PRACTICAL POINTERS

FOR

PRIMARY CARE

ABSTRACTED MONTHLY FROM THE JOURNALS

JANUARY 2002

PUBLISHED BY PRACTICAL POINTERS, INC.

JAMA, NEJM, BMJ, LANCET
ARCHIVES INTERNAL MEDICINE
ANNALS INTERNAL MEDICINE
WWW.PRACTICALPOINTERS.ORG

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HIGHLIGHTS JANUARY 2002

1-1 COLLABORATIVE META-ANALYSIS OF RANDOMIZED TRIALS OF ANTIPLATELET THERAPY FOR PREVENTION OF DEATH, MYOCARDIAL INFARCTION, AND STROKE IN HIGH RISK PATIENTS

Unless some definite contraindication exists, antiplatelet therapy (*low-dose aspirin*) should be considered routinely for all patients whose medical history implies a significant risk of occlusive vascular disease over the next few months or years (*secondary prevention*), and should generally be continued for as long as the risk remains high. Absolute benefits substantially outweigh the absolute risk of major extracranial bleeding.

Aspirin is protective in patients with a history of ischemic stroke, unstable and stable angina, previous myocardial infarction, previous stroke or cerebral ischemia, diabetes, peripheral vascular disease, or atrial fibrillation (when warfarin is not used).

Practical point: Primary care clinicians should prescribe aspirin more often for secondary prevention of cardiovascular events.

1-2 ASPIRIN FOR THE *PRIMARY* PREVENTION OF CARDIOVASCULAR EVENTS

Five trials have examined the effects of daily or every-other-day aspirin for primary prevention over 4 to 7 years. Most subjects were men over age 50. Meta-analysis of pooled data showed that aspirin reduced the risk of coronary heart disease by 28%. No effect on total mortality or stroke.

For patients at high risk of coronary heart disease (5% over 5 years) prophylactic aspirin would lead to avoidance of 6 to 20 CHD episodes over the 5 years.

Primary prevention is not recommended for those with a risk of 1% per year.

Practical point: The clinician's challenge is to judge the degree of risk and to match the patient's concerns and wishes with the risk. Many individuals will benefit from primary prevention with aspirin.

1-3 PREVALENCE OF THE METABOLIC SYNDROME AMONG US ADULTS

About 22% of Americans have the metabolic syndrome. (47 million) Implications for health care are critical. Correction and prevention of the syndrome is a national health-care priority.

Practical point: Correction and prevention of the syndrome in individual patients is a health-care priority.

1-4 ORAL ANTIHYPERGLYCEMIC THERAPY FOR TYPE 2 DIABETES: SCIENTIFIC REVUE

Large trials in the UK compared metformin with placebo and intensive sulfonylurea-insulin therapy. With similar HbA1c reductions, metformin was associated with up to 40% fewer diabetic-related deaths, all cause mortality, risk of myocardial infarction, and all macrovascular endpoints.

Metformin is the only drug associated with weight loss, or at least weight neutrality. It has become the most widely prescribed single antihyperglycemic drug. It is generally regarded as the best first-line agent, at least in the obese patient. (Most patients with DM2 are overweight.) Its virtual lack of hypoglycemia makes it an attractive option.

There is no compelling reason in terms of antihyperglycemic effect alone, to favor one of the major class over another. However, the benefit of metformin demonstrated in the UK study (UKPDS) (which showed a lack of hypoglycemia and no weight gain) make it one of the most attractive options for obese — if not all— patients with DM2.

Combination therapy is a logical approach, given the multiple pathophysiological lesions in DM2. Indeed, most patients after a few years will require more than one drug for good control. A second drug may provide additive effect on lowering HbA1c. There is no evidence that one specific combination is any more effective than another in lowering glucose levels.

Only sulfonylureas and metformin have been shown to reduce microvascular complication. Metformin exhibits additional benefits on macrovascular risk. The popularity of metformin and thiazolidinediones is increasing since these agents avoid the risk of hypoglycemia and allow treatment of patients already near the euglycemic range.

"Most patients will require combination as their disease progresses."

Practical point: Primary care clinicians consider selecting metformin as first-choice.

1-5 EFFECT OF PREOPERATIVE SMOKING INTERVENTION ON POSTOPERATIVE COMPLICATIONS

An effective smoking cessation program applied for at least 6 weeks prior to hip and knee surgery more than halved the frequency of postoperative complications.

Practical point: Primary care clinicians should stress this benefit.

1-6 REDUCING ANTIBIOTIC USE FOR ACUTE BRONCHITIS IN PRIMARY CARE

Most previously well adults who develop acute bronchitis were judged not to need antibiotics. Reassuring these patients and sharing uncertainty about the value of antibiotics in acute bronchitis is a safe strategy and reduces antibiotic use.

Practical point: Primary care clinicians should use the "if" prescription more often.

1-7 CHRONIC FATIGUE SYNDROME; A STEP TOWARD AGREEMENT

The Royal College of Physicians of the UK has issued a new report on the chronic fatigue syndrome (**CFS**) This editorial hopes it will mark a turning point in the history of the illness.

There was agreement that the illness "is a relatively common clinical condition which can cause profound illness and disability and can have a very substantial impact on the individual and family." It can affect both sexes, and a wide range of ages, even children. "It is no longer acceptable for clinicians to state that they do not 'believe' in CSF/ME. Inaction . . .due to ignorance or denial of the condition is not excusable." A significant minority of patients who are very severely affected often receive the least attention. Patients need a positive and early diagnosis and appropriate management and advice. Patient organizations have an important role to play in this.

Practical point: Primary care clinicians accept the fact that CFS is "real" and support the patient.

1-8 COMPARISON OF TWO DIETS FOR THE PREVENTION OF RECURRENT STONES IN IDIOPATHIC HYPERCALCIURIA

A diet containing normal amounts of calcium and low animal protein and salt was more effective than a low calcium diet for prevention of recurrent calcium oxalate stones in men with idiopathic hypercalciuria.

Aim to reduce concentration of oxalate in the urine, thus lowering saturation of Ca-oxalate, the chief stone former.

Practical point: This diet should be standard therapy for recurrent calcium-oxalate stones.

1-9 RECURRENT HYPERCALCIURIC NEPHROLITHIASIS — DOES DIET HELP?

Practical point: "Physicians should no longer prescribe a low-calcium diet to prevent recurrent nephrolithiasis in patients with idiopathic hypercalciuria."

1-10 LOW-DOSE PREDNISONE THERAPY FOR PATIENTS WITH EARLY ACTIVE RHEUMATOID ARTHRITIS

Prednisone 10 mg/d provided clinical benefit, particularly in the first 6 months, and substantially inhibited progression of radiologic joint damage in patients with early RA who had no previous treatment with DMARDs.

Because of the limited disease-modifying effects of prednisone, DMARDs should be added to prednisone.

Practical point: Primary care clinicians may consider low-dose prednisone as a first-line treatment in early RA

1-11 ERADICATION OF *HELICOBACTER PYLORI* AND RISK OF PEPTIC ULCERS IN PATIENTS STARTING LONG-TERM TREATMENT WITH NON-STEROIDAL ANTI-INFLAMMATORY DRUGS.

Screening and treatment of *H pylori* infection reduced the risk of development of peptic ulcer in patients starting long-term NSAID treatment.

Practical point: Consider screening and treatment of *H pylori* in select patients.

1-12 ANTIBIOTIC-ASSOCIATED DIARRHEA

C difficile infection should be considered in all patients with unexplained diarrhea who are receiving antibiotics or who have recently received antibiotics.

Enzyme assays to detect both toxins A and B are preferred. False negative results may occur if the only test is for toxin A.

Many patients will respond to withdrawal of the inducing antibiotic. If the patient's condition calls for continued antibiotic therapy, use an agent that is infrequently associated with AAD. (*See list in abstract.)*

If there is evidence of colitis or if discontinuation of the offending antibiotic does not result in resolution of the diarrhea, metronidazole is indicated. Lack of response to metronidazole is strong evidence against the *C difficile* colitis.

If assays for *C difficile* toxin are negative, and symptoms persist, repeat the test, expand the diagnostic evaluation to other causes (eg, look for staph and salmonella), or treat empirically.

Practical point: Patients who are informed of this risk may be less likely to demand antibiotics.

1-13 ALCOHOL CONSUMPTION AND RISK OF DEMENTIA: THE ROTTERDAM STUDY

Light-to-moderate alcohol consumption was associated with a reduced risk of dementia in elderly individuals over age 65. The effect seemed to be unchanged by the type of alcohol consumed.

Practical point: Although benefits in reducing incidence of dementia may be very modest, reports of low-dose alcohol consumption have been invariably favorable for a number of risks.

1-14 DIRECT THROMBIN INHIBITORS IN ACUTE CORONARY SYNDROMES

Direct thrombin inhibitors were superior to heparin in preventing MI and death in patients with acute coronary syndromes including those undergoing PTCA. But the NNT to benefit one patient was large, and equaled the NNT to harm.

The investigators recommend further development of DTIs for management of arterial thrombosis.

Practical point: Primary care clinicians wait for further developments.

1-15 EFFICACY OF ROFECOXIB, CELECOXIB, AND ACETAMINOPHEN IN OSTEOARTHRITIS OF THE KNEE

Rofecoxib 25 mg/d provided efficacy advantages over acetaminophen 4000 mg/d, and celecoxib 200 mg/d for symptomatic knee arthritis.

Practical point: Despite this report, primary care clinicians will consider individual-patient response to various NSAIDs. Acetaminophen may be the best first-choice.

1-16 PLATELET GLYCOPROTEIN IIB/IIIA INHIBITORS IN ACUTE CORONARY SYNDROMES

Glycoprotein IIb/IIIa inhibitors reduced cardiac complications in patients with acute coronary syndromes not routinely scheduled for early revascularization. Treatment might be considered early after admission in high-risk patients and continued for 2 to 4 days until a decision about revascularization is made.

Benefit was evident only in those with a positive troponin.

The number needed to treat to benefit one patient = 100

Practical point: Primary care clinicians, wait for further developments.

1-17 US RELAXES SUGAR BAN FOR PEOPLE WITH DIABETES

The American Diabetes Association has released new nutritional guidelines for diabetes control. It relaxes dietary restrictions on high sugar content foods. (*Diabetes Care 2002;25:148-98, 200-12*).

Now, someone with diabetes would be able to indulge in an occasional slice of sugary pie and drink moderate amounts of alcohol without violating their diet. A moderate amount of daily alcohol intake poses no threat and may be healthy.

Less than 10% of calorie intake should be derived from saturated fats and cholesterol intake should be no more than 300 mg/d.

Practical point: The original may be worth accessing.

Update On Aspirin For Secondary Prevention

1-1 COLLABORATIVE META-ANALYSIS OF RANDOMIZED TRIALS OF ANTIPLATELET THERAPY FOR PREVENTION OF DEATH, MYOCARDIAL INFARCTION, AND STROKE IN HIGH RISK PATIENTS

Previous studies of prophylactic antiplatelet therapy reported substantial benefits in secondary prevention of cardiovascular events. Some important questions remain: 1) Is there net benefit of immediate treatment of the acute phase of stroke? 2) Is there net benefit in patients with chronic conditions such as atrial fibrillation, stable angina, peripheral vascular disease, and diabetes? 3) What is the optimum dose of aspirin? 4) Does addition of other antiplatelets to aspirin benefit?

This meta-analysis updates trials of secondary prevention among high risk patients. It reviewed 287 studies involving 135 000 patients in comparisons of anti-platelet therapy versus controls, and 77 000 comparisons of various different antiplatelet regimens. The main outcome measure was a "serious vascular event" — non-fatal MI; non-fatal stroke; or vascular death.

Compared antiplatelet therapy vs controls in patients with previous MI, acute MI, previous stroke or TIA, acute stroke, and other high risk patients (unstable angina, CABG, coronary angioplasty, stable angina, heart failure, atrial fibrillation, cardiac valve disease, peripheral arterial disease, diabetes, and carotid disease).

RESULTS

1. Serious vascular events — aspirin vs control:

Category of trial	% odds reduction	Benefit/1000 patients	Mean months of treatment
Previous MI	25	36	27
Acute MI	30	38	1
Previous stroke/TIA	22	36	29
Acute stroke	11	9	0.7
Other high risk	26	22	22
All trials	22		

(NNT to benefit one person over the various time periods varied from 25 to 100.)

2. Reduction in risks in other high-risk patients:

Vascular deaths were reduced by 15%

All cause mortality was reduced by about 18%

Pulmonary embolism reduced by 25%

In patients with diabetes, serious vascular events were reduced by about 25%

3. Acute stroke

Antiplatelet therapy is associated with reduction in risk of a recurrent non-fatal stroke in about 4 fewer patients per 1000 treated, and a reduction in risk of death from a vascular cause in about 5 per 1000. This was associated with 2 more major extracranial bleeds per 1000. "There is now good reason to consider starting antiplatelet therapy as soon as possible for suspected acute ischemic stroke and continuing it for some years."

4. Effects of antiplatelet drugs other than aspirin:

Only clopidogrel (Plavix), among 7 other drugs (including dipyridamole; Persantine) showed any benefit above aspirin. (Clopidogrel blocks ADP dependent activation of platelets, acting in an entirely different manner than aspirin.) Compared with aspirin it reduced secondary occurrence of serious vascular events from 11.1% to 10.1%. Thus the NNT was low — about 100. (OnePlavix 75 mg costs over $3. In calculating the benefit/harm-cost ratio of long-term treatment, cost is an important factor, given the benefit which occurs in only 1 patient in 100. RTJ)

5. Effects of adding another antiplatelet drug to aspirin:

Adding a drug that acts through another pathway might provide additional benefit. Adding dipyridamole (Persantine) was associated with a non-significant reduction in serious vascular events. In patients with unstable angina, clopidogrel produced additional benefit.

Glycoprotein IIb/IIIa receptor blockers: The final common pathway of platelet aggregation is thought to be mediated by activation of platelet glycoprotein IIb/IIIa receptors. Many drugs that block this receptor have been developed. In patients with unstable angina or undergoing PTCA, short intravenous infusions (oral preparations are not effective) of a glycoprotein IIb/IIIa blocker added to aspirin produced a clinically significant reduction of 19% in serious vascular events. However, there was a 2.3% increase in major extracranial bleeds.

6. Dose of aspirin

Within a few days of beginning 75 mg daily, cyclo-oxygenase is virtually completely inhibited in platelets. High doses (500-1500) are more gastrotoxic but are no more effective than low doses. The available evidence supports daily doses of 75-150 mg for the long term prevention of serious vascular events in high risk patients. A loading dose of 300 mg produces an immediate antithrombotic effect and can be given when an immediate effect is needed; 300 mg produces a rapid and complete inhibition of thromboxane-mediated platelet aggregation.

7. Harms of aspirin:

Major extracranial bleeds increased. (Odds ratio = 1.6 compared with non-takers.)

"Our results suggest that among individuals at high risk of occlusive vascular disease, the proportional risk reductions with antiplatelet therapy are roughly similar in most categories of patients (although smaller in acute stroke)." A patient's absolute risk is likely to be more important than the proportional risk. In patients at particularly high risk of vascular events, the benefits of antiplatelet therapy are large. However there is a risk of upper GI bleeding or perforation. Doses of ≤ 300 mg daily given regularly are associated with a twofold risk. However benefits far outweigh risks. "Consequently, unless some definite contraindication exists, antiplatelet therapy (low-dose aspirin) should be considered routinely for all patients whose medical history implies a significant risk of occlusive vascular disease over the next few months or years, and should generally be continued for as long as the risk remains high." Absolute benefits substantially outweigh the absolute risks of major extracranial bleeding.

In practice, many eligible patients still do not receive this beneficial therapy.

SUMMARY

Aspirin is protective in most types of patients at increased risk of occlusive vascular events, including those with a history of ischemic stroke, unstable and stable angina, previous myocardial infarction, previous stroke or cerebral ischemia, diabetes, peripheral vascular disease, or atrial fibrillation (when warfarin is not used).

Low dose (75 mg) is effective for the long term. A higher loading dose may be required in some acute situations.

BMJ January 12, 2002; 324: 71-86 Systematic review by the Antithrombotic Trialists' Collaboration, Radcliffe Infirmary, Oxford, UK **http://www.bmj.com/cgi/content/full/324/7329/71**

Comment:

Trials and meta-analyses continue to report proportional (relative) risk reductions. This can be very misleading. Practical Pointers will attempt to report absolute differences and the number needed to treat (NNT) when the data presented allow calculations. For example, a relative risk reduction of 10% was reported to result from clopidogrel. The absolute benefit was only 1% (NNT = 100.) RTJ

Looking back over 60 years of primary care practice, there have been two clinical developments that truly astounded me. I would not have believed them until the proof became evident. One was the Helicobacter pylori-peptic ulcer connection. The other was the effectiveness of prophylactic aspirin. Just think — for years we had antibiotics that might have cured ulcers, and had aspirin close by in our medicine cabinets not knowing it would be life-saving. RTJ

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Aspirin, The Modern Miracle Drug

1-2 ASPIRIN FOR THE *PRIMARY* PREVENTION OF CARDIOVASCULAR EVENTS: Recommendations and Rationale

This is the 3rd US Preventive Services Task Force (USPTF) report on aspirin for the *primary* prevention of cardiovascular events (patients without known cardiovascular disease). It updates additional data from 3 recent trials.

The balance of benefits and harms is most favorable in patients at high risk for coronary heart disease (with a 5-year risk ≥ 3%). It is also influenced by patient preferences. Some persons at lower risk may consider the potential benefits of aspirin to outweigh the potential harms. Older persons may derive greater benefit from primary prevention because of their higher risk of coronary disease and stroke. Their risk of bleeding may also be higher.

Most cardiovascular events occur in older persons and in those with risk factors. (Abnormal lipids, high blood pressure, diabetes, smoking, poor physical fitness.)

BENEFITS OF ASPIRIN

Five trials have examined the effects of daily or every-other-day aspirin for primary prevention over 4 to 7 years. Most subjects were men over age 50. Meta-analysis of pooled data of patients at high risk showed that aspirin reduced the absolute risk of coronary heart disease by 28%. [NNT = 4] No effect on total mortality or stroke.

HARMS OF ASPIRIN

Aspirin increases the rates of gi bleeding episodes by about 2 to 4 per 1000 middle aged persons over 5 years; and from 4 to 12 older persons. Aspirin is also associated with an increased risk of hemorrhagic stroke (0 to 2 per 1000 per 5 years)

ESTIMATES OF BENEFITS AND HARMS OVER 5 YEARS

Baseline risk of CHD over 5 y	1%	3%	5%
Total mortality	No effect	No effect	No effect
CHD events	1-4 avoided	4-12 avoided	6-20 avoided
Hemorrhagic strokes*	0-2 caused	0-2 caused	0-2 caused
Major GI bleeding events*	2-4 caused	2-4 caused	2-4 caused

(Primary prevention not recommended for those with a 1% risk.)

(* Increases in hemorrhagic stroke may be offset by reduction in ischemic stroke. Rates of gi bleeding may be 2 to 3 times higher in persons over age 70. But they gain more benefit in preventing vascular events because of the greater risk at old age.)

DOSE OF ASPIRIN

Various doses (75mg/d; 100 mg/d; 325 mg/d) have reported benefit. 75 mg seems to be as effective as higher doses.

RECOMMENDATIONS OF OTHER ORGANIZATIONS

The American Diabetes Association recommends that clinicians consider aspirin for primary prevention in patients older than age 30 with diabetes. (Or younger if there are risk factors in addition to diabetes.)

The American Heart Association concluded that aspirin may be warranted for patients at high risk, but that clinicians must consider a patient's particular risk profile and the possible harms.

The European Society of Cardiology recommends 75 mg aspirin for patients with well controlled hypertension and for men at "particularly" high risk for coronary heart disease, but not for all persons at high risk.

Annals Int Med January 15, 2002; 157-160 "Clinical Guidelines" from the US Preventive Services Task Force. See also "A Summary of Evidence for the US Preventive Services Task Force" (pp 161-172) for a more detailed summary of evidence on which the guidelines are based. **www.annals.org**

Comment:

Decisions for aspirin in primary prevention are more difficult than for secondary prevention. Overall, I believe the benefit/harm-cost ratio is very favorable for selected patients.

In primary prevention of higher risk individuals the benefit/harm-cost ratio may be high: Benefits are great; harms, relatively low; cost, nil. If applied to the general population of persons at risk, the public-health efffect would be significant.

The clinician's challenge is to judge the degree of risk and to match the patient's concerns and wishes with the risk.

Several publications are available to calculate future risk of cardiovascular disease based on risk factors. **www.nhlbi.nih.gov/guidelines/cholesterol/atglance.pdf** outlines the National Cholesterol Education Program guidelines, and contains the Framingham estimate of 10-year risk for men and women based on age, total cholesterol, smoking, HDL cholesterol, and systolic BP.

When calculating risk factors the treatment decision does not concern merely whether or not to give prophylactic aspirin. We must address all risk factors and deal with them.

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1-3 PREVALENCE OF THE METABOLIC SYNDROME AMONG US ADULTS

In 2001, The Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol provided a working definition of the metabolic syndrome (MS):

Abdominal obesity -- waist circumference ≥ 102 cm (42") in men, and ≥ 88 cm (37") in women.

Hypertriglyceridemia -- ≥ 150 mg/dL

Low high density cholesterol (HDL-c) , < 40 mg/dL in men; < 50 in women

High BP ≥ 130/85

High fasting glucose ≥ 110 mg/dL

Individuals with 3 or more of these criteria met the definition.

This study estimated the prevalence of the MS in the US population.

Conclusion: MS is highly prevalent

STUDY

1. A cross sectional health survey of a nationally representative sample of non-institutionalized men and women (1988-1994) analyzed data from over 8500 subjects. All were over age 20.
2. Determined prevalence of MS according to the criteria.

RESULTS

1. Overall prevalence was 22%. About 47 million US residents have the MS.
2. Prevalence increased from 7% of those age 20-29 to 44% in those age 60 to 69.
3. Mexican Americans (especially women) had the highest prevalence.
4. Prevalence was similar among men and women except for African American women who had a prevalence about 57% higher than African American men.

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DISCUSSION

1. Up to 25% of US residents have the MS.

2. The unrelenting increase in prevalence of obesity suggests that the syndrome is likely more prevalent now.
3. Insulin resistance is thought to be an underlying feature of the MS. However, a significant proportion of *patients* with individual components of the MS do not have insulin resistance.
4. Some studies suggest that the association with hypertension is weak.
5. The cornerstones of treatment are management of weight and ensuring appropriate levels of physical activity.

6. Because improper nutrition and lack of physical activity are the root causes, there is an urgent need to develop comprehensive strategies directed at controlling obesity and improving physical activity.

CONCLUSION

The metabolic syndrome is highly prevalent among US residents. Implications for health care are critical.

JAMA January 16, 2002; 287: 356-59 Original investigation from the Third National Health and Nutrition Survey, first author Earl S Ford, Centers for Disease Control and Prevention, Atlanta GA **www.jama.com**

Comment:

It would be reasonable for primary care clinicians to check all overweight patients for the MS. Recognition of the associated risks might influence some to change their lifestyle.

Correction and prevention of the syndrome is a national health-care priority

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Is Metformin The Best First Choice?

1-4 ORAL ANTIHYPERGLYCEMIC THERAPY FOR TYPE 2 DIABETES: SCIENTIFIC REVUE

(*I hesitate to abstract long review articles. They are too all-inclusive. However, almost always I can find practical points which I did not know, had forgotten or which are worthy of emphasis RTJ*)

In some older groups, the prevalence of type 2 diabetes (**DM2**) and its forerunner, impaired glucose tolerance (**IGT**) approaches 25%.

The importance of glucose control lies in prevention of microvascular complications (nephropathy, retinopathy, neuropathy). Whether macro-vascular complications are prevented is less clear.

This systematic review of the literature discusses biguanides, alpha-glucosidase inhibitors, thia-zoli-dine-diones, sulfonylureas, and non-sulfonylurea secretagogs. Deciphering which agent to use in certain clinical conditions is a new dilemma for primary care.

Hyperglycemia is first exhibited in the postprandial state. The majority of ingested carbohydrate is taken up by skeletal muscle. Eventually hyperglycemia is evident during fasting. As insulin secretion decreases, hepatic glucose production increases. (Insulin normally attenuates hepatic glucose production.) Insulin resistance is also demonstrated at the adipocyte level, leading to unrestrained lipolysis and elevation of free fatty acids. The "lipotoxicity" dampens insulin response in skeletal muscle, further impairs pancreatic insulin production, and augments hepatic glucose production. Thus DM2 results from co-existing multiple organ sites: resistance to insulin action in muscle, defective pancreatic insulin secretion, and unrestrained hepatic glucose production.

Recent guidelines suggest a *pre*- prandial blood glucose level < 110 mg/dL; a 2-h *post*-prandial level less than 140, and HbA1c levels at 6.5%.

SULFONYLUREAS (SUs)

Second generation SUs (glyburide [*Micronase;DiaBeta*], glipizide [*Glucotrol*], and glimepiride [*Amaryl*] are more potent and probably safer than first-generation. They bind to a receptor on the beta-cells and allow insulin to be released at lower blood glucose levels. Compared with placebo, they decrease HbA1c levels by about 1% to 2%. They commonly lose efficacy over time. They may have the potential to exhaust beta-cell function. Common adverse effects are weight gain and hypoglycemia which is more likely in the elderly, in those with worsening renal function, and those with irregular meal schedules. SUs are approved for use as monotherapy and combined with all other agents except non-SU secretagogues, and insulin.

BIGUANIDES (METFORMIN; *Glucophage*)

Metformin does *not* stimulate insulin secretion. Its predominant effect is to reduce hepatic glucose production in the presence of insulin. Increased peripheral glucose disposal has been reported. It lowers HbA1c by 1% to 2% (similar to SUs).

Advantages: 1) weight loss (or no weight gain) and 2) much less hypoglycemia than SU therapy. Because of the lack of beta-cell stimulation, circulating insulin tends to decline. This may provide a cardiovascular advantage. Large trials in the UK compared metformin with placebo and intensive SU-insulin therapy. With similar HbA1c reductions, metformin was associated with up to 40% fewer diabetic-related deaths, all cause mortality, risk of myocardial infarction, and all macrovascular endpoints.

Adverse gastrointestinal effects can be minimized by consumption with food, and slow upward titration of dose. The need to discontinue therapy is uncommon. Lactic acidosis occurs once in 30 000 patient-years. Renal impairment is a contraindication. (Creatinine 1.5 mg/dL and over.)
It is approved for monotherapy and in combination with SUs, other secretagogues, TZDs and insulin.

ALPHA-GLUCOSIDASE INHIBITORS (ACARBOSE; *Precose*)

Alpha-glucosidase occupies the brush border of the proximal small bowel. It breaks down disaccharides and more complex carbohydrates. Competitive inhibition delays intestinal carbohydrate absorption and lessens postprandial blood glucose excursions.

However, efficacy is considerably less than SUs and metformin. The greatest effect is on postprandial glucose levels. No studies have reported long-term effectiveness.

THIA-ZOLI-DINE-DIONES— the "glitizones" rosiglitazone (*Avianda*) pioglitazone (*Actos*)

Mechanism of action is not completely understood. They do not increase insulin secretion by beta-cells. Their most prominent action is to increase glucose uptake by skeletal muscle. (Ie, decrease insulin resistance in peripheral tissues.) At the highest doses, hepatic glucose production may be decreased.

They lower HbA1c about as much as SUs and metformin.

Adverse effects include weight gain, which can be as great or greater than with SUs.

They are indicated as monotherapy and in combination with metformin and SUs. They are expensive.

NON-SU SECRETAGOGUES (repaglinide: *Prandin*)

Mechanism is similar to SUs. But their metabolic half lives are shorter. This results in brief episodes of beta-cell stimulation. Postprandial glucose excursions are attenuated because of a greater immediate insulin secretion after meals. Because less insulin is secreted several hours after a meal, the risk of hypoglycemia in the late postprandial phase is lowered. Comparisons with SUs have shown equal lowering of glucose levels. Weight gain is

less pronounced than with SUs. Dosing is required with meals. They are approved as monotherapy or with metformin.

MONOTHERAPY RECOMMENDATIONS

Except for the AGIs, which are generally less effective, each of the other drugs will lead to similar reductions in HbA1c. There are relative advantages and disadvantages to each. Metformin is the only drug associated with weight loss, or at least weight neutrality. It has become the most widely prescribed single antihyperglycemic drug. It is generally regarded as the best first-line agent, at least in the obese patient. (Most patients with DM2 are overweight.) Its virtual lack of hypoglycemia makes it an attractive option.

Non-SU secretagogues may be preferred by those who require secretagogue therapy and have irregular meals.

TZDs are interesting and of great promise. But there are no long-term data on microvascular or macrovascular risk. They may be most effective when used at the earliest form of diabetes, such as the drug-naive patient when insulin secretion is still substantial. They may have a unique benefit in preserving beta cell function. Unlike other drugs, they may take weeks or months to exert their full effect.

In summary, there is no compelling reason, in terms of antihyperglycemic effect alone, to favor one of the major class over another. However, the benefit of metformin demonstrated in the UK study (UKPDS) (which showed a lack of hypoglycemia and weight gain) make it one of the most attractive options for obese — if not all— patients with DM2.

COMBINATION THERAPY

Combination is a logical approach, given the multiple pathophysiological lesions in DM2. Indeed, most patients after a few years will require more than one drug for good control. A second drug may provide additive effect on lowering HbA1c. There is no evidence that one specific combination is any more effective than another in

lowering glucose levels, or more effective in preventing complications.

If control is not adequate, there should be no hesitation to add insulin either alone or in combination with oral drug(s), preferably in combination.

COMMENT

Only SUs and metformin have been shown to reduce microvascular complication. Metformin exhibits additional benefits on macrovascular risk. The popularity of metformin and TZDs is increasing since these agents avoid the risk of hypoglycemia and allow treatment of patients already near the euglycemic range.

"Most patients will require combination as their disease progresses."

JAMA January 16, 2002; 287: 360-72 "Scientific Review and Clinical Applications" by Silvio E Inzucchi, Yale University School of Medicine, New Haven Conn. **www.jama.com**

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1-5 EFFECT OF PREOPERATIVE SMOKING INTERVENTION ON POSTOPERATIVE COMPLICATIONS

Smoking is an important risk factor for interoperative and postoperative complications (pulmonary, circulatory, and infectious) as well as for impaired wound healing and postoperative admittance to intensive care.

The increased risk could be due to smoking-induced chronic pulmonary changes and impaired cardiovascular and immune function.

This study assessed the effect of preoperative smoking cessation on frequency of postoperative complications in patients undergoing hip and knee replacement.

Conclusion: Cessation for 6 to 8 weeks was associated with a large reduction in complications.

STUDY

1. Randomized trial assigned 100 daily smokers (mean age 65) to: 1) smoking intervention , or 2) control.
2. The intervention group met weekly for 6 to 8 weeks before surgery was scheduled. They received smoking counseling and nicotine replacement. They were strongly encouraged to stop smoking completely. They also had the option to reduce consumption by 50%.
3. Control group received standard care with little or no information about cessation.
4. At baseline they were consuming an average of 15 cigarettes daily with a history of 36 pack-years of smoking.
5. Registered all complications after the ensuing surgery.

RESULTS

1. In the intervention group, 36 stopped smoking; 14 reduced consumption; 6 continued to smoke.

2. Complication rate

	Intervention	Control
Wound-related	5%	31%
Cardiovascular	0%	10%
Secondary surgery	4%	15%

3. Overall complication rate was 18% in the intervention group; 52% in controls.
4. Median length of stay in hospital 11 days vs 13 days: days in intensive care 2 vs 32.
5. Risks in subjects who reduced smoking, but did not stop, did *not* differ from those who continued to smoke.

DISCUSSION

1. Postoperative complications can be substantially reduced by smoking cessation for 6 to 8 weeks prior to surgery.
2. Pulmonary complications were unusual, probably due to the distance of the operative site from the diaphragm and early mobilization. Abdominal and gynecological surgery wold be associated with greater risk of pulmonary complications.

CONCLUSION

An effective smoking cessation program applied for at least 6 weeks prior to hip and knee surgery more than halved the frequency of postoperative complications.

Lancet January 12, 2002; 359: 114-17 Original investigation, first author Ann M Moller, Bispebjerg University Hospital, Copenhagen, Denmark. **www.thelancet.com**

Comment:

These results are astounding— almost too good to be true. Replication is needed. Nevertheless, it is reasonable that complications will be fewer in non-smokers. Primary care clinicians should do their utmost to urge pre-operative patients to abstain**.**

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The Value Of The "If" Prescription

1-6 REDUCING ANTIBIOTIC USE FOR ACUTE BRONCHITIS IN PRIMARY CARE

Millions of antibiotic prescriptions for acute bronchitis are given each year by primary care clinicians, even though there is little evidence to justify them. Many prescriptions are given when, in the clinician's judgement, they are definitely *not* indicated. (*The clinician's bow to patient's expectations. RTJ*)

Overuse of antibiotics increases prevalence of drug resistance, causes adverse effects, and increases costs.

This trial determined the impact of a patient information leaflet on the use of antibiotics by patients with acute bronchitis.

Conclusion: Most previously well patients who develop acute bronchitis were judged not to need antibiotics. Reassuring them, and sharing the uncertainty about antibiotics, was a safe strategy which reduced antibiotic use.

STUDY

1. Single-blind, randomized, controlled trial entered over 250 *previously well* adults presenting with acute bronchitis.

   Defined as:

Lower respiratory illness present for less than 3 weeks, cough as the main symptom; at least one other lower respiratory tract symptom — sputum production, dyspnea, wheeze, chest discomfort or pain — and no alternative explanation (not sinusitis, pharyngitis, or new presentation of asthma).

2. Forty eight (only 19%) were judged by their primary care clinician to need antibiotics. All of them were given an antibiotic prescription and encouraged to use it. Almost all did.
3. The 212 (81%) judged *not* to need antibiotics were also given a prescription for an antibiotic to use only *if* they got worse. All received verbal information of antibiotic use based on a prompt card.
4. Then randomized to: 1) receive an information leaflet, or 2) not receive the leaflet about the natural course of lower respiratory tract symptoms and the advantages and disadvantages of antibiotic use. (*See copy of the prompt card and the leaflet at www.bmj.com/cgi/content/full/324/7329/91*)
5. End point = whether the patient took the prescribed antibiotic.

RESULTS

1. Fewer patients who received the information leaflet took the antibiotic — 47% vs 62%.
2. Numbers seeking reconsultation were similar (11 vs 14).

DISCUSSION

1. A simple information leaflet about use of antibiotics for acute bronchitis and giving reassurance that the condition is not serious resulted in a reduction in use of the antibiotic by nearly a quarter.
2. Extrapolated to national use, many thousands of patients with acute bronchitis would avoid antibiotics.
3. The effect of verbal reassurance alone was not determined, but probably reduced antibiotic use somewhat.
4. Most episodes of acute bronchitis resolve on their own. It is not clear how to identify those who may benefit from antibiotics.
5. Rates of reconsultation were no higher in the leaflet group. No patient required referral to the hospital during follow up.
6. For the many patients (about 80%) for whom the primary care clinician believes antibiotics are not indicated, sharing the uncertainty openly and honestly is safe and effective, and lowers the number using an antibiotic.

CONCLUSION

Most previously well adults who develop acute bronchitis were judged not to need antibiotics. Reassuring these patients and sharing uncertainty by verbal advice supported by an explanatory leaflet is a safe strategy and reduces antibiotic use.

BMJ January 12, 2002; 324: 91-94 original investigation, first author John Macfarlane, Nottingham City Hospital, UK **www.bmj.com/cgi/content/full/324/7329/91**

A following editorial (p 94) comments:

There is a strong perception among practitioners that most patients value a prescription for antibiotics. Reassuring and encouraging the patient to await the natural, benign course of the bronchitis without removing the possibility of antibiotic treatment reduced frequency of use. "The procedure takes away the power struggle between the patient and the general practitioner and focuses on the patient's decision." (*Ie, patient autonomy, not clinician authoritarianism*. RTJ)

Comment:

The same advice can be given to patients with pharyngitis, and upper respiratory infection (rhinosinusitis).

I believe use of the "if prescription" depends little on the patient's concern about development of antibiotic-resistance of bacteria in the general population. Stressing the possible adverse effects and the cost would be more effective.

Clinician's judgement about the need for antibiotic therapy can be accurate. Does the patient look ill? Is the fever high? Are there physical findings on chest auscultation? In doubt, a chest X-ray may reassure.

It was interesting that a written leaflet explaining the problem was much more effective than a verbal expression. Access the article if you want copies. RTJ

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1-7 CHRONIC FATIGUE SYNDROME; A STEP TOWARD AGREEMENT

The Royal College of Physicians of the UK has issued a new report on the chronic fatigue syndrome (**CFS**) This editorial hopes it will mark a turning point in the history of the illness.

Patient advocate groups have used the term “myalgic encephalitis” or “myalgic encephalopathy” (**ME**) to denote the syndrome. The fact that several names are used symbolizes respect for different viewpoints while acknowledging the continuing lack of a consensus on a universally acceptable name.

The committee arrived at a substantial amount of common ground between medical practitioners and patient advocates. However, there were serious and principled disagreements on several issues. This led 6 members of the committee (all clinicians) to decide they could not endorse the final report. Some argued that the report was insufficiently evidence-based and paid too little attention to the bio-psycho-social approach. Two patient members of the committee also failed to endorse the report believing that it paid too little attention to the pathological models, and portrayed rehabilitation approaches in too favorable a light.

Where is the center-ground? There was agreement that the illness “is a relatively common clinical condition which can cause profound illness and disability and can have a very substantial impact on the individual and family.” It can affect both sexes, and a wide range of ages, even children. “It is no longer acceptable for clinicians to state that they do not ‘believe’ in CSF/ME. Inaction . . .due to ignorance or denial of the condition is not excusable.” A significant minority of patients who are very severely affected often receive the least attention. Patients need a positive and early diagnosis and appropriate management and advice. Patient organizations have an

important role to play in this.

One of the main polarities has been about treatments such as cognitive behavioral therapy (**CBT**) and graded exercise therapy (**GET**). Trials have been criticized by patient organizations because of a still limited evidence base. Some have drawn the understandable but erroneous conclusion that the success of CBT of GET implies a psychogenic cause.

No rehabilitation approach is intended to be curative. No approach has been found to be beneficial for everyone.

Myths are still held by some patients and practitioners. Neither CBT nor GET insists on blind adherence to strict regimens. Indeed, CBT is based on the principle that activity, physical and mental, must first be made consistent and predictable. An additional approach to activity management is known as "pacing". This has been consistently reported by members of patient organizations as being helpful. Pacing proposes a balance, both of activity and rest, with the aim of maximizing recovery and promoting self-empowerment. It is still the subject of research.

Much controversy stems from the false view that therapies pioneered by psychiatrists imply that the illness is "all in the mind", or that the failure to respond is the patient's fault. "There are still too many reports of patients being treated with disrespect or disbelief, and not being true collaborators in treatment.

Ideologies both within and without the health profession have not served patients well in the past. Doctors and patient groups need continued humility in the uncertain area. "The time has come for patient advocates, practitioners, and researchers to work together to press for better services and fair benefits for sufferers, as well as for further research. "

Lancet January 12, 2002; 359: Editorial , first editorialist Christopher Clark, "Action for ME", London, UK **www.thelancet.com**

Comment:

Primary care clinicians deal with uncertainty every day. CFS is a good example. Many patients have conditions for which there is no good "diagnosis". And for many chronic diseases there is no cure. As with many chronic conditions, patients may gradually accept their limitations.

The primary care clinician's approach to treatment includes a respect for the patient's symptoms, patience, empathy, support and understanding. Clinicians should support the work of patient advocate groups. RTJ

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Aim To Reduce Urinary Oxalate Excretion

1-8 COMPARISON OF TWO DIETS FOR THE PREVENTION OF RECURRENT STONES IN IDIOPATHIC HYPERCALCIURIA

Idiopathic hypercalciuria is a common risk factor for stone formation. Uncontrolled hypercalciuria causes recurrences. Most patients with idiopathic hypercalciuria have intestinal hyper-absorption of calcium. Thiazides can reduce urinary calcium excretion, but since calcium excretion depends in part on diet, initial attempts to decrease hypercalciuria should involve dietary modification.

It has been common practice to recommend a low calcium diet. However, short-term studies have shown that, while a low calcium intake does indeed reduce urinary calcium, it can cause an increase in urinary oxalate. Some studies reported that, in men without a history of nephrolithiasis, those with a high intake of calcium had a *lower* risk of future calcium oxalate stone formation than those on a low calcium diet. The protective efficacy of a low calcium diet is doubtful.

Studies show that a diet low in animal protein and salt also have considerable influence on calcium excretion.

This study compared the efficacy of 1) the traditional low calcium diet with 2) a diet containing a normal amount of calcium combined with low salt and animal protein.

Conclusion: In men with recurrent calcium oxalate stones, the low protein-salt diet, combined with a normal calcium intake provided greater protection against recurrent stones than a low calcium diet.

STUDY

1. A five year randomized trial compared effects of the two diets in 120 men (mean age = 45).
   All had recurrent calcium oxalate stones (mean = 5) with several episodes of colic in the previous year and hypercalciuria (> 300 mg/d). About 40% had family history of stones.
2. Randomized to: 1) diet with a normal amount of calcium (1200 mg/d) and with reduced amounts of animal protein (52 g/d) and salt (3 g NaCl); and 2) a low calcium diet (400 mg/d).
3. All avoided foods rich in oxalate. All increased intake of water to 2 to 3 liters per day.
4. Follow-up = 5 years.

RESULTS

1. Incidence of recurrent stone over 5 years:

Normal Ca, low protein-low salt diet	12 of 60 men (20%)
Low calcium diet	23 of 60 men (38%) [NNT 5 years = 6]

2. Recurrence was reduced by half, but this advantage was evident only after several years of follow-up.
3. During follow-up urinary *calcium* levels dropped significantly in both groups. But, urinary oxalate *increased* in men on the low calcium diet, and *decreased* in those on the normal calcium-low protein-salt diet. (Ie, the determining factor is a low rate urinary excretion of oxalate)

DISCUSSION

1. In men with idiopathic hypercalciuria, the normal calcium, low protein, low salt diet was more effective in reducing risk of recurrent stones than the traditional low calcium diet.
2. The difference seemed to be due to different effects of the diets on oxalate excretion. Urinary oxalate *increased* in the low calcium diet; *decreased* in the normal Ca-low salt-low protein diet. These changes appeared in one week and persisted over 5 years.
3. A low calcium diet does reduce urinary calcium excretion, but may cause an increased absorption of

oxalate from the gut. This is because the low levels of calcium in the intestine reduce the amount of unabsorbable calcium-oxalate formed. This leads to less oxalate excretion in the stool, and leaves more to be absorbed and excreted in the urine where it complexes with Ca to form Ca oxalate stones.

4. Why the low animal protein? It lowers endogenous synthesis of oxalate.
5. Why the low salt? Sodium has a direct influence on calcium excretion. Low Na excretion — low Ca excretion.
6. The recommended high intake of water and the increased urine volume helped to reduce the relative oxalate saturation as did the low oxalate diet.

CONCLUSION

A diet containing normal amounts of calcium and low animal protein and salt was more effective than a low calcium diet for prevention of recurrent calcium oxalate stones in men with idiopathic hypercalciuria.

NEJM January 10, 2002; 346: 77-84 Original investigation, first author Loris Borghi, University of Parma, Italy.
www.nejm.com

Comment:

I congratulate the investigators and their patients on their long-term dedication to the study. It is likely that over 5 years compliance with the diet decreased. If strict adherence to the diet were maintained by all subjects, the benefits might have been more evident.

Increased water intake and decrease in foods rich in oxalate are also important

Why not add a thiazide to the diet?

Should these patients avoid vitamin D?

The chief protective mechanism, as I understand it — the high intake of calcium allows more unabsorbable calcium oxalate to be formed in the gut and excreted in the stool. This lowers the calcium-oxalate complex in the urine — the chief stone former. RTJ

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1-9 RECURRENT HYPERCALCIURIC NEPHROLITHIASIS — DOES DIET HELP?

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

In at least 70% of cases stones consist of calcium oxalate, often with calcium phosphate or sodium urate. Once a stone forms, there is about a 50% probability that, without treatment, a second stone will form within 5 to 7 years. Standard therapy is based on a reduction in urinary supersaturation.

Most cases of hypercalciuria are idiopathic. These patients absorb and excrete a greater proportion of dietary calcium than normal. Although a reduction in dietary calcium reduces urinary calcium, it increases urinary oxalate. This may result in supersaturation with respect to calcium oxalate.

Strong support for the hypothesis that a low-calcium diet actually increases risk of nephrolithiasis comes from a prospective epidemiological study. Stones were more likely to develop in subjects with the lowest calcium intake (mean of 516 mg/d) than in those with the highest (mean of 1326 mg/d). The study concluded "There is no benefit to the time-honored advice to eat a diet low in calcium".

This editorialist proposes several other mechanisms whereby the low protein-salt diet reduces tendency for calcium oxalate stone formation: 1) a reduction in animal protein reduces the production of metabolic acids. This results in a lower level of acid-induced urinary calcium excretion and increases the content of citrate which forms soluble complexes with calcium and reduces supersaturation with respect to calcium oxalate. 2) a reduction in animal protein should also limit the excretion of urate, crystals of which are a potential surface for heterogeneous nucleation 3) dietary sodium reduction is related to reduced urinary sodium excretion. Urinary sodium is directly related with urinary calcium excretion. Thus a reduction in sodium intake should reduce calcium excretion.

In this study, urinary calcium levels fell with both diets, as did the relative supersaturation with respect to calcium oxalate in the urine. However, the reduction in relative supersaturation was greater with the normal calcium diet because of a marked decrease in urinary oxalate. Oxalate excretion fell with the normal calcium diet and rose with the low calcium diet.

"We now know that, at least for men with idiopathic hypercalciuria, a diet with a normal amount of calcium and reduced amounts of animal protein and salt is superior to a low-calcium diet in preventing recurrent stones." For patients with a relative supersaturation with respect to calcium oxalate, calcium conserving thiazide diuretics have been shown to reduce risk of recurrent stones. Although increased water intake is recommended, it alone is not sufficient to prevent recurrence.

"Physicians should no longer prescribe a low-calcium diet to prevent recurrent nephrolithiasis in patients with idiopathic hypercalciuria."

NEJM January 10, 2002; 346: 124-25 Editorial by David A Bushinsky, University of Rochester School of Medicine and Dentistry, Rochester NY. **www.nejm.org**

Comment:

Amazing! We have been recommending a wrong (and harmful) treatment for years.

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1-11 ERADICATION OF *HELICOBACTER PYLORI* AND RISK OF PEPTIC ULCERS IN PATIENTS STARTING LONG-TERM TREATMENT WITH NON-STEROIDAL ANTI-INFLAMMATORY DRUGS.

Does infection with *H pylori* increase risk of development of peptic ulcers in patients taking NSAIDs? *H pylori* infection is widespread. “It is present in 50% of the US non-white population older than 60 years.” The important question is whether patients without previous exposure to NSAIDs are at increased risk of developing peptic ulcer disease associated with NSAIDs if they are infected with *H pylori*.

This study hypothesized that eradication of *H pylori* would reduce risk of NSAID-induced ulcers.

Conclusion: Screening and treatment for *H pylori* before starting long-term NSAIDs significantly reduced risk of development of ulcers.

STUDY

1. Double-blind, randomized, placebo-controlled trial followed 100 patients. None had taken NSAIDs before. All were judged to require long-term NSAID treatment.

2. All had a positive urea breath test for *H pylori*. All had history of dyspepsia or peptic ulcer and thus were at higher risk.
3. Randomized for one week to: 1) antibiotic eradication therapy + omeprazole (*Prilosec*; a proton-pump inhibitor) , or 2) omeprazole + placebo antibiotics.
4. All then received diclofenac (*Generic*) slow release NSAID — 100 mg daily for 6 months.
5. Endoscoped all at 6 months.

RESULTS

1. *H pylori* was eradicated in 90% of the eradication group.
2. Gastric ulcers developed in 5 of 51 in the eradication group and in 15 of 49 placebo group.
3. Six month probability of ulcer was 12% in the eradication group vs 34% in the placebo group.
4. For complicated ulcers (symptomatic or bleeding) probability was 4% vs 27%.

DISCUSSION

1. When patients who had a history of dyspepsia or ulcers and were positive for *H pylori* were started on long-term NSAID treatment, eradication of the infection beforehand reduced risk of developing ulcers.
2. Risk of ulcer is substantially increased during the first few months of NSAID treatment. This excess early risk is especially high in patients with *H pylori* infection.
3. The role of *H pylori* in NSAID-naïve patients seems to be different from that of those on long-term treatment. Preexisting *H pylori* infection contributes to an excess of ulcer development in patients starting NSAIDs. NSAIDs probably cause the majority of ulcers in long-term users *irrespective* of *H pylori*. Eradication alone is *not* sufficient to prevent recurrence of ulcers and ulcer bleeding in long-term users of NSAIDs
4. Even in patients treated with cyclo-oxygenase 2 inhibitors, ulcer risk is significantly higher in those with *H pylori* infection.
5. Screening and treatment of *H pylori* in patients starting on long-term NSAID treatment has the potential to reduce ulcer risk, eliminate a gastric pathogen and carcinogen, and reserve the use of expensive anti-ulcer drugs or COX-2 selective NSAIDs for patients at very high risk.
6. “Our study was designed to suit the primary care setting.”

CONCLUSION

Screening and treatment of *H pylori* infection reduced the risk of development of peptic ulcer in patients starting long-term NSAID treatment.

Lancet January 5, 2002; 359: 9-13 Original investigation, first author Francis K L Chan, Prince of Wales Hospital, Hong Kong. **www.thelancet.com**

A meta-analysis in this same issue of Lancet (pp 14-22) reported that both *H pylori* infection and NSAID use significantly increase risk of peptic ulcer and ulcer bleeding. Synergism between the two increases the risk. Peptic ulcer is rare in *H pylori* negative individuals who do not take NSAIDs.

An editorial (p 3-4) comments: It is now clear that most ulcers are due to gastric acid together with *H pylori* infection and/or NSAIDs. "Acid is always a vital ingredient in ulcerogenesis." Peptic ulceration is almost universal in the Zollinger-Ellison syndrome (gastrinoma producing excess acid). Benign ulcers almost never occur in patients with pernicious anemia (no stomach acid). Antisecretory drugs reliably speed healing and prevent recurrence. Patients who need long-term NSAID (including aspirin) remain at increased risk even if the infection is eradicated, so acid secretion should be controlled.

Comment:

With all the emphasis on NSAIDs and *H pylori*, we may forget the essential contribution of acid in pathogenesis of ulcer disease. RTJ

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1-12 ANTIBIOTIC-ASSOCIATED DIARRHEA

(*This "Clinical Practice" series begins with a case vignette highlighting a common clinical problem, various strategies for therapy, guidelines when they exist, end with the author's clinical recommendations.)*

Antibiotic-associated diarrhea (**AAD**) is defined as otherwise unexplained diarrhea that occurs in association with the administration of antibiotics. Depending on the antibiotic used, diarrhea occurs in about 5% to 10% of patients. (Up to 10%-25% of those treated with amoxicillin-clavulanate [*Augmentin*]. Rates of diarrhea associated with parenterally administered antibiotics are similar to rates associated with oral administration.

The spectrum of AAD extends from a "nuisance diarrhea" to (antibiotic-associated) colitis which can be a serious and progressive disease. Symptoms include abdominal cramping, fever, leukocytosis, fecal leukocytes, hypoalbuminuria, colonic thickening, and characteristic endoscopic findings.

Clostridium difficile is responsible for about 15% of cases of AAD. It accounts for the majority of cases of colitis associated with antibiotic therapy.

The challenge is to identify which cases are associated with *C difficile* since it is the most frequently associated and treatable pathogen. Clindamycin (*Cleocin*) cephalosporins, and penicillins are the antibiotics most often associated with *C difficile* diarrhea, although they may also cause AAD not related to this super-infection.

C difficile infection produces a florid colitis with cramps, fever, fecal leukocytes, and evidence of colitis on CT scan and endoscopy. Antiperistaltic agents are contraindicated. Prompt treatment with metronidazole (*Flagyl*) or vancomycin is indicated.

Multiple laboratories have reported that only about 15% of stool specimens submitted for testing are positive for the *C difficile* toxin. AAD can be caused by other enteric pathogens, by the direct effect of antibiotics of the intestinal mucosa, and by metabolic consequences of changed concentrations of fecal flora.

In the 1950, *Staph. aureus* was implicated as the chief cause of antibiotic-associated pseudomembranous colitis. It is not clear if this represented misdiagnosis of *C difficile* infection or that *Staph aureus* caused a different disease. The distinction is important since metronidazole is effective for *C difficile* infection, but not for *Staph aureus* infection.

Hospitalized patients have about 10 times the rate of colonization of *C difficile* as outpatients. Patients older than 60 are much more likely to acquire *C difficile* infection. Almost any antibiotic can be implicated, even short courses given prophylactically before surgery.

Histologic findings range from normal to pseudomembranous colitis. (**PMC**). PMC is uncommon, but specific for *C difficile* infection. Assays for *C difficile* toxin are the mainstay of diagnosis. Cytotoxin assay by tissue culture has been the gold standard. It is the most sensitive test. However, most laboratories do not offer it. Results may not be available for 48 hours. Enzyme immunoassay is now offered. The false negative rate varies up to 20%. Commercially available reagents are available that will detect both toxins A and B, although toxin B is uncommon. Results can be available within hours.

TREATMENT

The offending antibiotic should be discontinued. If antibiotic therapy is indicated, use an agent that is infrequently associated with AAD — aminoglycosides, macrolides, sulfonamides, vancomycin, tetracycline, or possibly fluoroquinolones.

Antiperistaltic agents should be avoided. They promote retention of the toxin.

Positive assays for toxin in patients with colitis call for treatment with metronidazole (oral 500 mg three times daily) or vancomycin (oral 125 mg four times daily). Metronidazole is preferred because it is less expensive, and not related to vancomycin-resistant enterococci. They have similar efficacy rates (over 90% response). Oral therapy is required because *C difficile* is restricted to the lumen of the colon. The usual course is for 10 days. If oral administration is not feasible, iv metronidazole is effective since it results in moderate concentrations of the drug in the colon.

RELAPSING INFECTION

This is the chief complication. It occurs in about 1/4 of cases. Most respond to another course of therapy.

THE AUTHOR'S SUGGESTIONS

C difficile infection should be considered in all patients with unexplained diarrhea who are receiving antibiotics or who have recently received antibiotics.

Enzyme assays to detect both toxins A and B are preferred. False negative results may occur if the only test is for toxin A.

Many patients will respond to withdrawal of the inducing antibiotic. *If the patient's condition calls for continued antibiotic therapy, see the recommended list above.*

If there is evidence of colitis or if discontinuation of the offending antibiotic does not result in resolution of the diarrhea, metronidazole is indicated. Lack of response to metronidazole is strong evidence against the *C difficile* colitis.

If assays for *C difficile* toxin are negative, and symptoms persist, repeat the test, expand the diagnostic evaluation to other causes (eg, look for staph and salmonella), or treat empirically.

NEJM January 31, 2002; 346: 334-39 "Clinical Practice" review article by John G Bartlett, Johns Hopkins School of Medicine, Baltimore MD **www.nejm.org**

Comment:

Overuse of antibiotics presents the danger of antibiotic resistance, a growing problem. For patients in whom antibiotics are of questionable value (eg, acute bronchitis) the possibility of adverse effects such as this one may convince patients to be less demanding.

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Another Benefit Of Low-To-Moderate Alcohol Consumption?

1-13 ALCOHOL CONSUMPTION AND RISK OF DEMENTIA: THE ROTTERDAM STUDY

Light-to-moderate alcohol consumption is associated with lower risks of coronary heart disease, ischemic stroke, and total mortality in elderly men and women

Evidence is increasing that vascular disease is associated with cognitive impairment and dementia. Might light-to-moderate alcohol intake reduce risk of dementia?

This study aimed to quantify the relation between alcohol consumption and risk of dementia and subtypes of dementia; specifically, whether the effect varied by the type of alcoholic beverage.

Conclusion: Light-to-moderate alcohol consumption was related to reduced risk of dementia in individuals over age 55.

STUDY

1. A prospective population-based study entered and followed over 5000 individuals aged 55
   (Mean age = 67). None had dementia at baseline. Followed to end of 1999. (Average = 6 years.)
2. Determined amount of alcohol consumed at baseline.
3. Compared risk of developing dementia between individuals who regularly consumed alcohol and those

who did not.

RESULTS

1. During follow-up 197 individuals developed dementia (146 Alzheimer's, 29 vascular, 22 other).
2. Consumption of one to three drinks per day was significantly associated with a lower risk of any dementia (Hazard ratio = 0.58). And lower risk of vascular dementia (Hazard ratio = 0.29).
3. No relation between type of alcoholic drink and risk.

DISCUSSION

1. Individuals over age 55 who consumed up to 3 alcoholic drinks per day had a lower risk of

developing dementia than abstainers.

2. Possible mechanisms for the protective value of alcohol: reduction in cardiovascular risk factors through inhibition of platelet aggregation, or alterations in lipid profile. The lower risk of vascular dementia is in agreement with this hypothesis.

CONCLUSION

Light-to-moderate alcohol consumption was associated with a reduced risk of dementia in elderly individuals over 65 years. The effect seemed to be unchanged by the type of alcohol consumed.

Lancet January 26, 2002; 359: 281-86 Original investigation, first author Annemieke Ruitenberg, Erasmus Medical Centre, Rotterdam, Netherlands. **www.thelancet.com**

Comment:

I was unable to determine the absolute risk reduction from the data. But since only 197 of the cohort of 5393 developed dementia, the number for whom alcohol seemed protective must have been small.

The data concerning the protective effect of alcohol for cardiovascular disease is strong , so much so that some authorities consider abstinence a risk factor.

It is becoming evident that there is a connection between vascular dementia and Alzheimer's dementia. Vascular disease accentuates or hastens the development of Alzheimer's dementia.

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Theoretically Attractive, But Limited Clinical Benefit.

1-14 DIRECT THROMBIN INHIBITORS IN ACUTE CORONARY SYNDROMES

Acute coronary syndromes (**ACS**) are characterized by intracoronary thrombus formation at the site of atherothrombotic plaque disruption.

Although aspirin and heparin are effective treatments, ACS patients remain at high risk of new myocardial infarction (**MI**) and death. The process of intracoronary thrombus formation is partly resistant to inhibition by both aspirin and heparin.

Large amounts of thrombin are generated when tissue factor is exposed at the site of plaque disruption. Fibrin-bound thrombin is protected from inhibition by heparin, but remains enzymatically active, promoting further thrombus accretion. Bound thrombin continues to activate platelets by mechanisms that are not blocked by aspirin.

Direct thrombin inhibitors (**DTI**) react directly with thrombin and inactivate both fluid and bound forms. This meta-analysis obtained estimates of efficacy of DTI in the management of ACS, including patients undergoing percutaneous coronary interventions.

Conclusion: DTIs were superior to heparin in the prevention of death and MI in patients with ACS.

STUDY

1. Meta-analysis included 11 randomized trials (over 35 000 patients) comparing DTI with heparin. All received aspirin.
2. DTIs included hirudin, bivalirudin, and 3 other agents. (*See text. The only one I have encountered before is hirudin. Hirudin is extracted from the salivary glands of leeches. RTJ)*
3. Patients with symptoms of ACS were included if they did not have ST elevation, or were undergoing percutaneous coronary intervention.
4. Patients received up to 7 days treatment and were followed for at least 30 days.

RESULTS

1. At 30 days, compared to heparin, DTIs were associated with a lower risk of death or MI. (4.3% vs 5.1% - absolute risk reduction = 0.8%
2. The benefit was largely due to reduction in MI, with no apparent effect on death.
3. Benefit was also evident in patients undergoing PTCA as well as those not undergoing PTCA.
4. Compared with heparin only hirudin and bivalirudin were beneficial. (No benefit from the other 3 agents.)
5. There was increased major bleeding with hirudin, but actually a *reduction* in those receiving bivalirudin.
6. No excess intracranial hemorrhage.

DISCUSSION

1. The NNT to benefit one patient = 125. For every 1000 patients treated, 8 patients benefited.
2. In contrast, the recently introduced antiplatelet agents such as glycoprotein IIb/IIIa are most beneficial only when used in combination with heparin. (Glycoprotein IIb/IIIa inhibitors have only antiplatelet activity and require addition of an anticoagulant such as heparin to be fully effective.)
3, DTIs may be superior to heparin because they have effects against platelets as well as coagulation.
4. Important differences in risk of major bleeding among individual agents occurred. Hirudin was

associated with almost a two-fold increased risk; bivalirudin with a 50% reduction in risk.

CONCLUSION

Direct thrombin inhibitors were superior to heparin in preventing MI and death in patients with acute coronary syndromes including those undergoing PTCA.

The investigators recommend further development of DTIs for management of arterial thrombosis.

Lancet January 26, 2002; 359: 294-302 Original investigation by "The Direct Thrombin Inhibitor Trialists' Collaborative Group **www.thelancet.com**

Comment:

I believe primary care clinicians should be cautious in applying a new, expensive agent with only one chance in 125 of benefiting the patient. And with the same chance of causing major bleeding.

Nevertheless, in theory DTIs would seem to have significant advantages. RTJ

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1-15 EFFICACY OF ROFECOXIB, CELECOXIB, AND ACETAMINOPHEN IN OSTEOARTHRITIS OF THE KNEE

The American College of Rheumatology guidelines recommend acetaminophen as first line therapy for the systemic treatment of symptomatic osteoarthritis (**OA**). This was partly due to concerns about gastrointestinal toxicity of non-steroidal anti-inflammatory drugs (**NSAIDs**) and lack of data confirming their superior efficacy over simple analgesics.

Most NSAIDs inhibit both cyclo-oxygenase-1 (COX 1) and cyclo-oxygenase-2 (COX 2). COX-2 inhibitors suppress the symptoms of inflammation without removing the protective effects of COX-1 on the stomach.

This study assessed the relative therapeutic efficacy of acetaminophen (*Tylenol*) and two COX 2 inhibitors, rofecoxib (*Vioxx*) and celecoxib (*Celebrex*) in adults.

Conclusion: Rofecoxib 25 mg/d provided efficacy advantages over acetaminophen 4000 mg daily and celecoxib 200 mg/d.

STUDY

1. Randomized double-blind multicenter trial followed 282 patients (mean age = 63). All had OA of the knee which had been present for at least 6 months. All had used a prescription strength NSAID or high doses of acetaminophen for at least 30 days.
2. Assessed symptoms by a 100 mm visual analog scales at baseline.
3. Randomized to: 1) rofecoxib 25 mg once daily; 2) celecoxib 200 mg once daily; and 3) acetaminophen 4000 mg (1000 mg 4 times daily) daily for 6 weeks. (*A 4th group assessed rofecoxib 12.5 mg. I omitted this data. RTJ*)

4. Assessments at 6 weeks included pain on walking, night pain, pain at rest, and morning stiffness as well as global response to therapy among the 3 groups.

RESULTS

1. Mean change on 100 mm visual analogue scales from baseline to 6 weeks:

	Acetaminophen 4000	Celecoxib 200	Rofecoxib 25
Walking pain	-30	-36	-42
Rest pain	-22	-23	-31
Morning stiffness	-22	-29	-36
Night pain	-24	-23	-32
Global pain	-25	-29	-35

2. Discontinued – lack of efficacy : 31%; 19%; 18%

3. Good or excellent response : 46%; 56%; 60%

4. Safety profile was similar among the 3 drugs.

DISCUSSION

1. In this study, rofecoxib 25 mg/d provided greater therapeutic benefit than maximum doses of acetaminophen in patients with OA of the knee. Differences in response were noted within 6 days and persisted for 6 weeks. (*Note that 39% of patients taking acetaminophen reported a good or excellent response. RTJ)*
2. Celecoxib also provided greater benefits than acetaminophen.
3. Rofecoxib provided greater benefits than celecoxib.

CONCLUSION

Rofecoxib 25 mg/d provided efficacy advantages over acetaminophen 4000 mg/d, and celecoxib 200 mg/d for symptomatic knee arthritis.

JAMA January 2, 2002; 287: 64-71 Original investigation first author Gregory P Geba, Merck & Co. West Point PA. **www.jama.com**

Comment:

The investigators made the main point that both COX 2 inhibitors were more effective than acetaminophen (4000 mg daily). They were less enthusiastic in stressing benefits of rofecoxib over celecoxib.

Nevertheless, as noted, about 40% of patients received considerable benefit from acetaminophen. Should we not begin with this less expensive drug and go on to others only if there is not a good response?

Note the study sponsor – Merck Rightly or wrongly, fairly of unfairly, the article would be more convincing if it were independent of sponsorship by the manufacturer.

My pharmacy quotes a cost of about $80 for 30 Vioxx 25 mg and 30 Celebrex 200. RTJ

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Beneficial When Troponin Levels Are Increased

1-16 PLATELET GLYCOPROTEIN IIB/IIIA INHIBITORS IN ACUTE CORONARY SYNDROMES

Activation of the platelet glycoprotein IIb/IIIa receptor is the final common pathway in the process leading to platelet aggregation. Blocking the receptor protects against peri-procedural death and myocardial infarction (**MI**) in patients undergoing percutaneous coronary interventions (**PCI**).

This meta-analysis included all large randomized trials designed to study the clinical efficacy and safety of glycoprotein IIb/IIIa inhibitors in patients with acute coronary syndromes who were not scheduled to undergo early coronary revascularization.

Conclusion: Glycoprotein IIb/IIIa inhibitors reduced death and MI in patients with acute coronary syndromes who were not routinely scheduled for early revascularization.

STUDY

1. Six trials enrolling over 31 000 patients (mean age = 64) were entered into the analysis of randomized trials.

2. All patients had acute coronary syndromes without persistent ST elevation. Indicators of myocardial ischemia included: ST depression, T wave inversion; creatine kinase MB elevation or evidence of coronary disease based on history and stress testing. Troponin levels were available in a minority.
3. Randomized to: 1) glycoprotein IIb/IIIa inhibitors given intravenously for up to 4 days, or 2) placebo or control therapy.
4. Glycoprotein IIb/IIIa inhibitors included tirofiban, eptifibatide, and abciximab.
5. Primary end point = composite of death and non-fatal MI.

RESULT

1. Glycoprotein IIb/IIIa inhibitors at 30 days were associated with an absolute reduction of death or development of a new MI (10.8% vs 11.8%). Absolute reduction = 1%. NNT = 100. For every 1000 patients treated 10 avoided the endpoint.

   2. An unexpected and significant interaction was seen between sex and allocated treatment. Overall, treatment benefited only men, not women. However women with a positive troponin also benefited.
3. Major bleeding complications were increased (2.4% vs 1.4%). Absolute difference = 1%. (NNT to harm = 100)
4. Risk reduction was evident only in subjects with a positive troponin.

5. Benefits were evident in those receiving heparin as well as those not receiving heparin.

DISCUSSION

1. Glycoprotein IIb/IIIa inhibitor treatment was associated with an absolute 1% reduction in death or MI at 30 days.
2. Glycoprotein IIb/IIIa inhibitor therapy was associated with increased bleeding, but not any increase in intracranial hemorrhage or stroke.
3. Glycoprotein IIb/IIIa inhibitor treatment was more beneficial in individuals at higher risk, especially in those with elevated troponin levels.

CONCLUSION

Glycoprotein IIb/IIIa inhibitors reduced cardiac complications in patients with acute coronary syndromes not routinely scheduled for early revascularization. Treatment might be considered early after admission in high-risk patients and continued for 2 to 4 days until a decision about revascularization is made.

Benefit was evident mainly in those with a positive troponin.

Lancet January 19, 2002 359: 189-198 Original investigation, first author Eric Boersma, University Hospital Rotterdam , Netherlands**. www.thelancet.com**

Comment:

At present, for most patients with acute coronary syndromes, referral for immediate intervention will be advised.

Fewer and fewer will fit the cohort of this study.

This is a disappointing result. The number needed to treat is high, and about equals the number needed to harm.

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Diet Now Less Restrictive.

1-17 US RELAXES SUGAR BAN FOR PEOPLE WITH DIABETES

The American Diabetes Association has released new nutritional guidelines for diabetes control. It relaxes dietary restrictions on high sugar content foods. (*Diabetes Care 2002;25:148-98, 200-12* [1]). The new guidelines replace the 1994 guidelines and are based on current research findings.

It emphasizes the importance of total carbohydrate intake rather than control of high sugar content, and the need to monitor the exact source of those carbohydrates.

Now, someone with diabetes would be able to indulge in an occasional slice of sugary pie and drink moderate amounts of alcohol without violating their diet. A moderate amount of daily alcohol intake poses no threat and may be healthy.

The current edition discusses carbohydrate nomenclature as well as nutritional and lifestyle considerations and contains recommendations for all age groups.

The revised recommendations also debunk the importance of diets based on a low glycemic index.

Less than 10% of calorie intake should be derived from saturated fats and cholesterol intake should be no more than 300 mg/d.

Weight loss, achieved through diet and exercise, coupled with lifestyle and behavioral modifications continues to be given a level A recommendation.

BMJ January 12, 2002; 342:70 "News" by Deborah Josefson, San Francisco

www.bmj.com/cgi/content/full/342/7329/70

1 Original would be worth accessing.