 Original investigation based on the Breast Cancer Detection Demonstration Project, first author Ashima K Kant, Queens College of the City University of New York, Flushing , NY

<http://jama.ama-assn.org/issues/v283n16/full/joc91695.html>

1 NEJM 1997; 336: 1117-24

<http://www.nejm.com/content/1997/0336/0016/1117.asp>

2 See citations 1,2,3 for reports from the National Research Council and the US Department of Health and Human Services, and the US Department of Agriculture.

Comment:

This is a basic practical clinical point leading to better health. The problem is to follow it ourselves and to lead our patients to it. RTJ

4-2 EFFECT OF SMOKING CESSATION ON MORTALITY AFTER MYOCARDIAL INFARCTION.

Individuals with ischemic heart disease who smoke are at increased risk of death due to adverse effects on coronary blood flow, myocardial oxygen demand, and risk of thrombosis.

This study asked – Will smoking cessation improve prognosis after a myocardial infarction (**MI**)? (Secondary prevention)

Conclusion: Cessation was associated with a significant decrease in mortality.

STUDY

1. A meta-analysis of 12 cohort studies (over 5800 patients) reported mortality of patients who had a MI in

the past who stopped smoking and compared them to those who continued.

2. Data were presented from studies in 6 countries over 2 to 10 years.

RESULTS

1. Cessation rate varied between 29% and 74%.
2. All studies reported a benefit from cessation. Benefit was consistent regardless of sex, duration of follow-up, and study site. The degree of heterogeneity between studies was surprisingly low.
3. The odds ratio of death in those who quit was 0.54 compared with those who continued.
4. Relative risk reductions varied from 15% to 61%
5. The number needed to treat by cessation to save one life was 13, assuming a mortality rate of 20% in continuing smokers.

DISCUSSION

1. These results are consistent with benefits reported by other studies of smoking cessation related to coronary by-pass surgery, angioplasty, and unstable angina. The evidence of benefit from cessation is compelling.
2. The odds ratio of benefit compares favorably with other interventions after MI: thrombolysis , beta-blockers, and aspirin.
3. The development of heart disease is a strong stimulus to induce smoking cessation. (But, note that up to 71% continued.)

Archives Int Med April 10, 2000; 160: 939-44 Original investigation, first author Kumaman Wilson, McMaster University, Hamilton, Ontario, Canada.

<http://archinte.ama-assn.org/issues/v160n7/full/loi90217.html>

Comment:

The message is self-evident. It is a highly beneficial “practical point”. The main message, of course, is to quit before MI occurs. RTJ

4-3 EFFECT OF METFORMIN AND ROSIGLITAZONE COMBINATION THERAPY IN PATIENTS WITH TYPE 2 DIABETES

About half of all patients with type 2 diabetes initially treated with monotherapy require additional therapy to achieve target glycosylated hemoglobin (HbA1c) levels within 3 years after diagnosis.

Rosiglitazone and metformin act through different mechanisms. Rosiglitazone (*Avandia*) improves insulin sensitivity at the cellular level (muscle, adipose tissue, and liver). Metformin (*Glucophage*) lowers glucose by reducing hepatic glucose production and gluconeogenesis, and by enhancing peripheral glucose uptake. Combined use may be more effective than using one alone.

This study evaluated the efficacy and safety of adding rosiglitazone to maximal doses of metformin in patients with poorly controlled type 2 diabetes.

Conclusion: Combined therapy improved glycemic control.

STUDY

1. Multicenter, randomized, double-blind, placebo-controlled trial entered 348 patients with type 2 diabetes (age 40 to 80; mean = 58).
2. Mean fasting glucose at baseline was 216 mg/dL; mean HbA1c, 8.8%; mean body mass index, 30.
3. Randomized to:
 - A. 2.5 g metformin + placebo
 - B. 2.5 g metformin + 4 mg rosiglitazone
 - C. 2.5 g metformin + 8 mg rosiglitazone
4. Duration of study = 6 months; 290/348 (83%) completed the trial.

RESULTS

1. Glycosylated hemoglobin levels, fasting plasma glucose, insulin sensitivity, and beta-cell function improved significantly with combined metformin-rosiglitazone in a dose-dependent manner.
2. In the 8 mg rosiglitazone group, mean HbA1c declined by 1.2% and fasting glucose declined by 53 mg/dL compared with the metformin-placebo group.
3. 28% of the 8 mg rosiglitazone group achieved a glycosylated hemoglobin less than 7%.
4. Dose dependent increases in weight and LDL-cholesterol and HDL-cholesterol occurred in the metformin-rosiglitazone groups. (LDL-c/HDL-c ratio was not significantly changed.)
5. Reported adverse experiences were comparable across all 3 groups. Symptomatic mild to moderate hypoglycemia occurred in 5 patients (5%) in the 8 mg rosiglitazone group. No one in the metformin-rosiglitazone groups experienced elevations of alanine aminotransferase levels greater than 3 times normal. (Actually, mean ALT decreased by 3.4 U/L in the 8 mg group.)

DISCUSSION

1. Metformin-rosiglitazone combined was effective and safe in patients with type 2 diabetes.
2. Compared with metformin alone, the combination significantly reduced HbA1c and fasting plasma glucose.
3. The combination may be a safe alternative therapy to attain optimal glycemic control when mono-therapy has failed.

CONCLUSION

Therapy with once-daily combined metformin-rosiglitazone improved glycemic control, insulin sensitivity, and beta-cell function more effectively than metformin alone.

JAMA April 5, 2000; 283: 1695-1702 Original investigation, first author Vivian Fonseca, Tulane University, New Orleans, LA. <http://jama.ama-assn.org/issues/v283n13/full/joc91387.html>

Comment:

I believe this is a valid and practical clinical application. Most patients prefer oral therapy RTJ

4-4 LOW MOLECULAR WEIGHT HEPARIN VERSUS ASPIRIN IN PATIENTS WITH ACUTE ISCHEMIC STROKE AND ATRIAL FIBRILLATION

In patients with atrial fibrillation (AF) anticoagulation with warfarin reduces risk of stroke (primary prevention). After a stroke, the prophylactic effect is of equal benefit (secondary prevention), but the best time to start warfarin is not known.

In patients who experience an acute ischemic stroke related to AF, there is an increased early risk of stroke recurrence. (Some observational studies report a 10% to 20% risk of a recurrent ischemic stroke during the first 2 weeks after onset of AF-related stroke.) Heparin therapy has been advocated in the immediate post-stroke period despite missing data on the balance between risk and benefit.

This study investigated whether low-molecular-weight-heparin (LMWH) is superior to aspirin for the prevention of *early recurrent* stroke in persons with AF.

Conclusion: LMWH was no better than aspirin in the first 2 weeks.

STUDY

1. A large multicenter, double-blind trial followed 450 patients (mean age = 80). All had an acute ischemic stroke associated with AF. All received a CT scan to rule out cerebral hemorrhage
2. Randomized to 1) 100 IU/kg of the LMWH dalteparin (*Fragmin*) twice daily, or 2) aspirin 160 mg daily.
3. Drug therapy was started within 30 hours of stroke onset.
4. Follow-up = 14 days.

RESULTS

- | 1. Outcomes at 14 days: | LMWH (n = 224) | Aspirin (n = 225) |
|---|----------------|-------------------|
| Recurrent ischemic stroke | 8.5% | 7.5% |
| Symptomatic cerebral hemorrhage (patients) | 6 | 4 |
| Symptomatic and asymptomatic cerebral hemorrhage (patients) | 26 | 32 |
| Progression within first 48 h (patients) | 24 | 17 |
| Death (patients) | 21 | 16 |
2. No significant differences in functional outcome or death at 14 days or 3 months.

DISCUSSION

1. Use of heparin in patients early after acute ischemic stroke associated with AF has long been controversial.
2. “Our results provide *no* evidence that high-dose LMWH is superior to aspirin, either for the prevention of recurrent ischaemic stroke or any other event during the first 14 days, or for the improvement of outcomes at 14 days or 3 months.
3. The study, however, did *not* show any significant increase in symptomatic cerebral hemorrhage for LMWH compared with aspirin. There was a trend toward more severe bleeding with LMWH.

CONCLUSION

LMWH was not superior to aspirin for the treatment of acute ischemic stroke in patients with atrial fibrillation.

Lancet April 8, 2000; 355: 1205-10 Original investigation The “Heparin in Acute Embolic Stroke Trial” by the HAEST Study Group, first author E Berge, Ullevål University Hospital, Oslo, Norway.

<http://www.thelancet.com/newlancet/sub/issues/vol355no9211/article1205.html>

Comment:

This study was a major undertaking. The results are clinically important and demonstrate preference for a simple, inexpensive therapy. Pharmacia and Upjohn supplied the dalteparin as an unconditional grant. I was pleased that there was no tilt toward use of the LMWH in the report.

The investigators did not consider when to start warfarin post-stroke. RTJ

4-5 PREVENTION OF PULMONARY EMBOLISM AND DEEP VEIN THROMBOSIS WITH LOW-DOSE ASPIRIN; The Pulmonary Embolism Prevention (PEP) Trial.

Many different strategies have been proposed for prevention of venous thromboembolism (VTE) after major surgery. For practical reasons prophylaxis with heparin and compression stockings is generally stopped at hospital discharge. The risk of VTE may persist for some weeks after discharge. Prophylaxis with a simple antiplatelet regimen such as low-dose aspirin might be effective during this vulnerable period. However, aspirin is generally not recommended or used for prevention of VTE.

Individual trials of aspirin for prevention of VTE have been inconclusive. A meta-analysis did, however, indicate a reduction in risk.

This trial was designed to confirm or refute the benefits of aspirin in preventing VTE in the month after hip surgery.

Conclusion: Aspirin reduced risk of VTE throughout the period of increased risk.

STUDY

1. Large multicountry study followed over 13 000 patients undergoing surgery for hip fracture, and

over 4000 patients undergoing elective hip arthroplasty.

2. Randomized to: 1) aspirin 160 mg daily, or 2) placebo starting preoperatively and continued for 35 days.
3. Other thromboprophylaxis as thought necessary was continued.

RESULTS

1. Hip fracture patients:

- A. Aspirin was associated with a 43% reduction in pulmonary embolism and a 29% reduction in symptomatic deep vein thrombosis.
- B. The absolute reduction in pulmonary embolism or deep-vein thrombosis was 0.9%.
(A reduction in about 1 in 100 patients).
- C. Aspirin was associated with a reduction in death from pulmonary embolism in 4 per 1000 patients.
- D. No apparent effect on death from any other vascular cause, or non-vascular cause.
- E. Deaths due to bleeding: 13 in aspirin group; 15 in placebo. Postoperative transfusions were more common in the aspirin group (excess of 6 per 1000 patients).

2. Hip elective arthroplasty patients:

- A. Rates of VTE were lower in the aspirin group and benefits comparable to those in the hip fracture patients.

DISCUSSION

1. Low-dose aspirin reduced the risk of post-operative VTE over at least one month.
2. Implications are that aspirin can be expected to reduce VTE by at least a third in a wide variety of surgical groups and perhaps in a wide variety of other types of patients at increased risk (including immobilized patients and those with a history of VTE).
3. The baseline risk in an individual patient is the key determinant to absolute benefits of aspirin.
4. Treatment longer than 35 days might be expected to yield further benefits.
5. Adverse effects of aspirin were few: slight increase in transfusion requirements. There was no increase in fatal, cerebral, or disabling bleeding.
6. Pulmonary embolism seems to have become a relatively infrequent cause of death after hip fracture (less than 10%). But overall mortality post-surgery remains high. Additional strategies might be required to prevent other vascular events (eg, routine use of beta-blockers).
7. The risk of bleeding in these surgical patients occurs mainly in the first few days, but risks of VTE and other vascular complications may continue for weeks or months.
8. Should aspirin be used in addition to, or instead of, some other forms of thromboprophylaxis? There is only limited evidence about the benefits and risks of adding heparin. LMWH does produce greater reductions in VTE than aspirin, but at increased cost, inconvenience, and bleeding.
9. This trial (in addition to others) shows that aspirin reduces risk of perioperative VTE by at least a third,

largely irrespective of the use of any other thromboprophylaxis, including heparin. Much of the benefit of aspirin emerged after the first postoperative week when other prophylactic strategies (such as stockings) have generally been stopped.

10. Routine use of aspirin should be considered in a wide range of surgical and medical patients at high risk of VTE. It should be continued during the entire period of increased risk.

CONCLUSION

Aspirin reduced risk of pulmonary embolism and deep-vein thrombosis by at least a third in hip-surgery patients during the post-operative month. “There is now good evidence for considering aspirin routinely in a wide range of surgical and medical groups at high risk of venous thromboembolism.”

Lancet April 15, 2000; 355: 1295-302 Original investigation by the Pulmonary Embolism Prevention (PEP) Trial Collaborative Group. Correspondence to Anthony Roger, University of Auckland New Zealand

<http://www.thelancet.com/newlancet/sub/issues/vol355no9212/article1295.html>

Comment:

This is an important practical clinical application in part because aspirin is so cheap, available, and easily self-administered. Patients will be more compliant in taking it. RTJ

4-6 SERUM LIPID EFFECTS OF HIGH-MONOUNSATURATED FAT DIET BASED ON MACADAMIA NUTS.

The “Mediterranean diet” is relatively high in fat (frequently containing more than typical American diets), much of it in form of olive oil. Olive oil contains high concentrations of the mono-unsaturated fat — oleic acid. Less than 10% of energy in such diets comes from saturated fat.

Nuts have also been a traditional part of the Mediterranean diet. Nuts are a complex food containing considerable amounts of mono-unsaturated fat. Macadamia nuts contain about 75% fat by weight (80% of this is mono-unsaturated) . Oleic acid predominates, but palmitoleic acid (another mono-unsaturate) is a component not present in substantial amount in olive oil. Macadamias also contain large amounts of carbohydrate and a number of vitamins and minerals.

Some nuts could be substituted for foods high in saturated fat as a potential element of a healthy diet.

This study examined variations in serum lipids in response to a high mono-unsaturated fat diet based on macadamia nuts.

Conclusion: The nut diet provided benefits on lipid levels

STUDY

1. Randomized, crossover trial of three 30-day diets followed 30 healthy volunteers in a free living population.
2. Randomized, and crossed over in random order to: 1) a typical American diet high in saturated fat (37%

of energy from fat), 2) American Heart Association step 1 “prudent” diet (30% of energy from fat), and 3) finely ground macadamia nut based monounsaturated fat diet (37% of energy from fat).

3. Fat composition (% of energy intake)	American	Step 1	Nut
Polyunsaturated	7	7	7
Saturated	14	9	9
Mono-unsaturated	12	15	20

(The energy intake of the nut diet contained 5% less saturated fat and 6% more mono-unsaturated fat than the typical American diet.)

RESULTS

1. Plasma lipid levels (mg/dL)

Baseline

Total cholesterol – 201; LDL-cholesterol – 134; HDL-cholesterol – 55

After each 30-days:	American	Step 1	Nut
Mean total cholesterol	201	193	191
LDL-cholesterol	130	124	125
HDL-cholesterol:	55	52	53

2. The changes in lipid values in the step 1 diet and the nut diet were similar and statistically significant compared with the American diet. (*And, I believe, clinically significant. RTJ*)

DISCUSSION

1. The results suggest that replacing saturated fats in the typical American diet with mono-unsaturated fats present in macadamia nuts has a favorable effect on lipid concentrations in healthy adults.
2. The effect was present in a wide range of ethnic groups and both sexes.
3. However, simply *adding* mono-unsaturated fats from nuts to the typical diet may be deleterious because of weight gain.
4. Other studies of almonds and walnuts have reported similar benefits on lipid levels. **1,2**

CONCLUSION

Compared with the typical American diet, a macadamia nut diet high in mono-unsaturated fat had potential beneficial effects on lipid levels similar to the AHA step 1 diet.

Archives Int Med April 24, 2000; 160: 1154-58 Original investigation, first author J David Curb, University of Hawaii <http://www.archinte.ama-assn.org/issues/v160n8/full/loi90156.html>

1. “A Possible Protective Effect of Nut Consumption on Risk of Coronary Heart Disease” Archives Int Med 1992; 152: 1416 –24

2 “Substituting Walnuts for Monounsaturated Fat Improves the Serum Lipid Profile of Hypercholesterolemic Men and Women” *Annals Int Med* April 4, 2000; 132: 538-46

This study carried the intervention of a nut-based mono-unsaturated fat diet a step farther. It compared 1) an already high mono-unsaturated fat diet (a Mediterranean diet) with 2) another high mono-unsaturated fat diet (walnut-based). Substituting walnuts led to a 6% decrease in LDL-cholesterol. The investigators suggested that other constituents in walnuts (in addition to their mono-unsaturated fat) led to the improved outcome.

Comment:

By my calculation the diet contained 2 to 3 ounces of walnuts daily. Although few would continue such a diet for long, I believe addition of nuts to a healthy diet is a valid and practical clinical application. We can recommend nuts (all kinds, including peanuts) as a snack to patients who do not have a weight problem. Certainly a healthier diet than pastry, chips, cake, candy and high trans-fat foods such as doughnuts. RTJ

REFERENCE ARTICLE

4-7 EVALUATION OF ABNORMAL LIVER-ENZYME RESULTS IN ASYMPTOMATIC PATIENTS.

Screening blood chemistry tests include alanine aminotransferase (ALA), aspartate aminotransferase (ASA), alkaline phosphatase, and gamma-glutamyl transferase. These enzymes are most often elevated in patients with liver disease. But, physicians are frequently faced with the problem of a patient with one abnormal result on a routine chemistry panel.

The first step in evaluation of abnormal enzyme levels in an asymptomatic patient is to repeat the test. If the result is still abnormal, evaluate the degree of elevation. A minor elevation (less than twice normal) may be of no clinical importance, and indeed in fact not be abnormal. The normal range of any laboratory test is the mean value in a group of healthy persons plus or minus 2 standard deviations. Thus, 2.5% of normal individuals will have levels below the lower limit of normal, and 2.5% of normal individuals will have levels above the higher limit of normal.

Aminotransferase levels:

Are sensitive indicators of liver cell injury. Both ALT and AST are normally present in serum at low levels (< 30 to 40 U per liter). However, the normal range varies widely among laboratories.

The cause of elevations of ALT varies greatly depending on the population studied. (*See table 1 p 1267 for a list of causes of chronically elevated aminotransferase levels and table 2 p 1267 for additional laboratory tests that may identify the cause.*)

1. Among 20 000 Air Force recruits, 99 (0.5%) had elevated ALT. A cause was found in only 12: hepatitis, cholelithiasis, appendicitis.
2. Among 1124 consecutive patients referred for chronic elevations in aminotransferase levels, 81 had no definable cause, and underwent liver biopsy: 41 had steatosis, 26 steatohepatitis, 4 fibrosis, 2 cirrhosis, and 8 were normal.
3. Among 100 consecutive blood donors with elevated ALT, 48% were related to alcohol, 22% fatty liver, 17 hepatitis. No cause was determined in 9 %.

4. In addition to the above list, medications, herbs, and substances of abuse can cause elevations. (*See table 3 p 1268 for a list. Indeed, I am surprised that more elevations were not identified as reactions to medications or to drug abuse. RTJ*)
5. Other rarer causes are mentioned in the article.

The only indication of hepatic steatosis may be a mild elevation of aminotransferase levels. Fatty infiltration of the liver can be identified by ultrasound and CT. “Ultrasonography should be part of the evaluation of patients with chronically elevated aminotransferase levels.”

The article goes on to consider elevations of alkaline phosphatase and gamma-glutamyltransferase. The latter has been advocated as a screening test for alcohol abuse. However, the test has a low specificity for alcohol abuse (many false positives). Use for this purpose is questionable. An elevated ALT/AST ratio of at least 2:1 may indicate alcohol abuse.

NEJM April 27, 2000; 342: 1266-71 “Primary Care”, commentary by Daniel S Pratt and Marshall M Kaplan, New England Medical Center, Boston Mass. <http://www.nejm.com/content/2000/0342/0017/1266.asp>

4-8 PRE-TEST PROBABILITY; POST-TEST PROBABILITY

Five steps to estimate the probability that a test for a disease indicates the presence of that disease:

1. Calculate the sensitivity and specificity of the results of the test run in a defined cohort of patients. (*See February 2000 issue of Practical Pointers.*)
2. Calculate the likelihood ratios of positive tests and negative tests (*See March 2000 issue of Practical Pointers.*)
3. Assign a pre-test probability that the patient has the disease.

Pre-test probability, an *estimate* of the probability that the patient has the disease, is based on clinical experience with other patients presenting similar signs and symptoms. The estimate may be variable and debatable. However, with some experience, we can come to a reasonable, educated guess of the probability of the disease presence.

Many screening tests are now performed in unselected persons who have a low pre-test probability of having the target disease (eg, mammography in younger women for breast cancer, PSA for prostate cancer). Even if the test is positive, the probability that the patient has the disease is lower than if the same test were positive in a patient with a breast mass or a hard lump in the prostate (pre-test probability high).

4. Modify the pre-test probability with the likelihood ratios:

Recalculate the probability that the patient has the disease based on the pre –test

probability modified by the likelihood ratios -- if the test is positive, modified by the positive likelihood ratio; if the test is negative, modified by the negative likelihood ratio.

5. This brings you to the post-test probability that the patient has the disease – a new probability based on the assigned pre-test probability modified by the likelihood ratios of the test.

(Steps 3, 4, and 5 are based on the now frequently cited 18th century work of Rev. Thomas Bayes (Bayesian statistics.)

For example:

In the 2 X 2 table in abstract “The Role of Clinical Suspicion in Evaluating a New Diagnostic Test for Active Tuberculosis” in the February 2000 issue of *Practical Pointers*:

	Low clinical suspicion (n=224)	
	TB present (n=12)	TB absent (n=212)
E-MTD positive	10 (True positive = 84%)	7 (False positive = 3%)
E-MTD negative	2 (False negative = 16%)	205 (True negative = 96%)

A. Pre-test probability of TB:

The experts assigned a low pre-test probability (~ 5%) of TB to a group of subjects -- the low clinical suspicion group.

B. Modify the pre-test probability by the likelihood ratios, both positive and negative:

1. If the test is positive:

- a. Apply the likelihood ratio of positive tests to the pre-test probability (5%) that TB is present.
- b. The likelihood ratio of positive tests in this cohort as determined by this specific test was $84\%/3\% = 28$.
- c. Calculate the post-test likelihood of TB following a positive test:

Although the pre-test probability was low (~ 5%), a positive test makes the probability that a subject in this group of low clinical suspicion subjects actually has TB much higher. Ie, the post-test probability can be considered 28 times more likely that he has TB than that he does not have TB. But, even with this higher likelihood, the fact that to begin with the probability of his having TB was low, the probability that he does indeed have TB is not assured. (Note: nomograms are available to determine post-test probabilities depending on pre-test probabilities and likelihood ratios.) Applying the likelihood ratio of 28 to a pre-test of 5% results in a post-test probability of TB of 60%. Ie, there is still a 40% probability that he does not have TB.

2. If the test is negative:

- a. Apply the likelihood ratio of negative tests to a pre-test probability (~ 5%) that TB is present.
- b. The likelihood ratio of negative tests in this cohort as determined by this specific test

was $16\%/96\% = 0.17$

c. Calculate the post-test likelihood of TB following a negative test:

The pre-test probability was low (~ 5%). A negative test makes the probability that a subject in this group has TB much less likely. Ie, the post-test probability can be considered just 0.17 times as likely that he has TB than that he does not have TB. With this new probability (5% times 0.17) it becomes very unlikely that he does have TB. (Although not absolutely so.) According to the nomogram, applying the likelihood ratio of 0.17 to a pre-test probability of 5% results in a post-test probability of TB of less than 1%. Ie, there is only a 1 chance in about 200 that he does have TB.

Comment:

I was guided in preparing these by a small volume “Evidence-based Medicine; How to Practice and Teach EBM”, Churchill Livingstone, first author David L Sackett

I entered the analysis of probabilities to: 1) to learn more about it, and to 2) attempt to present it in a clear, understandable way. It still looks complicated after my effort to clarify.

The calculations are simple, but they are tricky and must be applied with care. One misplaced step and the calculations will be meaningless. Indeed, I am not certain that I have not made a mistake.

The final destination (post-test probability) is based on several shaky foundations:

- 1) Pre-test probability is the least definitive for an individual patient. Clinicians of varying experience will place varying pre-test probabilities.
- 2) Likelihood ratios are based on the sensitivities and specificities of a test. Tests between laboratories vary according to the standardization of reagents, and the expertise of the technicians running the tests.
- 3) Thus, although the post-test probability seems definite, it is a “ball park” estimate based on compounding variables.

There is yet another step. After considering the post-test probability clinicians must decide if the probability of the disease is high enough to proceed with treatment, or only high enough to proceed with further tests or observation.

Clinicians apply these determinations daily to decide on treatments, although not in a structured manner. They apply them empirically and without conscious effort. RTJ

Clinical diagnosis of left ventricular dysfunction is difficult. There is no simple and reliable clinical method for identifying such patients, especially at early stages. The classic signs of raised jugular venous pressure and fine basal crepitations become evident at later stages.

Diagnosis is important because morbidity and mortality can be reduced by appropriate treatment.

Natriuretic peptides are released by heart muscle in response to increased pressure and stretch. The most commonly assessed is “brain natriuretic peptide (B-NP), released by ventricular myocardium. (*“Brain” is a misleading term applied in this context because the peptide was originally identified in brain tissue. RTJ*)

This study investigated the usefulness of measuring B-NP in the diagnosis of left ventricular dysfunction in elderly people in the community.

Conclusion; Measuring B-NP was useful as an initial test to *rule out* left ventricular systolic dysfunction. It was not a good test to *rule in* the diagnosis.

STUDY

1. Observational study of the prevalence of systolic dysfunction in general practice entered 155 elderly patients (age 70 to 84; mean = 76).
2. Determined sensitivity and specificity of B-NP for diagnosing left ventricular dysfunction using echocardiography as the “gold standard”.
3. Twelve patients had left ventricular dysfunction.

RESULTS

1. Median B-NP in patients with left ventricular systolic dysfunction was 39 pmol/L; vs 15 pmol/L in those without.
2. There was some overlap between those without dysfunction and those with dysfunction (*See figure 1 p 907*).
3. At a cut point set at 19 pmol/L and above, sensitivity of B-NP was 92% (92% true positive and 8% false negative)
4. At the same cut point, specificity was 65%. (65% true negative and 35% false positive.)
5. Predictive values are quite different:

Predictive value of a positive test (positive predictive value):

61 patients had a positive test (11 true positive and 50 false positive). Thus only 11 of 61 (18%) with a positive test had left ventricular dysfunction. The predictive value of a positive test was low because there were more false positive tests than true positive tests.

Predictive value of a negative test (negative predictive value):

94 patients had a negative test (93 true negative and 1 false negative). Thus almost all who had a negative test did not have left ventricular dysfunction. The predictive value of a negative test was high (99%) because there were many more true negative tests than false negative tests.

[*Thus B-NP tests at this cut point are of much more clinical value in ruling out left ventricular dysfunction than ruling it in.*]

6. The predictive values vary when other cut points are chosen.

DISCUSSION

1. "The measurement of plasma concentrations of B type natriuretic peptide in elderly patients in general practice could be an invaluable aid in the diagnosis of left ventricular dysfunction." "Measuring plasma concentrations of B type natriuretic peptide is feasible in general practice."
2. However, B-NP might be elevated in elderly persons for reasons other than heart dysfunction (eg, renal dysfunction). Its diagnostic function may be of less value in the elderly than in younger persons. "The test performs less well in elderly than in young persons, but it still works."
3. The test could be used as an initial screen in persons suspected of having left ventricular dysfunction. If the test is negative, left ventricular dysfunction is unlikely; if positive, further study (eg, echocardiography) is needed to rule in or rule out dysfunction. (Ie, the false positive rate is high.)
5. In an elderly patient with breathlessness on walking the probability of ventricular dysfunction is about 15%. (Pre-test probability = 15%) If the B-NP is negative, the probability that the patient has left ventricular dysfunction is very low.

CONCLUSION

B-NP has diagnostic value in elderly patients. It could be used effectively as an initial screening test as a means of *ruling out* left ventricular systolic dysfunction. It is not a good test to *rule in* the diagnosis.

BMJ April 1, 2000; 320: 906-08 Original investigation, first author H Smith, University of Southampton, UK
<http://www.bmj.com/cgi/content/full/320/7239/906>.

Comment:

This is a provocative early study. More experience is required to establish the clinical utility of natriuretic peptides and determine the most favorable cut point.

I believe the application will prove to be clinically useful. RTJ

4-10 TREATMENT OF HEART FAILURE GUIDED BY PLASMA AMINOTERMINAL BRAIN NATRIURETIC PEPTIDE (N-BNP) CONCENTRATIONS.

Even with intensive treatment, mortality and morbidity from heart failure (**HF**) are high. Questions remain about how proven therapies should be implemented and at what doses.

"To date, brain natriuretic peptide (BNP) and particularly its aminoterminal portion (N-BNP), appears to be the most powerful neurohormonal predictor of left-ventricular function and prognosis." It is secreted from the left ventricle in response to changes in filling pressure and wall stretch. BNP accurately discriminates between decompensated HF and other causes of breathlessness. (According to the preceding study, the discrimination applies only to ruling out HF. If the B-NP is not elevated., HF is unlikely.) Concentrations fall after treatment with diuretics and ACE inhibitors.

The investigators hypothesized that drug therapy for HF could be guided by plasma N-BNP concentrations and would produce outcomes superior to trial-based therapy directed by clinical acumen.

Conclusion: Using N-BNP as a guide produced superior outcomes as compared with clinically guided treatment.

STUDY

1. Followed 69 patients (mean age 70) with impaired systolic function (ejection fraction < 40%) and symptomatic HF (NYHA class II III and IV). Used Framingham criteria (a standardized heart-failure score based on 10 symptoms of HF) to diagnose decompensated HF. (*See table p 1127.*)
2. Randomized double-blind to: 1) treatment guided by plasma N-BNP concentrations, or 2) standardized clinical assessment.
3. End-point = prespecified total cardiovascular events (death + hospital admission for any cardiovascular event + any new outpatient episode requiring an increase in medication).
4. Follow-up = 10 months.

RESULTS

- | | | |
|--|---------------|-----------------|
| 1. Medication changes (mean at 6 months) | N-BNP (n=32) | Clinical (n=29) |
| ACE inhibitors (Enalapril equivalents) | + 4.8 mg | + 1.2 mg |
| Furosemide | + 76 mg | + 54 mg |
| Spirololactone | 6 patients | 1 patient |
| Beta-blocker | No difference | |
| Adverse events | 13 patients | 9 patients |
| 2. Outcomes during follow-up | N-BNP (n=32) | Clinical (n=29) |
| Change in mean N-BNP | -79 pmol/L | -3 pmol/L |
| Total cardiovascular events | 19 | 54 |
| Experience a first CV event at 6 months | 27% | 53% |
3. Changes in left-ventricular function, renal function, quality of life , and adverse events were similar in both groups.
 4. The N-BNP group required a few more visits for adjustment during the 6 months.

DISCUSSION

1. The treatment of HF is increasingly complex. The investigators surmised that drug therapy for HF guided by plasma N-BNP concentrations would prove more effective than usual clinical management of HF.
2. Circulating N-BNP concentrations can be reduced by intensification of drug therapy.
3. Mean concentrations of N-BNP in the treatment group declined to well within the target range. In the clinical group concentrations remained above the target range.

4. Treatment guided by N-BNP reduced the number of clinical events including cardiovascular death, hospital admissions, and new episodes of decompensated HF.
5. The low use of beta-blockers and spironolactone reflected the uncertain status of these agents when the study began. The effect of these drugs on N-BNP is not known. And the usefulness of N-BNP monitoring these drugs is not clear.

CONCLUSION

N-BNP guided drug therapy of HF reduced total cardiovascular events as compared with conventional clinically-guided treatment. “Treatment to lower N-BNP is beneficial.”

Lancet April 1, 2000; 355: 1126-30 Original investigation, first author Richard W Troughton, Christchurch School of Medicine, New Zealand. <http://www.thelancet.com/newlancet/sub/issues/vol355no9210/article1126.html>

Comment:

Studies on natriuretic peptides are appearing more frequently. There is still uncertainty about effectiveness in diagnosis of HF and as an aid to treatment. More experience is necessary before application can be generalized.

Note that reduction in BNP is not the reason for clinical improvement. Improvement of left ventricular function by adjustment of therapy provides the benefit. B-NP is merely a marker, secondary to the improvement. RTJ

4-11 A BRAIN NATRIURETIC PEPTIDE AS BRIDGE TO THERAPY FOR HEART FAILURE.

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

The natriuretic peptides are endogenous cardiac hormones synthesized, stored, and released from cardiac tissue in response to increased intramural pressure. They have a compensatory function in heart failure — increasing glomerular filtration rate, enhancing renal sodium excretion, promote peripheral vasodilation, attenuating actions of the renin-angiotensin systems, and inhibiting endothelin release.

BNP may an especially sensitive marker of symptomatic HF. The degree of increase in its concentration correlates with the severity of HF.

Use of N-BNP to aid therapy is not simple. These editorialists nevertheless consider it a milestone in the development of strategies for therapy beyond the search for specific drugs.

Lancet April 1, 2000; 355: 1112-13 “Commentary” by Daniel L Dries and Lynne Warner Stevenson, Harvard Medical School, Boston Mass.

<http://www.thelancet.com/newlancet/sub/issues/vol355no9210/commentary1112.html>

Comment:

For another cutting edge of technologic assessment of HF see “Salivary Endothelin Concentrations in the Assessment of Chronic Heart Failure” *Lancet* February 5, 2000; 355: 468-69. Endothelin 1 is a vasoconstrictor peptide. Plasma and salivary levels are raised 2-6 fold in patients with chronic HF. The study reported levels rose progressively as the severity of HF increased. The test discriminated between controls and patients with mild symptoms. Keep an eye open for developments. RTJ

4-12 SURGERY FOR PRIMARY HYPERPARATHYROIDISM — SOONER RATHER THAN LATER.

Most patients with primary hyperparathyroidism are symptom-free. However, after parathyroidectomy, some patients realize that their non-specific symptoms (eg, fatigue, depression), have improved. (They were possibly due to the hypercalcemia.)

Diagnosis has been increased many-fold since introduction of multichannel analyzers. Annual incidence is highest among middle-aged and elderly women.

The clinical features that once prompted the diagnosis have become rare. Renal stones are present in only 5%. Osteitis fibrosa cystica is exceptional. Bone radiography is usually normal, although osteopenia can usually be found by measuring bone mineral density.

Most would agree that surgery is indicated in patients under age 50, even if the hypercalcemia is slight, because of the likelihood of progression over the next 10 to 20 years. However, long-term studies have indicated that hypercalcemia often remains stable over 10 years. Thus, there has been a tendency to adopt a conservative approach in middle-aged and elderly symptom-free patients who have serum calcium between 10.5 and 12 mg/dL (2.6 and 3.0 mmol/L). Patients who do not undergo surgery should receive serum calcium determinations every 6 months and bone-mineral density measurements every 2 years.

The disease does progress in about 25% of patients. It is impossible to predict which individuals will progress. Furthermore, parathyroidectomy is associated with a substantial increase in bone density, indicating less likelihood of fracture. The editorialist therefore recommends early surgery.

Additional factors tilting toward early surgery include possible links between hyperparathyroidism and increased incidence of cardiovascular disease, hypertension, hyperinsulinemia, insulin resistance and diabetes. Studies have shown an improvement in glycemic control after surgery.

“Perhaps, therefore, conservative management . . . should be the exception — reserved for patients who are deemed by reason of advanced age or other disease to be unfit for surgery.”

“Experienced surgeons rarely have difficulty identifying abnormal parathyroid glands, so the preoperative localization in patients without previous neck surgery is rarely indicated.” However, adenomas and hyperplastic glands may be more difficult to locate early in the disease rather than late. Preoperative imaging with technicium 99m is likely to be helpful in this cohort.

Lancet April 29, 2000: 355: 1478-79 “Commentary” by A D Toft, Royal Infirmary of Edinburgh, UK

Comment:

A practical clinical application. RTJ

4-13 ALCOHOL CONSUMPTION AND RISK OF TYPE 2 DIABETES AMONG U.S. MALE PHYSICIANS.

This study examined the association between low to moderate alcohol consumption and incidence of type 2 diabetes.

Conclusion: Apparently healthy men who self-selected light to moderate alcohol consumption had a decreased risk of developing type 2 diabetes.

STUDY

1. Prospective cohort study followed over 20 000 participants in the Physician's Health Study¹ (age 40 to 84; mean = 52 at baseline).
2. All were free of cardiovascular disease, cancer, and diabetes at baseline.
3. All provided data on alcohol consumption.
4. Follow-up = 12 years. Main outcome = onset of type 2 diabetes after randomization.

RESULTS

1. Over 775 cases of type 2 diabetes were reported during follow-up. (Definition of diabetes was not specified.)
2. Relative risk by consumption:

Rarely/never	1-3 drinks per month	1 /wk	2 to 4/w	5 to 6/w	1 or more per day
1.00 (Referent)	1.03	0.89	0.74	0.67	0.57

(Only 3% reported alcohol consumption over 1 drink per day.)

3. Associations persisted after multiple adjustments for other risk factors (including family history).

DISCUSSION

1. This indicates an inverse association between light-to-moderate alcohol consumption and risk of incident type 2 diabetes over a subsequent 12 years.
2. Other large studies have also reported an inverse association (*Citations 5.6.7*) One study reported an *increased* risk in *heavier* drinkers. (Larger amounts of alcohol and alcoholism increase insulin resistance.)
3. Studies have suggested that moderate intake of alcohol may increase insulin sensitivity and lower insulin resistance, increase insulin secretory responses, and enhance glucose disposal.

CONCLUSION

This supports the hypothesis that there is an inverse association between consumption of alcohol up to 1 drink a day and development of type 2 diabetes over the subsequent 12 years.

Archives Int Med April 10, 2000; 160: 1025-30 Original investigation, first author Umed A Ajani, Harvard Medical School, Boston, Mass. <http://archinte.ama-assn.org/issues/v160n7/full/ioi90299.html>

1 NEJM 1989;321:129-35 This was the study demonstrating a primary protective effect of aspirin against myocardial infarction in men over age 50.

Comment:

By my calculation, in absolute terms, light alcohol use (compared with abstinence) was associated with 2 chances in 100 that, over 12 years, type 2 diabetes would not occur

I believe the preventive effects of alcohol would be even greater if the new definition of diabetes (fasting glucose over 125 mg/dL) had been used in the study.

The epidemiologic evidence demonstrating a protective effect of light alcohol consumption against cardiovascular disease is strong. The question remains — in a never-drinker should we advise beginning alcohol use at age 50 and above? Indeed, if alcohol were a drug subject to prescription constraints, many clinicians might prescribe it. However, it is not. Thus, I believe most clinicians would not so advise because of possible abuse and litigation. For persons already using alcohol, I would suggest no more than one glass of wine with dinner or one cocktail before dinner, not both. RTJ

4-14 LOW CARDIORESPIRATORY FITNESS AND PHYSICAL INACTIVITY AS PREDICTORS OF MORTALITY IN MEN WITH TYPE 2 DIABETES

Exercise is a standard therapy for patients with type 2 diabetes. Regular exercise improves conventional clinical risk factors and components of the insulin resistance syndrome.

This study asks — does physical fitness reduce mortality?

Conclusion: It did.

STUDY

1. Preventive medicine clinic entered over 1200 men (mean age – 50) with type 2 diabetes.
2. Determined cardiorespiratory fitness at baseline by a maximal exercise test, and self-reported physical activity.
3. Follow-up for mortality an average of 12 years.

RESULTS

1. Over follow-up, 180 men died.
2. After adjustment for multiple possible confounders, men in the lowest fitness group had a relative risk for all-cause mortality of 2.1 compared with fit men. And those reporting inactivity had a relative risk of 1.7.
3. Fitness had the same protective effect in overweight men as in normal weight men.

DISCUSSION

1. This study does not prove a causal pathway between exercise and mortality, but the data do suggest that, in patients with type 2 diabetes, a regular physical activity program may reduce risk of death.

Annals Int Med April 18, 2000; 132: 605-11 Original investigation, first author Ming Wei, Cooper Institute, Dallas TX <http://www.annals.org/issues/v132n8/full/20000180-000020/html>

Comment:

Weight loss and weight control are major considerations of diabetes care. But, patients often do not achieve them. This study suggests that achieving fitness benefits even if weight is not lost – an important practical clinical application. RTJ

4-15 INFLUENCE OF SOCIAL NETWORK ON OCCURRENCE OF DEMENTIA: A COMMUNITY-BASED LONGITUDINAL STUDY

Studies over the past few decades have led to a general acceptance that social support helps a person to remain healthy. Social environment is important for psychological balance in the elderly. However, there is little evidence on the effect of social support on the occurrence of dementia. Does involvement in social activities delay the onset of dementia?

This study explored whether social connections affect incidence of dementia.

Conclusion: An extensive social network seems to protect against dementia.

STUDY

1. Followed a community-based cohort of over 1200 non-demented people living at home. All were over age 75. All had good cognition at baseline. (Mini Mental Status Examination [MMSE] score over 23.)
2. Obtained information on social network at baseline. This included marital status; living arrangements (living with partner, children, siblings, or others — or living alone); having children and frequency of contacts with children; satisfaction with these contacts; and close social ties with relatives and close friends. (Note: social networks prior to baseline were not considered.)
3. Determined incident cases of dementia over the following 3 years.

RESULTS

1. Over the 3-year follow-up, 176 persons became demented. (136 Alzheimer; 32 vascular.)
2. Female sex, advanced age, low educational level, and low cognitive level were associated with higher dementia incidence.
3. Individuals living alone, and those without any close social ties, had an adjusted relative risk of developing dementia of 1.5.

4. Compared with married people, single people and those living alone had an adjusted relative risk of 1.9.
5. Infrequent contacts with network resources did not increase risk provided the contacts were experienced as satisfying.
6. Combining all components, a poor or limited social network increased the risk of dementia by 60%.
7. The perception that contacts with others was not satisfying increased relative risk to 1.5.
8. Being single and living alone was the strongest determinant of risk, almost doubling the risk.
Having children with unsatisfying contact also increased risk.
9. Only 84 persons had combined favorable network factors: married and living with someone; having children with daily or weekly satisfying contacts; having relatives/friends with daily to weekly satisfying contacts. The incidence of dementia was lowest in this group — 19 per 1000 person-years. Of those without any of these factors, incidence was 157 per 1000 person-years.

DISCUSSION

1. Three main results emerged from the study:
 - 1) Individuals living alone and having no friends or relatives had an increased risk of developing dementia.
 - 2) When the number of contacts and satisfaction with such contacts were combined, the absence of close social ties emerged as a risk factor in comparison with the reference situation of frequent and satisfying contacts.
 - 3) Infrequent contacts with network resources did not increase risk if such contacts were experienced as satisfying.
2. A significant gradient was found for different degrees of social connections.
3. The study did not take into account social activities such as participation in religious or secular organizations. The study did not take into account the past social status — only that during the average 3 years before onset of dementia.
4. “An extensive social network can delay . . . onset by providing emotional and intellectual stimulation, and practical support. In this situation, an elderly person could more easily compensate for any mild cognitive impairment.”

CONCLUSION

An extensive satisfying social network seems to protect against dementia.

Lancet April 15, 2000; 355: 1315-19 Original investigation, from the Swedish Kingsholmen Project, first author Laura Fratiglioni, Stockholm Gerontology Research Centre, Sweden.

<http://www.thelancet.com/newlancet/sub/issues/vol355no9212/article1315.html>

Comment:

No mention if incidence of dementia in patients with vascular dementia differed from Alzheimer's.

Interesting, but what is the clinical importance of this study? How could clinicians intervene to change outcomes? RTJ

4-16 WHICH INFLUENCES COGNITIVE FUNCTION: LIVING ALONE OR BEING ALONE?

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

Two social conditions emerge as consistent and powerful determinants of risk for dementia:

1) degree of educational attainment, and 2) patterns of social-network.

The preceding study suggests that satisfaction with relationships is more important than the frequency of contact. "Particularly alarming is the indication that risks are higher among those having unsatisfactory contact with children than among those having no children at all."

Being single carries the highest risk.

Social engagement probably challenges people to communicate effectively and to participate in complex interpersonal exchanges. Such a dynamic environment is likely to engender the mobilization of cognitive capacities, setting in place a "Use it, or lose it" phenomenon so important to successful aging. It also provides a sense of purpose to community and family that rests on the bidirection of commitments. The mutuality of commitment moves beyond the unidirectional provision of emotional and instrumental support provided to the older person, which may even, in the extreme, inhibit functioning. "Thus, the power of engagement and worthiness it provides may be the critical pathway through which social networks influence the onset of dementia or cognitive decline. Being alone is what is risky, not living alone."

Diversity of relations is critical. Having one strong bond (eg, marriage or only close contact with children) is not enough. Risks are lowest among those with strong relationships in several domains. One type of tie may substitute for another. Risk rises substantially when there are no close ties across several domains.

An important question remains: will intervention in late life alter onset and progression? Perhaps network assessments predict risk because they represent life-long cumulative exposures.

Lancet April 15, 2000; 355: 1291-92 commentary by Lisa F Berkman, Harvard School of Public Health, Boston, Mass.

<http://www.thelancet.com/newlancet/sub/issues/vol355no9212/commentary1291.html>

4-17 SEDATION WITH NON-SEDATING ANTIHISTAMINES: Four Prescription-Event

Monitoring Studies In General Practice.

The first generation antihistamines have been associated with side effects, particularly sedation. Second generation antihistamines are favored, not because of greater efficacy, but because they have fewer side effects. But, are all second generation drugs alike in causing sedation?

This study investigated the frequency of sedation reported in post-marketing surveillance studies of 4 second generation drugs:

Loratadine (*Claratin*)

Fexofenadine (*Allegra*)

Cetirizine (*Zyrtec*)

Acrivastine (*Semprex*)

Conclusion: Loratadine and fexofenadine were less sedating.

STUDY

1. Post-marketing study monitored prescription-events for each drug. Obtained data from over 43 000 patients regarding sedation or drowsiness.

RESULTS

1. Odds ratio of incidence of sedation compared with loratadine:

Fexofenadine = 0.63

Acrivastine = 2.8

Cetirizine = 3.5

2. No statistically significant difference between loratadine and fexofenadine.
3. The number of reports of sedation was low for all 4 drugs.
4. No increase in accident or injury was evident with any of the 4 drugs. No cardiotoxic events were reported.

DISCUSSION

1. Assessment of drug safety depends not only on pre-clinical studies, but also on post-marketing surveillance.
2. Prescription monitoring avoids any selection bias inherent in clinical trials. It is carried out on a national basis and represents the whole population using the drug. It is dependent on general practitioners returning report forms.

CONCLUSION

“Although the risk of sedation was low with all four drugs, fexofenadine and loratadine may be more appropriate for people working in safety critical jobs.”

BMJ April 29, 2000; 320: 1184-897 Original investigation, first author Ronald D Mann, Southampton University, UK <http://www.bmj.com/cgi/content/full/320/7243/1184>

Comment:

In general, primary care physicians should await post-marketing experience before prescribing a new drug, especially a “me too” drug, unless the new drug has a unique and valuable application. RTJ

REFERENCE ARTICLE

4-18 RENAL ARTERY STENOSIS

This article reviews pathophysiology, clinical features, diagnosis, prognosis, and treatment.

Boxes list characteristics of renal artery stenosis, prevalence of atheromatous renal artery stenosis, clinical features and pointers to diagnosis, non-invasive imaging techniques (it presents several images of stenosis), treatment options, indications for revascularization, complications of interventions, and recommendations for treatment.

I abstracted a few highlights. RTJ

CLINICAL FEATURES

Atheromatous renal artery stenosis typically occurs in male smokers over age 50 with co-existent vascular disease. It is underdiagnosed and may present with a spectrum of clinical manifestations. Although conventionally thought as a cause of hypertension, atheromatous renal artery stenosis is *not* commonly associated with mild to moderate hypertension. It is present in up to a third of patients with malignant or drug resistant hypertension. Renal artery stenosis is a cause of end stage renal failure. Patients commonly present with chronic renal failure (with or without hypertension). Typically, patients have a bland urine sediment and non-nephrotic range proteinuria with focal glomerulosclerosis on renal biopsy. Patients may also present with acute renal failure, particularly those with bilateral renal artery stenosis (or stenosis of a single functioning kidney) who are taking drugs that block the renin-angiotensin system.

Rapid onset “flash” pulmonary edema is a less common presentation.

Patients with unilateral renal artery stenosis have raised circulating concentrations of renin and aldosterone with associated hypokalemia. Plasma sodium concentration is normal or reduced in contrast to an increase in patients with primary hyperaldosteronism,.

DIAGNOSIS

“The main differential diagnoses of atheromatous renal artery stenosis in patients with hypertension and renal impairment are benign hypertensive nephrosclerosis and cholesterol-microembolic disease. Differentiating between these conditions may be difficult, particularly as all three can occur simultaneously.

Angiography remains the standard test for diagnosing atheromatous renal artery stenosis and is widely available. However, it is not without risk and may worsen renal function. Non-invasive imaging techniques are beginning to replace conventional angiography. Although acceptable results have been reported by single enthusiastic centers, it remains to be seen whether these can be reproduced. Each has its own limitations. Doppler ultrasonography is very operator sensitive and is often impossible in obese patients. Spiral computed tomography requires the use of iodinated contrast media and radiation. Isotope renography (with or without captopril) had the advantage of providing information on renal function, but is of little value in bilateral disease or when renal function is seriously impaired. Magnetic resonance angiography is the most promising imaging technique. It requires no contrast media and permits reconstruction of the image in different planes.

None of the available imaging techniques identify the patients who will respond to revascularization. The aim of investigation is to establish the diagnosis and to decide whether revascularization is possible or appropriate.

TREATMENT

Hypertension can be controlled by drugs alone in almost 90% of cases. ACE inhibitors should be used with utmost caution. They reduce the glomerular filtration rate in patients with high grade atheromatous stenosis.

Revascularization must be tailored to the individual and should be undertaken in the expectation that it will prolong life. Angioplasty is the traditional revascularization procedure. Technical advances have revolutionized angioplasty, but few trials have examined its effects. The available trials comparing angioplasty with drug treatment have shown modest reductions in blood pressure and antihypertensive drug requirements. Unlike treatment of fibromuscular dysplasia, cure of atheromatous renal artery stenosis by angioplasty alone is rare.

Most atheromatous renal artery stenosis is due to plaques encroaching on the ostium of the renal artery. Angioplasty is less than ideal in this situation because of elastic recoil of the aortic plaques, The introduction of stents has helped overcome this problem. Recent controlled trials comparing stent insertion with angioplasty alone in patients with ostial stenosis found higher initial success in the stent patients. There is little to argue against a policy of primary stenting of ostial stenosis. Surgery should probably be reserved for patients in whom stenting fails.

The quality of evidence available and the paucity of controlled trials make treatment recommendations difficult. Surgical revascularization is rarely indicated, but may have a role in patients for whom angioplasty or stenting is not technically feasible, or in patients with complex disease having abdominal vascular surgery.

“Whatever recommendations we suggest, there will be disagreement.”

BMJ April 22, 2000; 320: 1124-27 Review article, first author Devin McLaughlin, University of Calgary, Canada.

<http://www.bmj.com/cgi/content/full/320/7242/1124>

Comment:

As with any established atherosclerotic cardiovascular disease, all-out efforts should be made to control the process. Smoking cessation is paramount. BP can be controlled in many patients with medical therapy. The atherosclerotic process can be retarded and plaque stabilization achieved by lipid control.

A recent study from the Netherlands (NEJM April 6, 2000; 342: 1007-14 “The Effect of Balloon Angioplasty on Hypertension in Atherosclerotic Renal-artery Stenosis”) concluded that angioplasty has little advantage over anti-hypertensive drug therapy. RTJ

REFERENCE ARTICLE

**4-19 USE AND INTERPRETATION OF AMBULATORY BLOOD PRESSURE MONITORING:
Recommendations of The British Hypertension Society.**

This review comments on methods, type and choice of monitor, training, fitting the monitor, preparing the patient, analyzing and presenting the data, and clinical indications.

Illustrations of blood pressure patterns are reproduced on p 1131 (eg, normal BP, white coat hypertension, isolated systolic hypertension).

See p 1132 for comments on white coat hypertension.

“One of the most important indications for ambulatory monitoring is to exclude white coat hypertension. The technique is also valuable in diagnosing and treating elderly patients and is used increasingly in pregnancy”

“There is now firm evidence that ambulatory blood pressure monitoring is a more sensitive predictor of cardiovascular outcome than conventional measurement.”

“Regardless of the technique used to diagnose hypertension, it is only one factor in determining a patient’s risk profile and must be assessed in relation to concomitant disease, such as diabetes mellitus and in relation to the degree of target organ involvement.”

The technique is specialized and should be approached with care. Training and experience are required.

BMJ April 22, 2000; 320: 1128-34 Review article, first author Eoin O’Brien, Beaumont Hospital, Dublin Ireland.

<http://www.bmj.com/cgi/content/full/320/7242/1128>

Comment:

I believe some primary care practices should assign individuals who will interest themselves in learning and applying ABPM. It would be a valuable addition to the clinical medicine in the community. There is a learning curve.

RTJ

REFERENCE ARTICLE

4-20 ULCERATIVE COLITIS

This review includes clinical features and diagnosis, differential diagnosis, causal and immunological aspects, management, medical treatment, failure of medical management and indications for surgery, malignant complications, and associated sclerosing cholangitis.

Most patients can be managed wholly as outpatients. Symptomatic relapses are the rule. Maintenance treatment with oral 5-amino-salicylic acid preparations is important to keep these to a minimum. Most have distal disease that is amenable to topical applications of 5-amino-salicylic acid or corticosteroid preparations. Many patients will begin self-treatment with these at the first signs of a flair-up. The overall prognosis is good. With the exception of the first year of diagnosis, when the risk of colectomy is statistically highest, there is no significant excess in mortality.

BMJ April 22, 2000; 320: 1119-23 “Clinical Review”, first author Subrata Ghosh, University of Edinburgh, UK

<http://www.bmj.com/cgi/content/full/320/7242/1119>

REFERENCE ARTICLE

4-21 EVALUATION OF THE PATIENT WITH ACUTE CHEST PAIN

Patients with acute myocardial infarction who are mistakenly discharged home from the emergency department have a short-term mortality twice that which occurs if they are admitted.

Conversely, if patients at low risk are admitted, costs increase.

This article presents approaches to improve efficiency of care of patients with acute chest pain. The authors comment on clinical evaluation; emergency treatment; macromolecular markers of myocardial injury; decisions to admit: aids and guidelines; where to admit and how long; and exercise tests, scintigraphy, echocardiography, and early angiography.

Figures present diagnostic sensitivity of macromolecular markers over 24 hours after onset of pain and division into risk groups (very low to high)

Tables present the American College of Emergency Physicians clinical policy for evaluation of acute chest pain; determination of short-term risk of fatal or non-fatal myocardial infarction; and recommended strategies for determining where to admit patients.

NEJM April 20, 2000; 342: 1187-95 "Primary Care" review article, first author Thomas H Lee, Harvard Medical School, Boston MA <http://www.nejm.com/content/2000/0342/1187/asp>

Comment:

Patients presenting with acute chest pain who are discharged as being at low risk (normal enzymes and ECG) should be followed up the next day at least by telephone. A recent study reported that over 1 in 20 such patients had elevated troponin levels 24 hours after presentation, indicating some degree of myocardial damage. RTJ

REFERENCE ARTICLE

4-22 ARTERIAL ANEURYSMS

This review focuses on abdominal aortic aneurysms (AAA). I abstracted a few clinically relevant points.
RTJ

Screening and medical treatment:

Studies of screening with ultrasound report a 2.5% prevalence of AAA larger than 4 cm in men age over 60. Advocates of screening have suggested that diagnosis and treatment following a single scan of men at age 65 would exclude 90% of the population from future aneurysm rupture. There would be an 85% reduction in rupture. This is considered cost-effective. One problem, however, is that screening identifies small AAAs. If no treatment is advised other than surveillance, the patient may experience an adverse effect on his quality of life.

Indications for surgery:

In patients with asymptomatic AAA, decisions for surgery are based on the balance between benefits and risks. The risk of rupture is related to many factors, the main one is the diameter of the aneurysm. Risk

increases exponentially at and above diameter of 5.5 cm. There is broad consensus that repair is indicated in these patients if there are no contraindications. For smaller aneurysms, a recent study of over 1000 AAA 4.0 to 5.5 cm found a 30 day operative mortality of 6% and a mean risk of rupture of 1% a year. There was no difference in survival between groups over 6 years. Surgery was associated with an improvement in quality of life.

Endovascular repair with a graft may change the risk/benefit ratio. It has theoretical advantages.

Trash foot:

This is a point warranting emphasis. Multiple microscopic emboli from an AAA cause ischemic gangrene-like infarcts in the toes. Seen in patients with easily palpable foot pulses, this strongly suggests a proximal aneurysm. (*Illustration p 1193*)

BMJ April 29, 2000; 320: 1193-96 "Clinical Review" by MM Thompson and PRF Bell, Leicester Royal Infirmary and University of Leicester, UK

<http://www.bmj.com/cgi/content/full/320/7243/1193>

Comment:

Some studies have reported a benefit from beta-blockers in retarding growth of aortic aneurysms – possibly due to a decrease in the frequency, strength, and rapidity of the systolic stretch of the arterial wall.

Since patients with AAA have established coronary heart disease, beta-blocker therapy would be indicated anyway. RTJ

REFERENCE ARTICLE

4-23 COOLING METHODS FOR HEATSTROKE VICTIMS

Rapid cooling is the most important intervention to reduce morbidity and mortality from heatstroke. This report from the U.S. Armed Services presents current recommended cooling methods. It has been used in over 200 exertional heat stroke patients without a fatality. Ice water is the basis of therapy.

See table p 678 for details.

Annals Int Med April 18, 2000; 132: 678 First author Stephen L Gaffin, U.S. Army Research Institute for Environmental Medicine, Natick, MA <http://www.annals.org/issues/v132n8/full/200004180-00023/html>

REFERENCE ARTICLES

4-24 RED CELLS I: Inherited Anaemias

Considers structure and function of red cells, production and destruction of red cells, definition of anemia, adaptive changes, sickling, thalassemia, red cell enzyme defects, and red cell membrane defects.

Lancet April 1, 2000; 355: 1169-75 Review article by D J Weatherall and A B Provan, University of Oxford and Southampton General Hospital, UK

<http://www.thelancet.com/newlancet/sub/issues/vol353no9210/series1169.html>

4-25 RED CELLS II: Acquired Anaemias and Polycythemia

Considers anemia due to iron deficiency, macrocytic anemias, hemolytic anemias myelodysplastic syndromes, paroxysmal nocturnal hemoglobinemia, aplastic anemia, polycythemia.

Lancet April 8, 2000; 355: 1260-68 Review article by Drew Provan and David Weatherall, Southampton University Hospitals, and John Radcliffe Hospital, Oxford, UK

<http://www.thelancet.com/newlancet/sub/issues/vol355no9211/series1260.html>

Read The Original !

4-26 CHEQUE YOUR SPELLING

Eye Halve a spelling chequer;

It came with my pea sea

It plainly marques four my revue

Miss Steakes eye kahn knot sea

Eye have run this filler threw it

I am shore your pleased two no

Its letter perfect awl the weigh

My chequer tolled me sew.

BMJ April 5, 2000; 320: 990 "When I use a Word" a filler by Jeff Aronson, Clinical Pharmacologist Oxford, UK <http://www.bmj.com/cgi/ontet/full/320/7240/990>

