# PRACTICAL POINTERS

# FOR

# PRIMARY CARE

# ABSTRACTED MONTHLY FROM THE JOURNALS

# APRIL 2001




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# HIGHLIGHTS APRIL 2001

**4-1 HOW DO YOU DEFINE DIABETES?**

The American Diabetes Society and the World Health Organization define "diabetes", "impaired fasting glucose" and "impaired glucose tolerance" differently. Primary care physicians must be aware of the sometimes modest changes in glucose metabolism which can lead to later development of diabetes and its devastating consequences. The abstract presents definitive cut points for glucose levels.

Practical point: This is an important reference for primary care clinicians. We must be attuned to milder abnormalities of glucose concentration. Frequently this gives the best opportunity to improve lifestyles to lessen the risk of future development of harmful effects of elevated glucose concentrations.

**4-2 RELATION OF IMPAIRED FASTING AND POSTLOAD GLUCOSE WITH INCIDENT TYPE 2 DIABETES IN A DUTCH POPULATION: The Hoorn Study**

The cumulative incidence of diabetes was strongly related to both impaired fasting plasma glucose and impaired glucose tolerance, and, in particular, the combined presence of both.

Practical point: A fasting plasma glucose of 110 to 125 will predict a high risk of later progression to diabetes. An impaired glucose tolerance (post challenge glucose of 140-200 will also predict high risk. The combination of both will predict almost inevitable progression to diabetes over the years.

Early determination of these defects in glucose metabolism permits clinicians to emphasize the importance of lifestyle changes to retard development of diabetes. The cumulative incidence of diabetes was strongly related to both impaired fasting plasma glucose and impaired glucose tolerance, and, in particular, the combined presence of both.

**4-3 ADVERSE DRUG EFFECTS, COMPLIANCE, AND INITIAL DOSES OF ANTIHYPERTENSIVE DRUGS RECOMMENDED BY THE JOINT NATIONAL COMMITTEE VS THE *PHYSICIANS' DESK REFERENCE***

The PDR does not reflect the lowest doses recommended for initiation of therapy for hypertension recommended by the JNC. Because avoidance of adverse drug reactions is essential in maintaining compliance, and because many ADEs are dose-related, physicians must use the very lowest, effective, least ADE-prone doses.

Practical point: It is basically important to start therapy with the lowest reasonable dose of drugs, especially drugs for long-term use. Most adverse effects are related to dosage. Starting low and slowly titrating up will avoid many adverse effects.

**4-4 RESULTS OF CURE TRIAL FOR ACUTE CORONARY SYNDROME**

Clopidogrel (*Plavix*— an antiplatelet drug), acts to inhibit adenosine diphosphate, an activator of platelet aggregation.

This randomized, double-blind trial entered over 12 500 patients with acute coronary syndromes. For every 1000 persons treated for 9 months, an estimated 28 cardiovascular deaths, MIs, or strokes would be prevented.

Practical point: The treatment of acute coronary events, including myocardial infarction, is in a state of flux. Use of thrombolysis is giving way to use of platelet inhibitors and early coronary revascularization. Primary care clinicians should be able to identify patients with acute coronary syndromes and begin treatment as early as possible. They should correlate the best current treatment with their cardiologist consultants. Watch for evolving developments.

**4-5 PRIOR ALCOHOL CONSUMPTION AND MORTALITY FOLLOWING MYOCARDIAL INFARCTION**

Moderate alcohol consumption in the year prior to an acute MI was associated with reduced mortality following infarction.

Practical point: What should we advise abstainers when discharged from the hospital following an acute MI? The number needed to treat (among those using alcohol in the year prior to the MI) to benefit one patient is comparable to other pharmacotherapeutic interventions. I believe some competent stable patients and their families should be informed of the likely (but not proven) benefits of one drink a day.

They may then choose for themselves. Just as for any drug, a prescription for "A cocktail before dinner (1 oz spirits), or a glass of wine (4 oz) with dinner — not both" may be written. Individuals who do drink moderately and develop left ventricular dysfunction, heart failure, or other effects of CHD generally should *not* be told to discontinue consumption.

**4-6 MODERATE ALCOHOL CONSUMPTION AND RISK OF HEART FAILURE AMONG OLDER PERSONS.**

Moderate alcohol consumption was associated with lower risk of heart failure among older persons. The observed benefits may not be entirely mediated by a reduction in risk of MI.

Practical point: Primary care clinicians must consider the consistently substantial benefits of alcohol reported by epidemiological studies. Advice must be individualized. Stable individuals who consume small amounts of alcohol daily should not be told to stop. Abstinent individuals may be told of the risks and benefits and a prescription for "one drink daily" may be considered.

**4-7 EFFECTS OF ATORVASTATIN ON EARLY RECURRENT ISCHEMIC EVENTS IN ACUTE CORONARY SYNDROMES: The MIRACL Study**

High dose atorvastatin started within 1 to 3 days after presentation for acute coronary syndromes was associated with a reduction in risk of early recurrent ischemic events, but with no other significant clinical benefit.

Practical point: Statin drugs given immediately after onset of acute myocardial infarction or unstable angina may be associated with only small benefits over 4 months. Nevertheless, statins should be started for secondary prevention and maintained over years. Starting early in the hospital will encourage compliance.

**4-8 EFFECT OF LIPID-LOWERING THERAPY ON EARLY MORTALITY AFTER ACUTE CORONARY SYNDROMES.**

Prescription of a lipid-controlling drug at hospital discharge for patients with unstable angina or MI, was independently associated with reduced short-term mortality over 1 month and 6 months.

Practical point: There is good reason for prescribing statin drugs to patients with acute coronary syndromes (ie, established coronary disease) during their hospitalization or at discharge.

**4-9 COMPARISON OF CORONARY-ARTERY BYPASS SURGERY AND STENTING FOR THE TREATMENT OF MULTIVESSEL DISEASE**

At one year, in patients with multivessel coronary disease, angioplasty with stenting and CABG offered the same protection against death, stroke, and MI. Stenting was less costly, but resulted in more revascularization procedures. The recent application of newer antiplatelet drugs (glycoprotein IIb/IIIa receptor blockers) may further tilt advantage toward stents.

Practical point: In areas where logistic problems have been overcome, patients may be given full information about local experience and be given a choice between CABG and stenting. Many may choose stenting because of its more timely administration and less disability-time. And because of the reported cognitive declines reported in patients undergoing CABG.

**4-10 RISK, CAUSES, AND PREVENTION OF ISCHAEMIC STROKE IN ELDERLY PATIENTS WITH SYMPTOMATIC INTERNAL-CAROTID STENOSIS.**

"If elderly people are denied therapy for reasons of prejudice and not of science, they may justifiably feel that they have been abandoned on the basis of age alone."

In the secondary prevention (after TIA or non-disabling stroke) of ipsilateral stroke, patients over age 75 with 50-99% symptomatic stenosis, benefited more from endarterectomy than younger patients.

And much more than those in the group receiving medical treatment alone.

Practical point: Elderly patients who have experienced a TIA or non-disabling stroke are at extremely high risk of a second stroke. Since the elderly live now live longer than in the past, in patients over age 75 the benefits of surgery may outweigh the risks of surgery and of continued medical treatment. They should be informed about the local experience of endarterectomy and given the opportunity to choose for themselves.

**4-11 HAEMATURIA IN ASYMPTOMATIC INDIVIDUALS**

Hematuria is often detected incidentally by “dipstick”. It is common. Should hematuria in asymptomatic individuals always be investigated or should it be disregarded?

In most cases the next step is to examine the urine by phase contrast microscopy to confirm the hematuria and to determine whether the red cells have originated from the glomerulus or elsewhere in the urinary tract. “Dysmorphic” or “glomerular” red cells are present when there is glomerulonephritis with proliferative features. “Non-glomerular” red cells appear when the bleeding comes from elsewhere in the urinary tract – usually infections, stones, or a tumor.

Renal biopsy most often shows "*thin basement membrane disease*". Prognosis is excellent.

Practical point: Primary care clinicians should be aware of this entity. It may save patients much anxiety and useless investigations

**4-12 THE ANAEMIA OF CHRONIC DISEASE.**

Practical point: Is the microcytic anemia of a sick patient due to iron deficiency or to the anemia of chronic disease? Testing the soluble transferrin receptor (STR) in serum may differentiate. STR is raised in iron deficiency; normal in ACD.

**4-13 THE DOCTOR’S LETTER OF CONDOLENCE**

Practical point: Reviving the old custom of writing letters of condolence to families of deceased patients may help relieve the burden of bereavement and hasten closure for physicians as well as families. ". In this medical world, shaped by technological advances, we must maintain our humanity."

**4-14 ANTIBIOTICS FOR ACUTE BRONCHITIS**

No doubt — acute viral bronchitis does *not* respond to antibiotics. This has led to the oft repeated admonition not to prescribe antibiotics for acute bronchitis.

The editorialist point out that in a group of patients presenting with acute bronchitis, there will be a subset who have a bacterial infection, including pneumonia. The problem is how to separate those who would benefit from antibiotics from those who will not.

Practical point: Primary care clinicians must use clinical judgement to suspect those patients with acute bronchitis who have a bacterial infection. Patients who are aged, have physical signs of congestion, and who appear acutely ill are more likely to fit this category.

**4-15 UNDERSTANDING THE EXPERIENCE OF PAIN IN TERMINALLY ILL PATIENTS**

Although half of terminally ill patients experience moderate to severe pain, only 30% of these wanted additional pain treatment. The number of patients experiencing pain remains too high, but the number is not as large as perceived.

Many patients are willing to tolerate pain for fear of addiction; dislike of mental or physical side effects; not wanting to take more pills or injections. Physicians must communicate more effectively that addiction to opioids given for pain relief is a myth.

Practical point: As usual, pain control as well as other aspects of treatment must be negotiated , and concordance reached, with each individual patient.

**4-16 RISK OF FRACTURE IN WOMEN WITH LOW SERUM LEVELS OF THYROID-STIMULATING HORMONE**

Older women with biochemical evidence of physiological hyperthyroidism (low TSH), mainly due to too high doses of exogenous thyroxine, but also due to endogenous "subclinical hyperthyroidism", had an increased risk of hip and vertebral fracture.

Practical point: Consider any woman with evidence of excess thyroid hormone production or administration at risk of increased severity of osteoporosis. Exogenous thyroxine dosage must be carefully monitored.

**4-17 "HIGH" EAR PIERCING AND THE RISING INCIDENE OF PERICHONDRITIS OF THE PINNA**

Young persons who pierce the upper part of the ear may develop infection resulting in life-long ear deformity.

Practical point: We should warn our young patients about this complication, and advise them to seek early medical treatment if it arises.

**4-18 TAKE HOME NALOXONE AND THE PREVENTION OF DEATHS FROM OPIATE OVERDOSE**

Practical point: Naloxone, a rapidly acting opioid antagonist will save lives of the opioid abusers who overdose. It should be given routinely, on request, to all abusers.

We cannot abandon compassionate care of those who cannot or will not care for themselves.

**4-19 ANTIBIOTIC DATABASE LAUNCHED**

Johns Hopkins has a free to all peer reviewed database presenting the latest information on antibiotics and infectious diseases. (www.hopkins-abxguide.org).

Practical point: This easily accessed website should be most helpful to primary care clinicians.

**4-20 A NEW WEB SITE AND A NEW POLICY**

The NEJM's web site has been changed from www.nejm.com to www.nejm.org. An improved search system makes it possible to search the full text of all NEJM articles as far back as 1993.

Beginning six months after publication, the full text of all original articles and special articles will be available on line *free of charge*.

**REFERENCE ARTICLE**

**4-1 HOW DO YOU DEFINE DIABETES?**

(*This data was extracted from the following article to clarify terms. RTJ* )

The American Diabetes Society (**ADA**) and the World Health Organization (**WHO**) differ in their definitions of "diabetes", "impaired glucose tolerance" and impaired fasting glucose".

**ADA**: (Requires a fasting plasma glucose only)

A. "Normal fasting glucose" — consistently under 110

B. "Impaired fasting glucose" — present when the fasting plasma glucose is between 110 and 125.

C. "Diabetes" — diagnosed when repeated fasting plasma glucose levels are at or above 126 mg/dL.

(Note, the glucose tolerance test is not required. Only one glucose concentration need be considered; diagnosis depends solely on the fasting glucose concentration. There is a gradient of risk of developing "diabetes" over a subsequent 10 years related to the concentration of fasting glucose. Some individuals with glucose < 100 will subsequently progress to "diabetes"; more with levels 100-110 will progress; still more with levels 110-125 will progress. We are not exempt from prudent lifestyles just because our fasting glucose is well below normal.)

**WHO**: (Requires a fasting plasma glucose + plasma glucose 2 hours after a 75 g glucose challenge. Two glucose concentrations need be considered. This makes determinations of glucose status more complicated. The term "glucose tolerance" is added.)

In 1999 the WHO criteria for fasting glucose were redrawn to more closely match those of the ADA. The 2-hour cutoff point was continued. Post-load glucose levels are still taken into account. The cut point for fasting glucose was lowered from 140 to 126. Data from epidemiological studies suggest that the risk of microvascular complications is closer to 126 than to 140.

| <u>1999 criteria:</u> | Fasting plasma glucose | | 2h post 75 g glucose | |
|---|---|---|---|---|
| A. Normal GT | <110 | | <140 | |
| B. IFG and NGT | 110-126 | | < 140 | |
| C. NFG and IGT | < 110 | | 140-200 | |
| D. IFG and IGT | 110-126 | | 140-200 | |
| E. Diabetes | 126 and above | <u>or</u> | >200 | or both |

(*To calculate mmol/L multiply by 0.0555*)

IFG = Impaired fasting glucose

NFG = normal fasting glucose

NGT = normal glucose tolerance

IGT = impaired glucose tolerance

The ADA criteria are simpler and used more often. The WHO criteria are stricter. The oral glucose tolerance test will identify more individuals at risk of future development of diabetes than will the ADA . This is because some individuals will have a normal fasting glucose (< 110), but an impaired glucose tolerance (2-h post challenge glucose = 140-200). The ADA criteria would not discover these individuals.

JAMA April 25, 2001; 285: 2109-13 Extracted from the following article "Relation of Impaired Fasting and Postload Glucose with Incident Type 2 Diabetes in a Dutch Population" **www.jama.com**

Comment:

I found trying to remember these details somewhat difficult, confusing, and annoying. Remember 4 cut-points— 110; 126; 140, and 200. Since the ADA depends on fasting glucose levels alone, the term "impaired fasting glucose" alone is used. Since the WHO requires a glucose tolerance test, it uses an additional term— "glucose tolerance". The criteria are of greatest value as definitions in epidemiological studies.

We must be careful in making a diagnosis of diabetes based solely on glucose levels. What is "diabetes" by one criteria may not be "diabetes" by another. The social, employment, and insurance burden placed on patients by making the diagnosis based on glucose levels may be harmful and unwarranted. In addition to calling a defect in metabolism "diabetes" by one criteria and not "diabetes" by another, the glucose levels may change over time with diet, weight control, and exercise. Thus, "diabetes" in 1999 may not be "diabetes" in 2001.

I would tilt toward making the diagnosis of "diabetes" only if classical symptoms are present or if the glucose level is consistently above 200.

Those with lesser degrees of glucose intolerance should be notified that changes in lifestyle will likely improve their defect in "metabolizing sugar", and must be wholeheartedly embraced. RTJ

To determine the WHO 1985 criteria, eliminate 126 and substitute 140 for fasting plasma glucose:

| | Fasting plasma glucose | | 2h post 75 g glucose | |
|---|---|---|---|---|
| A. Normal GT | <110 | | <140 | |
| B. IFG and NGT | 110-140 | | < 140 | |
| C. NFG and IGT | < 110 | | 140-200 | |
| D. IFG and IGT | 110-140 | | 140-200 | |
| E. "Diabetes" | 140 and above | or | >200 | or both |

IFG = Impaired fasting glucose

NFG = normal fasting glucose

NGT = normal glucose tolerance

IGT = impaired glucose tolerance

The 1985 WHO criteria continue to be relevant because studies in the past literature still refer to the 1985 criteria.

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**4-2 RELATION OF IMPAIRED FASTING AND POSTLOAD GLUCOSE WITH INCIDENT TYPE 2 DIABETES IN A DUTCH POPULATION: The Hoorn Study**

Persons with impaired glucose tolerance (2-h post 75 g glucose challenge of 140 to 200 mg/dL) have an elevated risk of developing diabetes mellitus.

This study asks — what is the risk of developing diabetes in persons with impaired fasting glucose (110-125) and normal glucose tolerance (2-h post glucose < 140); with normal fasting glucose (< 110) and impaired glucose tolerance (2-h post glucose 140-200); and with both.

Conclusion: The cumulative incidence of diabetes was strongly correlated with both impaired fasting glucose (ADA) and impaired glucose tolerance (WHO). When combined, the risk is very great.

STUDY

1. Population-based cohort study followed over 1300 residents of Hoorn, the Netherlands. All were age 50 to 75.
2. At baseline measured fasting plasma glucose and glucose levels 2 hours after a 75 g glucose load. None had diabetes.
3. Repeated the tests after a follow-up of 4 to 9 years. (Mean = 6 years)
4. Defined diabetes by 3 different criteria: 1) ADA, 2) WHO 1999. (*The study also considered the 1985 WHO concentrations. I omitted these data. RTJ* )

RESULTS

1. Cumulative incidence of diabetes over the mean follow-up:

| | |
|---|---|
| By WHO 1999 | 9.9% |
| By ADA | 8.3% |

2. Cumulative incidence of progression to diabetes by WHO 1999 criteria over the mean follow-up for combinations of IGF and IGT determined at baseline:

| Category | No. | Cutoff values | Cumulative incidence (%) | Odds ratio |
|---|---|---|---|---|
| Normal | 1125 | < 110/<140 | 5 | 1.0 (referent0 |
| IFG and NGT | 106 | 10-125/<140 | 33 | 10 |
| NFG and IGT | 80 | < 110/140-200 | 33 | 10 |
| IFG and IGT | 31 | 110-125/140-200 | 65 | 40 |

(*See preceding article for definitions. RTJ* )

DISCUSSION

1. The cumulative incidence of progression to diabetes (according to the WHO 1999 criteria) of individuals who had both impaired fasting plasma glucose and impaired glucose tolerance was 65% in 6 years. Of those with normal glucose at baseline (< 110), 5% developed diabetes
2. The cumulative incidence of progression to "diabetes" depends on the definition used. The WHO criteria will diagnose diabetes more often. Screening with ADA vs the WHO 1985, and the new WHO 1999 criteria diagnosed about 1.5% to 3.8% more cases of diabetes. (Ie, the WHO 1999 is the more sensitive test; the ADA is less sensitive.
3. By ADA criteria, the cumulative incidence of diabetes over 6 years was 5% for those with normal fasting plasma glucose, and 38% for those with impaired fasting plasma glucose. (Ie, if fasting plasma glucose is 110 to 125, there is one chance in 3 that you will develop diabetes within 6 years. This is an excellent opportunity to apply lifestyle changes which will modify this adverse prognosis.)
4. Almost 2/3 of participants in this study who had both impaired fasting plasma glucose and impaired postload glucose levels at baseline progressed to diabetes within 6 years.
5. Impaired fasting glucose and impaired glucose tolerance represent 2 different physiological abnormalities: 1) IFG is caused primarily by the elevated rate of basal hepatic glucose production in the presence of hyperinsulinemia. 2) IGT is characterized by defects in both insulin secretion and insulin sensitivity.

CONCLUSION

The cumulative incidence of diabetes was strongly related to both impaired fasting plasma glucose and impaired glucose tolerance, and, in particular, the combined presence of both.

JAMA April 25, 2001; 385: 2109-13 Original investigation, first author Femmie de Vegt, Institute for Research in Extramural Medicine, Vrije Universiteit, Amsterdam. Netherlands. **www.jama.com**

Comment:

Primary care clinicians in the US will use the ADA criteria more often. Discovering those with an impaired fasting glucose by these criteria will allow prediction of high risk of future development of diabetes. It will miss those with a normal fasting glucose and an impaired glucose tolerance because the 2-hour post challenge test is not done. These patients also have a high risk of later development of diabetes. The ADA will also miss those with both IFG and IGT, a group which almost inevitably will progress to diabetes.

A compromise would be to perform a 2-h post challenge test on those who have IFG (110-125). RTJ

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**4-3 ADVERSE DRUG EFFECTS, COMPLIANCE, AND INITIAL DOSES OF ANTIHYPERTENSIVE DRUGS RECOMMENDED BY THE JOINT NATIONAL COMMITTEE VS THE *PHYSICIANS' DESK REFERENCE***

Compliance problems are common causes of inadequate treatment of hypertension. Many patients discontinue treatment within one year. This may be due in part to dose-related adverse drug events **(ADEs).** Many ADEs occur due to too-high initial doses.

It is an established tenet to initiate treatment with low doses to avoid ADEs.

This study asks – What are the lowest effective doses of antihypertensive drugs? Does the PDR present adequate advice?

Conclusion: The PDR does not reflect the lowest initial doses recommended by the JNC.

STUDY

1. Compared initial doses recommended by the PDR (1999 and 2000) with those recommended in the Sixth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI — 1997).

RESULTS

1. JNC VI recommends substantially lower initial doses than the PDR for over half of 40 drugs. In almost all instances, the PDR did not recommend lower doses for elderly or frail patients.

2. Examples

| | PDR | JNC |
|---|---|---|
| Hydrochlorothiazide | 25 mg | 12.5 mg |
| Ramipril 2.5 | | 1.25 |
| Losartan | 50 | 25 |
| Atenolol | 50 | 25 |

DISCUSSION

1. The JNC cautions against trying to bring mild to moderate hypertension under control quickly. This is to avoid the adverse effects of too great or too abrupt a reduction in BP. (Exception – when acute target organ damage is present.)
2. Initial interventions are usually aimed at life-style modifications, giving the patient an opportunity

to avoid drugs if possible. Drugs may be started later.

3. Some physicians prescribe subtherapeutic doses at the start rather than the "correct" dose.
4. Treatment of hypertension in the most commonly affected group (those over age 60) can be especially challenging because of their altered pharmacokinetics and reduced liver and kidney function, and increased receptor sensitivity. The overall incidence of ADEs in the elderly is 2 to 3 times greater than in the young.
5. Treatment of hypertension requires a flexible approach, involving a low initial dose of antihypertension drugs. The dose is often lower than that recommended by the manufacturer.

CONCLUSION

The PDR does not reflect the lowest doses recommended for initiation of therapy for hypertension recommended by the JNC. Because avoidance of adverse drug reactions is essential in maintaining compliance, and because many ADEs are dose-related, physicians must use the very lowest, effective, least ADE-prone doses.

Archives Int Med March 26, 2001; 161: 880-85 Original investigation by Jay S Cohen, University of California, San Diego. **www.archinternmed.com**

Comment:

This is an important practical point. Most adverse effects of drugs are due to inappropriately high dosage, not to allergy or to idiosyncrasy. Adjusting dosage is a major task for primary care clinicians. We all recognize that for a 100 pound woman the dose of a drug to achieve a satisfactory blood level and clinical response would be less than that for a 200 pound man. And less for an elderly, frail patient. A pill cutter will benefit in 2 ways: 1) Lower cost – the less expensive, higher dose tablets can be purchased at a lower cost per mg, and 2) With a little training, patients and families can cut tablets to achieve an individually titrated dose.

See also: "Dose Discrepancies Between the Physicians' Desk Reference and the Medical Literature, and Their Possible Role in the High Incidence of Dose-related Adverse Drug Effects" Archives Int Med April 9, 2001; 161: 957-64 by the same author. The article provides information on lower, effective doses for 48 major medications recommended in the literature compared with higher doses recommended in the PDR. (List on p 960) RTJ

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**4-4 RESULTS OF CURE TRIAL FOR ACUTE CORONARY SYNDROME**

(*This is a news report of what seems to be an important therapeutic advance. I have not seen any original journal articles. The study was reported at a recent American College of Cardiology Scientific Session. RTJ* )

Clopidogrel (*Plavix*— an antiplatelet drug), acts to inhibit adenosine diphosphate, an activator of platelet aggregation.

This randomized, double-blind trial entered over 12 500 patients with acute coronary syndromes. Over 1 year, the primary endpoints — cardiovascular death, MI, and nonfatal stroke occurred in 11.5% of the placebo+aspirin group vs 9.3% of the clopidogrel+aspirin group. (Absolute risk reduction = 2.2%; NNT(benefit one patient-1 year) = 45). For every 1000 persons treated, an estimated 28 cardiovascular deaths, MIs, or strokes would be prevented.

The benefit was evident within 2 hours after taking the medication.

Major bleeding events increased from 2.7% in the placebo group to 3.6% in the treatment group — for every 1000 persons treated, 3 life-threatening bleeding episodes, and an additional 3 patients needing transfusions.

Patients in the study could receive heparin, ß-blocker, statins, and calcium channel blockers. Clopidogrel was effective regardless of cotherapies.

Patients taking glycoprotein IIb/IIIa receptor antagonists were excluded.

Clopidogrel is currently indicated for reduction of atherosclerotic events in patients with recent stroke, MI, or established peripheral vascular disease. It was dubbed a "super aspirin" following the positive results of the "Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events" (CAPRIE) trial. [Lancet 1996; 348: 1329-39]

The cost of clopidogrel is between $2 and $3 daily for treatment which will last a lifetime.

In a press conference at which the CURE results were presented the investigators said the results were so clear and positive that only economics stand in the way of clopidogrel being accepted as standard therapy for acute coronary syndromes.

JAMA April 11, 2001; 285: 1828-29 News report of the "Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events" (CURE) trial. **www.jama.com**

Study supported by Sanofi-Synthelabo SA and Bristol-Myers Squibb.

Comment:

I am hesitant to abstract accounts of studies before the original trial is presented in a major peer-reviewed journal. I suspect, and look for "spin" on the results.

How will clopidogrel compare with the anti-platelet drugs (glycoprotein IIb/IIIa blockers)? Clopidogrel has the advantage of long-term oral administration.

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**4-5 PRIOR ALCOHOL CONSUMPTION AND MORTALITY FOLLOWING MYOCARDIAL INFARCTION**

In the general population, individuals who drink 1 alcoholic drink every 1 to 2 days have lower rates of a first nonfatal myocardial infarction (**MI**) and death from coronary disease compared with abstainers and heavy drinkers. There is a "U" shaped pattern related to amount of alcohol imbibed.

Patients with diabetes and hypertension receive similar benefits.

This study asks — what is the effect of prior alcohol consumption on long-term mortality among early survivors of acute MI?

Conclusion: Moderate alcohol consumption in the year prior to an acute MI was associated with reduced mortality following acute MI.

STUDY

1. Prospective cohort study followed over 1900 patients who survived hospitalization for acute MI.
2. Determined self-reported average weekly consumption of alcohol in the year prior to the MI.
3. Follow-up = 4 years.

RESULTS

1. 53% were drinkers — 36% consumed less than 7 alcoholic drinks per week; 17% consumed more than 7 drinks per week.
2. Compared with abstainers, patients who consumed < 7 drinks per week had a lower all-cause mortality (3.4 deaths per 100 person-years vs 6.3; NNT(benefit-1 year)= 34 )
3. Those who drank 7 or more drinks weekly also had a lower all-cause mortality (2.4 deaths per 100 person-years vs 6.3 for abstainers; NNT(benefit-1year)= 25 )

4. The association was similar for cardiovascular mortality among both men and women, and among different types of alcoholic beverages.

DISCUSSION

1. Adults who abstained from alcohol prior to an acute MI appeared to be at particularly high risk of long-term mortality.
2. The results of the study are consistent with the hypothesis that light to moderate alcohol use following acute MI is safe, although studies that formally assess post-MI consumption are needed to confirm this.[1]
3. Determination of the risks and benefits of alcohol consumption for an individual requires consideration of numerous personal, clinical, and social factors that cannot be addressed with aggregate-level observational data.

CONCLUSION

Moderate alcohol consumption in the year prior to an acute MI was associated with reduced mortality following infarction.

JAMA April 18, 2001; 285: 1965-70 Original investigation, first author Kenneth J Mukamal, Beth Israel Deaconess Medical Center, Boston Mass. **www.jama.com**

Comment:

**1** The investigators speculate on this important point, but present no data. I presume those who did drink before their MI continued at the same level. Should patients who survive an acute MI and who imbibed alcoholic beverages beforehand, continue to use alcohol? If so, they should be advised not to exceed 1 drink a day.

What should we advise abstainers discharged from the hospital following an acute MI? The number needed to treat (among those using alcohol in the year prior to the MI) to benefit one patient is comparable to other pharmacotherapeutic interventions. I believe some competent stable patients and their families should be informed of the highly likely (but not proven) benefits of one drink a day. They may then choose for themselves. Just as for any drug, a prescription for "A cocktail before dinner (1 oz spirits), or a glass of wine (4 oz) with dinner — not both" should be written.

It's a shame alcohol has such a societal downside. Epidemiologic evidence of benefits is so strong, alcohol otherwise would be one of the most prescribed drugs. RTJ

An editorial in this issue comments: A recent meta-analysis including 51 studies estimated a 20% risk reduction in coronary heart disease among those drinking up to 2 drinks daily vs those abstaining. The lower CHD risk in drinkers has been observed in patients with diabetes, hypertension, and prior myocardial infarction. The consistency of benefits argues for a causal protective effect. Heavy drinking (> 3 drinks daily) increases risk.

The possible consequence of alcohol abuse has led to great caution in prescribing alcohol to patients with heart failure and left ventricular dysfunction. Advice must be individualized. Age, family history, personal drinking habits, and personal medical history must be considered. Individuals who do drink moderately and develop left ventricular dysfunction, heart failure, or other effects of CHD generally should *not* be told to discontinue consumption. The problem is whether to advise alcohol for individuals who do not drink. Most have a reason for abstaining. "The data do not justify advising lifelong nondrinkers . . . to start drinking." JAMA April 18, 2001; 285: 2004 Editorial by Arthur L Kaltsky.

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**4-6 MODERATE ALCOHOL CONSUMPTION AND RISK OF HEART FAILURE AMONG OLDER PERSONS.**

Heavy alcohol consumption has a toxic effect on the heart. Light to moderate consumption among persons with existing left ventricular dysfunction favorably influences prognosis. The relationship between moderate alcohol consumption and heart failure **(HF)** is largely unknown.

Light to moderate consumption is also associated with a reduced risk of myocardial infarction **(MI).** Although MI is a major risk factor for HF, it may be that a favorable effect of alcohol on HF is due to factors in addition to benefits in reducing MI.

This study assessed the long-term effect of light to moderate consumption among persons free of HF at baseline. It was designed to determine if moderate alcohol consumption predicts HF risk among older persons.

Conclusion: Increasing levels of moderate alcohol consumption were associated with a decreasing risk of HF among older persons. The association did not appear to be entirely mediated by a reduction in risk of MI.

STUDY

1. Prospective population-based cohort study entered over 2200 non-institutionalized elderly persons (mean age 74) in 1982. Followed to 1996.
2. All were free of HF at baseline.
3. Determined baseline consumption of alcohol in the month preceding entry. Excluded those who consumed more than 70 oz of alcohol.
4. Maximum follow-up = 14 years. Main outcome: Time to first fatal or non-fatal HF event.

RESULTS

1. About half of the subjects used no alcohol; 40% used 1 to 20 oz of pure alcohol in the month prior to entry: 10% used 21 to 70 oz. (1 to 20 oz is equivalent to an average of 1 to 1.5 drinks per day; 21 to 70 oz equivalent to an average of 1.5 to 4 drinks per day.)
2. Increasing alcohol consumption in the moderate range was associated with decreased rates of HF.
3. Crude HF rates per 1000 person-years of follow-up:

| No alcohol | 1 to 1.5 drinks daily | 1.5 to 4 drinks daily |
|---|---|---|
| 16 | 12 | 9 |

4. After multiple adjustment for possible confounders, relative risk of HF over 14 years:

| No alcohol | 1 to 1.5 drinks daily | 1.5 to 4 drinks daily |
|---|---|---|
| 1.00 (referent) | 0.8 | 0.5 |

(*Four drinks daily would not be considered "moderate". However, few subjects used this amount. RTJ* )

DISCUSSION

1. Compared with no alcohol consumption, increasing levels of low to moderate consumption were associated with a lower risk of HF among community based older persons. (*Although the authors did not comment, the inference was that the level of alcohol use continued during the follow-up period. RTJ* )
2. There was no association with different types of alcoholic beverages. This suggests that it is pure alcohol, not the type of beverage that is associated with lower risk of HF.
3. Alcohol was associated with lower HF risk even after controlling for baseline history of MI and MI during follow-up.

This suggests that the reduction in risk of MI may not substantially explain the association observed.

4. Other studies have reported moderate alcohol consumption reduces risk of diabetes and also is associated with lower BP. "Even among people with heart failure, modest alcohol consumption lowers blood pressure in the short term." But, after controlling for hypertension, diabetes and pulse pressure at baseline, the inverse relationship persisted.
5. The authors speculate that alcohol may have effects on several neurotransmitters which may reduce risk of HF.

CONCLUSION

Although this observational study may be subject to confounding, it suggests that moderate alcohol consumption is associated with lower risk of heart failure among older persons. The observed benefits may not be entirely mediated by a reduction in risk of MI.

JAMA April 18, 2001; 285: 1971-77 Original investigation, first author Jerome L Abramson, Emory University School of Medicine, Atlanta, GA. **www.jama.com**

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*Patients with established coronary disease are at high risk of recurrence of acute coronary events. The two following studies suggest that secondary prevention with statin drugs should be started s soon as possible.*

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**4-7 EFFECTS OF ATORVASTATIN ON EARLY RECURRENT ISCHEMIC EVENTS IN ACUTE CORONARY SYNDROMES: The MIRACL Study**

Patients with unstable angina and acute myocardial infarction experience their highest rate of death and recurrent ischemic events in the first month. This study tested the hypothesis that early (within 1 to 3 days after onset) treatment with a statin, would improve prognosis.

Statins may have immediate effects in addition to their delayed effect of lipids. These drugs may improve endothelial function, decrease platelet aggregability and thrombus formation, and reduce vascular inflammation.

Conclusion: Early treatment with atorvastatin (*Lipitor*) reduced recurrent symptomatic ischemia requiring rehospitalization. No other benefit was evident.

STUDY

1. Multicenter, randomized, double-blind trial entered over 3000 patients with unstable angina or non-Q-wave infarction.
2. Randomized to: 1) atorvastatin 80 mg/d (a very high dose), or 2) placebo beginning within 24 to 96 hours after presentation (mean = 63 hours).
3. Follow-up = 16 weeks.

RESULTS

1. No significant differences in death, non-fatal MI, or cardiac arrest.
2. No significant differences in coronary revascularization, worsening heart failure, or worsening angina.
3. The only favorable outcome was a lessening of recurrent symptomatic ischemia requiring emergency rehospitalization. (6.2% vs 8.4%; NNT (benefit 1 patient- 16 weeks) = 45)

DISCUSSION

1. In this group of patients with unstable angina and non-Q-wave infarction, atorvastatin initiated within 24 to 72 hours of onset was associated with a statistically significant reduction in emergency re-hospitalization for recurrent ischemia.
2. Although death, non-fatal MI, and cardiac arrest occurred slightly less frequently in the atorvastatin group, the differences were not statistically significant.
3. The benefit did not appear to depend on baseline LDL-cholesterol levels.
4. As expected LDL-cholesterol declined – from a mean of 124 mg/dL to 72 mg/dL
5. Atorvastatin was well tolerated. Abnormal liver transaminases (> 3 times normal) occurred in 2.5% vs 0.6% in the placebo group.

CONCLUSION

High dose atorvastatin, started within 1 to 3 days after presentation for acute coronary syndromes, was associated with a reduction in risk of early recurrent ischemic events, but with no other significant clinical benefit.

JAMA April 4, 2001; 285: 1711-18 Original investigation by the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering Study Investigators: The MIRACL Study, First author Gregory G Schwartz, Denver CO VA Medical Center**. www.jama.com**

Comment:

This is a disappointing result. However, I believe statins should be started in the hospital for patients with acute MI or unstable angina. They are greatly beneficial over the long term. Beginning treatment in the hospital will encourage compliance. Statins are a mainstay in secondary prevention over months and years.

The 80 mg dose of atorvastatin is high. A lower, less expensive dose, followed with repeat lipid measurements would be more appropriate in primary care. RTJ

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**4-8 EFFECT OF LIPID-LOWERING THERAPY ON EARLY MORTALITY AFTER ACUTE CORONARY SYNDROMES.**

Lipid control reduces long-term mortality in patients with stable coronary disease as well as those with significant risk factors. This observational study assessed the effect of administration of statin drugs at discharge from the hospital for patients with acute coronary syndromes (ACS).

The American Heart Association notes that there is little evidence to support starting lipid-lowering therapy early, recommending a trial of dietary treatment first.

Because lipid-lowering agents can improve endothelial function, decrease platelet activity, and reduce inflammation, the investigators postulated that therapy begun shortly after onset of acute coronary syndromes might improve early prognosis.

Conclusion: Early administration of lipid-controlling medication reduced mortality at 6 months

STUDY

1. Used data from 2 large trials [1,2]. Compared all cause mortality among patients with acute coronary syndromes who were discharged from the hospital on lipid-lowering agents (**LLA**) vs those discharge without.
2. Over 20 000 patients were involved, including patients with acute myocardial infarction (**MI**). (MI with ST elevation; non-ST elevation MI; and unstable angina. )

3. Over 3500 (18%) received lipid-lowering therapy at hospital discharge. (In addition to other appropriate drugs.)
4. Follow-up = 6 months.

RESULTS

| 1. Mortality | LLA | No LLA | % Difference | NNT |
|---|---|---|---|---|
| At 30 days | 0.5% | 1% | 0.5 | 200 (benefit 1 patient —1 month) |
| At 6 months | 1.7% | 3.5% | 1.8 | 55 (benefit 1 patient— 16 months) |

DISCUSSION

1. In this pooled data from 2 large international randomized trials, patients discharged on lipid-controlling therapy after hospital admission for unstable angina or acute MI had a lower mortality rate than those discharged without such therapy.
2. There was no clear association between lipid-lowering and the rate of acute MI over 6 months. (The association was only for death.)
3. The reduction in mortality was evident as early as 30 days. The absolute difference was greater at 6 months.

CONCLUSION

Prescription of a lipid-controlling drug at hospital discharge for patients with unstable angina or MI, was independently associated with reduced short-term mortality over 1 month and 6 months.

Lancet April 7, 2001; 357: 1063-68 Original observational investigation, first author Herbert D Aronow, Cleveland Clinic Foundation, Cleveland Ohio. **www.thelancet.com**

Comment:

The authors did not comment on the type of lipid-lowering drug. Presumably most were statins. Fortunately statins are safe drugs and have established long-term benefit for secondary prevention Cost remains a problem. Some statins will go off patent soon.

Starting statins during hospitalization will aid concurrence with the patient and improve compliance with taking the drug long-term. RTJ

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**4-9 COMPARISON OF CORONARY-ARTERY BYPASS SURGERY AND STENTING FOR THE TREATMENT OF MULTIVESSEL DISEASE**

"Approximately 60 percent of patients treated with balloon angioplasty or bypass surgery **(CABG)** have multivessel disease that could be treated by either procedure." The most appropriate procedure is debatable.

Coronary artery stenting has improved the long-term outcomes of patients treated with angioplasty. This study re-evaluated the relative benefits of CABG vs angioplasty with stenting.

Conclusion: Stenting offered the same protection against death, stroke, and myocardial infarction. It was associated with more repeat re-vascularization procedures.

STUDY

1. Randomly assigned over 1200 patients with multivessel disease to: 1) angioplasty (**PTCA**) with stenting, or 2) CABG.

2. The cardiac surgeons and interventional cardiologists agreed that the same degree of revascularization could be achieved by either procedure.
3. Follow-up = 1 year.

RESULTS

1. At one year, no significant differences in rates of death, stroke, or myocardial infarction **(MI).**
2. Among those who survived without stroke or MI, a second revascularization procedure was required more often in the stent group (17% vs 4%; 13 of every 100 patients). The event-free survival favored CABG.
3. Costs were less in the stent group despite the need for repeat procedures.

DISCUSSION

1. There was no difference between groups in rates of death, stroke, or MI.
2. More revascularization procedures (PTCA or CABG) were required in the stent group
3. Angioplasty with stenting is less invasive, less costly, and was associated with faster recovery and a better quality-of-life at 1 month.
4. CABG is associated with a lower incidence of angina, less need for anti-anginal drugs, and fewer repeat interventions in the first year.
5. Stenting can be performed with less delay than CABG. The interval between randomization and treatment was about 3 times longer in the CABG group. More adverse events will occur in this time period. (In this study 8 major events in those assigned to CABG vs 1in the PTCA-stenting group— a clinically important point.)
6. The risk of stent thrombosis may be reduced by platelet glycoprotein IIbIIIa receptor blockade or by use of heparin-coated stents.

CONCLUSION

At one year, in patients with multivessel coronary disease, angioplasty with stenting and CABG offered the same protection against death, stroke, and MI. Stenting was less costly, but resulted in more revascularization procedures.

NEJM April 12, 2001; 344: 1117-24 Original investigation, by the Arterial Revascularization Therapies Study Group, first author Patrick W Serruys, Academisch Zeikenhuis Rotterdam Dijkzigt, Netherlands. **www.nejm.org**

Comment:

As usual, for procedures of near equivalent benefits/harms, the decision will depend on local experience and expertise, as well as the fully-informed patient's preference.

The investigation was done before the results of studies of the newer antiplatelet drugs (short-term glycoprotein IIb/IIIa blockers and long-term clopidogrel) became available. Now combined PTCA combined with new antiplatelet drugs provide even greater benefits.

The recently described risk of cognitive decline after CABG may tilt some toward angioplasty and stenting. RTJ

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**4-10 RISK, CAUSES, AND PREVENTION OF ISCHAEMIC STROKE IN ELDERLY PATIENTS WITH SYMPTOMATIC INTERNAL-CAROTID STENOSIS.**

"If elderly people are denied therapy for reasons of prejudice and not of science, they may justifiably feel that they have been abandoned on the basis of age alone."

Two large multicenter trials (*see citations p 1160*) have demonstrated the efficacy of carotid endarterectomy in patients with recently symptomatic severe carotid stenosis (70% to 99%) in preventing subsequent stroke. Those with 50% to 69% stenosis receive less benefit.

This study asks if the benefits persist in patients over age 75.

Conclusion: In the prevention of ischemic stroke, elderly patients with symptomatic carotid stenosis *benefited more* from endarterectomy than younger patients.

STUDY

1. Reviewed data from the NASCET[1] study. Compared patients over age 75 (n = 409) with those age 65-74, and those younger than 65.
2. Assessed baseline characteristics and risk of ipsilateral ischemic stroke at 2 years by degree of stenosis and treatment group.
3. All had experienced a transient ischemic attack **(TIA)** or non-disabling ischemic stroke within the previous 6 months. All had 50% to 99% stenosis in the ipsilateral carotid.
4. Patients were assigned to 1) the best medical care, or 2) the best medical care plus endarterectomy.

RESULTS

1. Outcome at 2 years: Absolute risk reduction in ipsilateral stroke following endarterectomy, compared with medical therapy alone:

| | |
|---|---|
| Age over 75 | 29% |
| 65-74 | 15% |
| < 65 | 10% |

2. Among patients with 50-69% stenosis, the absolute risk reduction was significant only in those over age 75 (17% reduction).
3. Perioperative risk of stroke and death at any degree of stenosis:

| | |
|---|---|
| Age over 75 | 5.2% |
| 65-74 | 5.5% |
| < 65 | 7.9% |

4. The number of patients aged over 75 needed to treat with endarterectomy to prevent one ipsilateral stroke within 2 years:

| | |
|---|---|
| 70-99% stenosis | 3 |
| 50-69% | 6 |

5. The 2-year risk of ipsilateral stroke in the group receiving medical treatment alone was over 35% in those over age 75 with 70-99% stenosis, considerably higher than in those under age 75. (Ie, the benefit of surgery is this age group is partly due to the high risk of stroke in those treated without surgery.)

DISCUSSION

1. There has been unease about the performance of carotid endarterectomy in elderly persons. However, the elderly patients (> age 75) in this study benefited more than younger patients.
2. The rate of perioperative stroke and death (about 5%) in the elderly group, was actually less than in the

younger groups. The investigators attributed this to a greater number of vascular risk factors in the younger group (smoking, hyperlipidemia, diabetes). The elderly patients actually had less severe carotid disease, a lower frequency of intermittent claudication, and a lower prevalence of contralateral stenosis. "It is reasonable to speculate that the paucity of risk factors in elderly patients is the consequence of the early deaths of those who had many risk factors."

3. "Our study suggests that the risk reduction of ipsilateral ischemic stroke by carotid endarterectomy in the elderly subgroup is due to a decrease in large-artery stroke and to a lesser degree in lacunar stroke." (Most lacunar strokes are caused by small penetrating artery disease. At times carotid disease may cause lacunar stroke by embolic or by hemodynamic mechanisms resulting in decreased perfusion of penetrating arteries.)
4. Elderly patients in the NASCET study represent a select group with large-artery disease. They differed from most patients in the community. They had a lower frequency of associated disease, especially cardiac disease. "Therefore we recommend carotid endarterectomy only for selected elderly patients with symptomatic carotid-artery disease."
5. "These good results can only be achieved in elderly patients after scrupulous clinical evaluation to exclude disorders that could put the patients at increased risk from anesthesia or immediate cardiac complications, and with endarterectomy done by skilled surgeons."

CONCLUSION

In the secondary prevention (after TIA or non-disabling stroke) of ipsilateral stroke, patients over age 75 with 50-99% symptomatic stenosis, benefited more from endarterectomy than younger patients.

And much more than those in the group receiving medical treatment alone.

Lancet April 14, 2001; 357: 1154-60 Original investigation, first author Sonia Alamowitch, Tenon Hospital, Paris, France**.**
**www.thelancet.com**

**1** "North American Symptomatic Carotid Endarterectomy Trial" NEJM 1991; 325: 445-53

An editorial in this issue (Lancet April 14, 2001; 357: 1142-43 Editorial by Peter M Rothwell, University of Oxford, UK) comments:

Patients who enter randomized trials are generally healthier than those who do not. The endarterectomy trials excluded patients with severe concurrent disease. The trial populations may not have been typical of routine clinical practice. However, this observation does not invalidate the findings. In patients 75 years and older, the increased risk of stroke without surgery is much higher than in younger patients. Even if the operative risk were higher than in the young, the risk of surgery would be acceptable because of the dim prognosis with medical therapy. "Endarterectomy in routine practice is therefore likely to benefit reasonably fit patients over 75 years old." However, in very elderly patients (85-90) treatment decisions must be made without trial data.

In the past, one justification for a less aggressive approach to disease prevention in the elderly has been that they will not survive long enough to benefit. This assumption now does not stand up to scrutiny. The average life-expectancy at age 85 in the USA is 6 years. The benefit of endarterectomy in preventing stroke is evident in 6 months, and peaks at 2 years.

"Elderly patients commonly do not wish to undergo endarterectomy, but they should at least be given the choice. It is therefore difficult to justify not investigating carotid disease in an otherwise fit elderly person who is willing to consider surgery and who has an appropriate operative risk profile."

Comment:

Several important points: 1) This is a secondary prevention intervention. 2) It applied to a select group of elderly. The results cannot be generalized to the entire population of elderly. 3) Elderly patients who seem eligible for investigation and who might consider surgery must be given complete information about risks and benefits. This includes a review of the experience of local hospitals and surgeons. Despite the best care, at least one in 20 elderly patients undergoing endarterectomy will experience a stroke or die. Such an event is devastating to patient, family and physicians alike. Surgery may lead a patient who has experienced a non-disabling event (a TIA) into extreme harm's way. RTJ

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**4-11 HAEMATURIA IN ASYMPTOMATIC INDIVIDUALS**

Hematuria is often detected incidentally by “dipstick”. Should hematuria in asymptomatic individuals always be investigated or should it be disregarded? One correspondent chided – why do you test if you are going to ignore the result?

In most cases the next step is to examine the urine by phase contrast microscopy to confirm the hematuria and to determine whether the red cells have originated from the glomerulus or elsewhere in the urinary tract. “Dysmorphic” or “glomerular” red cells are present when there is glomerulonephritis with proliferative features. “Non-glomerular” red cells appear when the bleeding comes from elsewhere in the urinary tract – usually infections, stones, or a tumor.

Finding hematuria without proteinuria cannot be used to infer a non-glomerular origin. Glomerular bleeding is not necessarily accompanied by proteinuria.

A recent study found that 10% of community based adults had hematuria. What is the usual source of hematuria in asymptomatic individuals? On phase contrast microscopy, two thirds were found to have red cells originating from the glomerulus. Ie, hematuria in otherwise healthy adults most often is due to bleeding from the glomerulus.

What causes the glomerular bleeding? Renal biopsy most often shows "*thin basement membrane disease*". There is uniform thinning of the glomerular basement membrane and a very mild proliferative glomerulonephritis. Thin basement membrane disease is also known as "*benign familial hematuria*". Affected individuals typically have lifelong glomerular hematuria, minimal proteinuria, and normal renal function. Family members are often affected due to a genetic mutation. Half of offspring inherit the mutation and most develop hematuria. Diagnosis is confirmed when another family member also has persistent glomerular hematuria. A renal biopsy is warranted only if the diagnosis is unclear, especially if the X-linked Alport syndrome[1] cannot be excluded or a superimposed glomerulonephritis is suspected.

Prognosis is generally excellent. However, these patients often face unnecessary worry and investigations when doctors are unfamiliar with the condition.

A major differential diagnosis is IgA glomerulonephritis. This is characterized by episodic macroscopic hematuria associated with intercurrent infections (eg, pharyngitis) proteinuria, and hypertension. Progressive renal impairment occurs in one third of individuals. Differentiation is usually not difficult on these clinical features alone.

BMJ April 21, 2001; 322: 942-43 Editorial, first author Judy Savige, Austin and Repatriation Medical Centre, Heidleberg, Germany. **www.bmj.com/cgi/content/full/322/7292/942**

**1** Alport’s syndrome is a better understood, but less common inherited disease. It affects the glomerular basement membrane in a lamellated fashion rather than thinned. Renal failure, deafness, and ocular abnormalities often occur.

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**4-12 THE ANAEMIA OF CHRONIC DISEASE.**

Iron has *no* effective role in treating the most common type of anemia affecting hospital inpatients — the anemia of chronic disease (**ACD**). Recent developments have made ACD somewhat easier to diagnose.

ACD was established as a distinct entity in 1962 by studies on the anemia associated with infection. All agree on the "big three" clinical causes: infection, inflammation (including connective tissue disorders), and neoplasia. Although the chronic disease that leads to the ACD is usually easily identified, this is not always so. Occult disease must be considered in every case of unexplained anemia.

ACD typically occurs despite adequate reticuloendothelial iron stores. It is characterized by: 1) reduced concentrations of serum iron, transferrin, and total iron binding capacity; 2) normal or raised ferritin; and 3) high erythrocyte sedimentation rate.

It can mimic or coexist with other types of anemia. The red cells are often normocytic, normochromic, but may show hypochromic indices similar to the effects of iron deficiency. The latter case is often associated with rheumatoid arthritis and Crohn's disease. It raises the everyday problem of how to differentiate between the microcytosis of ACD and that due to iron deficiency.

Measuring serum ferritin is essential in the investigation of unexplained anemia. Serum ferritin concentration is directly related to reticuloendothelial iron stores. One ug/L roughly corresponds to about 8 mg of storage iron. Reduced serum ferritin provides unequivocal evidence of diminished iron stores. It occurs in no other condition. Thus, in patients with unexplained anemia, one might think that a decreased ferritin would point to iron deficiency anemia and away from ACD. Unfortunately, ferritin concentrations show acute phase responses to inflammation. Ferritin may rise independently of the reticuloendothelial iron stores. Thus, in the presence of inflammation, ferritin concentrations may remain normal even when reticuloendothelial iron stores are absent. In an anemic patient, a normal ferritin does not rule out iron deficiency and suggest ACD.

Two theories have been advanced as the mechanism of ACD: 1) depressed response to erythropoetin and 2) a change in the dynamics of iron recirculation. Although the first mechanism may be important in chronic renal failure, it probably plays only a small part in other cases. The second theory proposes that inflammation leads to retention of iron in the reticuloendothelial system (so called reticuloendothelial block), rather than being released to developing red cells in the marrow.

How best to differentiate microcytic anemia of chronic disease from genuine iron deficiency when ferritin levels are normal? Examination of the bone marrow for iron is the definitive test for iron deficiency. Measurement of a *soluble form of transferrin receptor in serum* may now provide an alternative. Iron is transported to developing red cells in the marrow by the glycoprotein transferrin. Transferrin binds iron with high affinity, and in plasma is usually 30% saturated. Developing red cells regulate their iron uptake via a transferrin receptor. In response to iron deficiency, surface expression of the transferrin receptor increases. This is a compensatory mechanism allowing more iron to be bound and internalized by the developing red cells. Soluble transferrin receptor is cleaved from the cell surface receptor and appears in the serum. Values of both soluble transferrin receptor and the soluble transferrin-ferritin index are raised in iron deficiency even in the presence of chronic disease, but are normal or only slightly raised in ACD.

The diagnostic point: In the presence of microcytic anemia, raised serum transferrin receptor points to iron deficiency and away from ACD.

A raised serum soluble transferrin receptor concentration has high sensitivity and specificity for identifying iron deficiency in anemic patietns with rheumatoid arthritis, and compares well with bone marrow aspiration as a diagnostic test for absent iron stores.

Treatment of ACD generally means treating the underlying disorder, whereupon hemoglobin concentrations should rise.

In one type of ACD, response to treatment is dramatic. In the hypochromic microcytic anemia of temporal arteritis and polymyalgia rheumatica, treatment with prednisolone rapidly corrects the anemia. A normal hemoglobin can be maintained long term with low dose steroids.

BMJ April 7, 2001; 322: 811-12 Editorial by E J Fitzsimons and J H Brock, Western Infirmary, Glasgow, Scotland **www.bmj.com/cgi/content/full/322/7292/811**

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**RECOMMENDED READING**

**4-13 THE DOCTOR'S LETTER OF CONDOLENCE**

This editorial begins quoting a letter from the daughter of a deceased patient. She wrote her mother's physician expressing her appreciation for his care. She never received a reply. This troubled her.

The editorialists continue: "A physician's responsibility for the care of a patient does not end when the patient dies. There is one final responsibility – to help the bereaved family members. A letter of condolence can contribute to the healing of the bereaved family and help achieve closure in the relationship between the physician and the patient's family."

Writing a letter of condolence may help relieve the physician's burden of grief and distress about the loss of a patient. Physicians, like the family, need to have a sense of closure about the death.

There are ways to ease the difficult task of writing a condolence letter. The letter may describe the extent and depth of the relationship between the physician and the patient. Or, it may be a short expression of sympathy – a direct expression of sorrow. It may point out the comfort the patient received from the family's love. It is important to avoid superficial attempts to assuage grief, such as "It was meant to be" or "I know how you feel". The letter should focus on the sadness of death, rather than revisit the clinical details of the illness. References about achievement at work, devotion to family, courage during the illness, and the patient's character can bring life to the letter. A statement that it was a privilege to have participated in the patient's care may be added.

The letter of condolence, which was standard practice in the 19th century, is worth reviving. In this medical world, shaped by technological advances, we must maintain our humanity.

NEJM April 12, 2001; 344: 1162-63 "Sounding Board", editorial, first author Susanna E Bedell, Lown Cardiovascular Center, Boston, Mass. **www.nejm.org**

Comment:

During my years in active practice, I did not write letters of condolence. Looking back, this was a missed opportunity to connect with families, and to enhance my own self esteem and satisfaction as a clinician. I do remember calling on a widow of a favorite patient who died suddenly when I was out of town. Years later, in expressions to her friends, she recalled her gratitude for my visit. RTJ

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**4-14 ANTIBIOTICS FOR ACUTE BRONCHITIS**

Four systematic reviews have compared antibiotics with placebo for treating bronchitis. All have reached clinically unhelpful conclusions. This exposes the perennial problem for all systematic reviews that demonstrate no benefit, or only

marginal benefit, from interventions. Is there a subgroup that might derive benefit? "It also exposes the procrustean[1] nature of our definitions of acute bronchitis."

All 4 studies came to similar ambiguous and clinically unhelpful conclusions, the most negative being "the current literature does not support antibiotic treatment for acute bronchitis". The most positive concluded "antibiotics may be modestly effective for a minority of patients with acute bronchitis".

The editorialists speculate that these findings conceal a small group of patients with pneumonia within a larger group of patients with viral infections, bronchospasm, or minor bacterial infection.

The problem stems from the multiple definitions of acute bronchitis in the primary studies, all of which have been treated as a single entity for the purposes of review. The primary trials accept patients with acute cough and either purulent or productive sputum. This is contrary to the accepted diagnostic classification criteria for bronchitis (which is consensus based, not evidence based) in which patients must have an acute cough and scattered or generalized abnormal chest signs (wheeze and coarse or moist sounds) — that is, signs of lower respiratory tract disease.

The lower respiratory signs are central to the editorialists' argument. It is not possible to exclude pneumonia when lower respiratory signs are present. (Conversely, pneumonia may be present when the chest is clear.)

One review found a statistically significant improvement from antibiotics in patients diagnosed as acute bronchitis when lower respiratory signs were present. "This suggests that antibiotics are effective in patients with lower respiratory signs and a clinical diagnosis of acute bronchitis." "This does not help us decide if there is really an entity that can be called acute bacterial bronchitis because we do not know how many of those patients had pneumonia."

What should the primary care clinician do? The use of antibiotics may be justified in patients with lower respiratory signs or in those who are aged and those who feel ill and look or have frequent day time cough. Others may benefit more from bronchodilators.

BMJ April 1, 2001; 322: 939-40 Editorial, first author Bruce Arroll, University of Auckland, New Zealand.
**www.bmj.com/cgi/content/full/322/7292/939**

**1** Procrustes was a mythical Greek who adjusted the size of his guests so that they would fit his iron bed. "We suggest that acute bronchitis is one size fits all diagnosis."

Comment:

This calls to mind the oft quoted remark that "science can tell us nothing about an individual patient". Primary care clinicians must deal with uncertainty and exceptions to conclusions of systematic reviews. This is termed "clinical judgement".

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**4-15 UNDERSTANDING THE EXPERIENCE OF PAIN IN TERMINALLY ILL PATIENTS**

The prevalence of physical pain in terminally ill patients varies. Often, as death approaches, pain increases. The widely quoted SUPPORT study[1] reported many terminal patients suffered unrelieved pain.

But pain in itself is only one of the critical outcome measures for quality of life care. Complaints about pain could actually be a way to express concerns about loneliness, hopelessness, care needs, and other symptoms. [2]

Not all patients in pain want additional treatment. The meaningful outcome measure should be the proportion of dying patients who experience pain, but do *not* want additional pain treatment as well as those who do want it.

Pain and pain management are not consistent across racial groups. Minority patients are less likely to receive analgesic prescriptions.

Although cancer accounts for less than 25% of all deaths, only a handful of studies describe the experience of pain in terminally ill patients with other diseases.

Most data are derived from a heterogeneous group of cancer patients at various stages in the course of the disease. Patients are variously described as advanced, metastatic, and terminal – classifications that are not necessarily interchangeable or comparable. Some studies are done in hospice patients who differ from those not in hospices.

Few data show how pain is actually managed.

This study aimed to provide additional data on the experience of pain in terminally ill patients.

Conclusion: Although half of terminal patients experienced moderate to severe pain, only 30% of them wanted additional pain treatment. The number of patients experiencing pain remains too high, but is not as large as perceived. Most patients are willing to tolerate pain to avoid the perceived downside of opiates.

STUDY

1. Interviewed over 950 terminally ill patients. Asked whether they wanted more pain medication, or why they did not want more.

RESULTS

1. Half the patients reported moderate or severe pain
2. Of those treated in primary care, 30% wanted more pain therapy; 60% wanted their therapy to remain the same; 10% wanted the therapy decreased or stopped.
3. Reasons for not wanting additional therapy included: fear of addiction; dislike of mental or physical side effects; not wanting to take more pills or injections.
4. There was no association between disease and the amount of pain; no association between the disease and the desire for more treatment.
5. Black patients were more likely to seek more pain therapy, but also to fear addiction.

DISCUSSION

1. Although the extent of pain at the end of life has received much attention as a sign of poor end-of-life care, such a conclusion is questionable. The results showed that less than a third of patients with moderate to severe pain wanted additional therapy.
2. This contrasts with the perception that despite the availability of effective analgesics, pain among terminally ill patients is undertreated. The number of terminally ill patients in substantial pain is indeed too high, but the number is not as large as perceived.
3. Most patients were willing to tolerate pain. Among dying patients, other factors were often more important than pain relief. We should not focus merely on pain. The prevalence of pain might *not* be the best outcome measure for the assessment of the quality of end-of-life care.
4. About a third of terminally ill patients cited aversion to the side effects of opioid analgesia – constipation and confusion – as the primary reasons for not wanting to increase treatment. In many cases patients were willing to tolerate pain to avoid troublesome side effects.
5. Fear of addiction was reported in about one third of patients. “Therefore, physicians must communicate more effectively that addiction to opioids given for pain relief is a myth, and remove this belief as a barrier to adequate analgesia. Medical use of opioid analgesics is unrelated to increase in addiction or abuse.”

6. Patients of ethnic minorities have more reported pain. They are more likely to receive inadequate amounts of analgesia than white persons. Barriers include poor access to medication and inadequate prescribing, as well as fear of addiction.
7. Patients with non-cancer disease experience substantial pain at the end of life. It is a prevalent misconception that pain at the end of life is greater in patients with cancer than with other diseases. In reality, pain is prevalent in those with heart disease, chronic obstructive pulmonary disease, and other illnesses. Cardiologists, pulmonologists, and other specialists should receive adequate training in pain management.

CONCLUSION

Although half of terminally ill patients experience moderate to severe pain, only 30% of these wanted additional pain treatment. The number of patients experiencing pain remains too high, but the number is not as large as perceived. The experience of pain is constant across major terminal diseases.

Many patients are willing to tolerate pain for fear of addiction; dislike of mental or physical side effects; not wanting to take more pills or injections.

Lancet April 28, 2001; 357: 1311-15 Original investigation, first author Stefan C Weiss, National Institutes of Health, Bethesda, MD **www.thelancet.com**

Comment

**1** " A Controlled Trial to Improve Care for Seriously Ill Hospitalized Patients" JAMA 1995; 274: 1591-98

**2** "Pain" is too narrow a term to describe the discomfort of terminal life. "Suffering" is a more inclusive term which includes pain, but also includes fear, loneliness, being unforgiven, feeling of inadequate closure.

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**4-16 RISK OF FRACTURE IN WOMEN WITH LOW SERUM LEVELS OF THYROID-STIMULATING HORMONE**

Osteoporotic fractures are associated with florid hyperthyroidism. What about the effect of excess endogenous thyroid hormone (subclinical hyperthyroidism) or higher than necessary exogenous thyroid hormone dosage on risk of osteoporotic fracture?

This study examined the association between low levels of the pituitary thyroid-stimulating hormone (TSH) and risk of fracture in older women.

Conclusion: In women over age 65, a low serum TSH was associated with increased risk of fracture.

STUDY

1. Prospective cohort study followed over 650 women over age 65. (Mean age = 73)
2. At baseline, measured calcaneal bone mass, performed spine radiography, and determined history of thyroid disease.
3. Measured TSH at baseline. (Low TSH, indicating increased thyroid function, considered if under 0.1 mIU/L.) (Normal = 0.5 to 5.5)
4. Follow-up = mean of 3.7 years for evidence of new fractures.

RESULTS

1.About 11% of patients were currently using thyroid hormones. This accounted for 86% of the low TSH levels in the cohort.

2. TSH levels were low in about 9% of those with fractures; and in about 3% of those with no fracture.
3. After adjustment for possible confounders, women with a low TSH had a three-fold increased risk of new hip fracture and a four-fold increased risk of new vertebral fracture compared with women with normal TSH.
4. A history of hyperthyroidism was independently associated with a two-fold increase in hip fracture, even after adjustment for TSH levels and bone mineral density.

DISCUSSION

1. In this cohort, most women over age 65 with a TSH of 0.1 mIU/L or less were taking thyroxine medication.
2. Those with low TSH levels had a significantly increased risk of new hip and vertebral fractures.
3. The risk for vertebral fracture was also significantly elevated among women with borderline low TSH (0.1 to 0.5).
4. Biochemical markers of bone turnover were elevated in women with low TSH. This reflects the increased skeletal remodeling caused by excessive thyroid hormone.
5. Those receiving thyroid hormone therapy whose dose is too large (as indicated by a low TSH) should have the dose reduced. Level of TSH should be carefully maintained in the normal range.
6. Use of suppressive doses of thyroid hormone for benign conditions should be reconsidered in light of the adverse skeletal consequences of low TSH.

CONCLUSION

Older women with biochemical evidence of physiological hyperthyroidism (low TSH), mainly due to too high doses of exogenous thyroxine, but also due to endogenous "subclinical hyperthyroidism", had an increased risk of hip and vertebral fracture.

Annals Int . Med April 3,2001; 134: 561-68 Original investigation by the Study of Osteoporotic Fractures Research Group, first author Douglas C Bauer, University of California, San Francisco. **www.annals.org**

Comment:

This is a practical clinical point. TSH is being determined frequently in older patients. Subclinical hypo- and hyper-thyroidism are common.

Patients with hyperthyroidism, be it subclinical, clinical, endogenous or exogenous, are at increased risk of osteoporosis. The prevalence of endogenous subclinical hyperthyroidism in elderly women is moderately high. The numbers of patients taking thyroid supplements is higher still. These older patients should receive bone-sparing therapy — calcium and vitamin D supplements; estrogens or raloxifene or bisphosphonates — and weight bearing activity. Dosage of thyroxine must be carefully monitored. RTJ

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**4-17 "HIGH" EAR PIERCING AND THE RISING INCIDENE OF PERICHONDRITIS OF THE PINNA.**

Multiple piercing of the ear has become increasingly fashionable. Often this involves "high" piercing, which requires puncture through the cartilage of the upper third of the pinna. Infection at this site results in auricular perichondritis. The usual infective agent is *Pseudomonas aeruginosa*.

An associated subperiosteal abscess often leads to loss of cartilage, and unsightly deformity known as "cauliflower ear". The chance of good reconstruction is poor.

The authors present three cases (with illustrations ) in which perichondritis and abscess formation was associated with high piercing. Despite prompt intervention, including drainage under general anesthesia, cosmetic deformity proved difficult to avoid. The abscess peels the perichondrial layer off the cartilage. Since the cartilage derives its nutrition by diffusion from the perichondrium, necrosis and structural deformity follow.

Early treatment should focus on eradicating *P aeruginosa* and *Staphylococcus aureus*. (Eg, oral ciprofloxacin)

A survey in Greater Manchester found that almost all local general practitioners had treated complications of body piercing – mainly infections. Children as young as 6 were having their navels, ears, and noses pierced.

BMJ April 14, 2001; 322: 906-07 Original investigation, first author Junaid Hanif, University Hospital of Wales, Cardiff.
**www.bmj.com/cgi/content/full/322/7292/906**

Old timers recognize "cauliflower ear" as a complication of ear trauma due to wrestling and boxing.

I wish the authors had commented and explained to me the root cause of why young persons pierce their bodies. RTJ

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**4-18 TAKE HOME NALOXONE AND THE PREVENTION OF DEATHS FROM OPIATE OVERDOSE**

Should persons suffering from opiate dependence, their friends, or families be given take-home naloxone (*Narcan*) to be used in case of overdose? A survey of drug users has shown extensive support for such use.

This article describes two pilot schemes to provide naloxone.

One, the Berlin project, supplied naloxone to drug users beginning in 1999. A mobile van offered training in emergency resuscitation after overdose. Two 400 ug ampoules of naloxone were supplied along with needles, syringes, and an information handbook. After 16 months, 29 individuals had received emergency naloxone. All survived. Sudden onset of opiate withdrawal occurred in 1/3 of patients. No other adverse effect was noted. In only one case (cocaine overdose) was the drug considered inappropriate.

Ready prepared syringes of naloxone cost about $10. Naloxone can be given more quickly intramuscularly. This results in rapid, but less violent recovery than when given iv.

The article reports two anecdotes in which the drug saved lives.

BMJ April 14, 2001; 322: 895-96 Commentary, first author Kerstin Dettmer, Fixpunkt e V Mobilex, Berlin Germany
**www.bmj.com/cgi/content/full/322/7292/895**

Comment: Naloxone has no opioid or agonist activity. I can think of no other drug which acts more rapidly or dramatically.

This life-saving treatment should not be denied these uncured, and perhaps uncurable individuals.

We cannot abandon compassionate care of those who cannot or will not care for themselves. RTJ

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**4-19 ANTIBIOTIC DATABASE LAUNCHED**

Johns Hopkins has a free to all peer reviewed database presenting the latest information on antibiotics and infectious diseases. (www.hopkins-abxguide.org). This is in part due to rising worldwide concerns about inappropriate use and antibiotic resistance

It offers diagnostic criteria and drug options.

It is continually updated to reflect the best available information. Emergency alerts will be available immediately.

It contains information on over 160 drugs and 140 diseases.

BMJ April 14, 2001; 322: 881 "News" by David Spurgeon, Quebec **www.bmj.com/cgi/content/full/322/7292/881**

Comment:

I easily accessed this web site. It provides searches by diagnosis, by pathogen, and by antibiotic. The service is free, but registration is necessary.

The first web page I encountered presented a helpful guideline for management of adults with community-acquired pneumonia. (posted 6/25/01)

Certainly worth accessing periodically. RTJ

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**4-20 A NEW WEB SITE AND A NEW POLICY**

The NEJM's web site has been changed from www.nejm.com to www.nejm.org. An improved search system makes it possible to search the full text of all NEJM articles as far back as 1993.

The new web site also makes it possible to search more than 240 medical and scientific journals hosted in Stanford University's *High Wire Press*, including 8 of the journals most often cited by NEJM.

Beginning six months after publication, the full text of all original articles and special articles will be available on line *free of charge*. For non-subscribers, a brief one-time registration is required to gain access and to receive the contents each week by e-mail. However, non-subscribers no longer have free access to editorials, "Sounding Board" articles, and letters to the editor. The web site will recognize the password of subscribers to NEJM who have registered previously.

This new policy relates to the steps takes by the National Institutes of Health to create a public repository for the full texts of articles from biomedical journals (http://pubmedcentral.nih.gov). It should be possible someday to establish a single searchable archive of biomedical research reports in a way that does not threaten the peer-reviewed journals that help create the literature.

NEJM May 31, 2001; 344: 1710-11 Editorial, first author Edward W Campion, NEJM staff. **www.nejm.org**

Comment:

I congratulate NEJM for taking this most important step, following the lead of BMJ. . I am sure other journals will follow. The new access provided will allow individuals and libraries around the world to access articles of importance at essentially no cost. The 6-month delay will be a relatively minor disadvantage. Developing countries are eager to access the best of Western Medicine. This will add to the efforts to foster peace and mutual understanding between nations throughout our world. RTJ