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EDITED BY RICHARD T. JAMES JR. MD

400 AVINGER LANE, SUITE 203

DAVIDSON NC 28036 USA

Rjames6556@aol.com

www.practicalpointers.org

HIGHLIGHTS AND *EDITORIAL COMMENTS* APRIL 2004

4-1 CORTICOSTEROID INJECTIONS FOR OSTEOARTHRITIS OF THE KNEE

This is the first meta-analysis aimed to determine the efficacy of intra-articular corticosteroids. Are intra-articular injections of corticosteroids more efficacious than placebo in improving symptoms of OA of the knee? How long does the beneficial effect last?

Six short-term studies showed a significant improvement. The pooled relative benefit (steroid *vs* placebo injection) was 1.6 with the number needed to treat to obtain improvement in one patient = between 1.3 and 3.5. No important harms were reported other than transient redness and discomfort. Only one of the 6 studies investigated potential loss of joint space and found no difference between corticosteroid and placebo up to 2 years.

Two longer-term, high-quality trials reported a relative benefit of 2.1 with a NNT to benefit one patient in 4.4 over 16 to 24 weeks. One study investigated potential loss of joint space and found no difference between corticosteroid and placebo up to 2 years. This study used higher dose triamcinolone (40 mg—equivalent to 50 mg prednisone) than most others studies and also gave repeated injections (every 3 months for 2 years). No difference in loss of joint space over 2 years. "Currently, no evidence supports the promotion of disease progression by steroid injections.. Repeat injections seem to be safe over two years." This requires confirmation.

Evidence supports short term (up to two weeks) improvement in symptoms of OA of the knee after corticosteroid injections. Significant improvement was also shown in the only methodologically sound studies addressing longer term use. Multiple doses of the equivalent of 50 mg prednisone may be needed to show benefit at 16-24 weeks.

The data regarding high doses of corticosteroid, repeated periodically, may encourage some clinicians to increase the dose. I believe many physicians are reluctant to recommend multiple high-dose injection for fear of further damaging the joint. The report that high-dose repeated injections over 2 years did not lead to further damage is interesting and reassuring. This is an important clinical point which urgently requires confirmation. I believe there is currently concern that joint damage does occur after repeated injections. If this is not the case, many patients would benefit from repeated injections of higher dose steroids, and would welcome a delay in the need for knee replacement RTJ

4-2 PHARMACOLOGIC LIPID-LOWERING THERAPY IN TYPE 2 DIABETES

Most adverse outcomes from diabetes are due to vascular complications, either micro-vascular or macro-vascular. Macro-vascular complications are more common and severe. Up to 80% of patients with type 2 diabetes **(DM2)** will develop or die of macrovascular disease. Associated costs are 10 times greater than for microvascular complications.

The foremost goal of therapy in type 2 diabetes should be prevention of cardiovascular disease through optimization of risk factors. This includes aggressive treatment of hypertension, lipid-controlling therapy, smoking cessation, and use of daily aspirin.

Current evidence suggests that lipid control leads to about a 25% reduction in major cardiovascular events.

For primary prevention (statins vs no statin in patients without established cardiovascular disease) the NNT over 4 years to prevent one cardiovascular event = 35; for secondary prevention the NNT = 14 to prevent one event over 5 years.

"Given the absolute risk reductions observed, treatment will probably be cost-effective under most circumstances." This simplifies and reduces the cost of treatment and would be similar, for example, to simply prescribing a daily aspirin for a patient with diabetes."

This study presents a simplifying common- sense clinical approach. for primary care. We need more guidelines like this. RTJ

4-3 INTENSIVE VERSUS MODERATE LIPID LOWERING WITH STATINS AFTER ACUTE CORONARY SYNDROMES

Enrolled over 4000 patients (mean age 58) who had been hospitalized for an acute coronary syndrome (ACS) within the preceding 10 days. ACS defined as acute myocardial infarction (with or without ECG evidence of ST-elevation), or high risk unstable angina.

Randomized to: 1) moderate-intensity treatment with 40 mg pravastatin (*Pravachol*), or 2) high-intensity treatment with 80 mg atorvastatin (*Lipitor*) daily.

Mean achieved LDL-cholesterol was 95 mg/dL in the pravastatin group and 62 in the atorvastatin group

Over 2 years, the more intensive regimen with atorvastatin resulted in a lower risk of death and major cardiovascular events as compared with the moderate pravastatin regimen. The NNT for 2 years to prevent one death, myocardial infarction, angina requiring rehospitalization, revascularization, or stroke = 53

"Although prior placebo-controlled studies have shown that a standard-dose statin is beneficial, we demonstrated that more intensive lipid-lowering significantly increases this clinical benefit."

Although both drugs were "generally well tolerated", there were significantly more liver-related side effects with high-dose atorvastatin. About 1/3 of all patients in both groups dropped out over the 2 years.

"Our results suggest that after an acute coronary syndrome, the target LDL-cholesterol level may be lower than that recommended in the current guidelines."

This was a secondary prevention trial in a very high risk group. Benefits would be considerably less if high-dose atorvastatin were used in primary prevention. Certainly, these results cannot be extrapolated to primary prevention.

The authors suggest that the high-dose regimen "significantly" increased clinical benefit. Primary care clinicians must ask - is this "clinical" benefit applicable to every day practice? Patients with an acute coronary syndrome and their doctors must decide if one chance in 53 over 2 years is worth while, Note that harms (liver disturbance) were statistically significant, and, I believe, as clinically significant as the reported benefits in the high-dose patients. Cost, adverse effects, and likelihood of discontinuation of treatment must be considered. Some patients, knowing they are at very high risk of death or recurrence, would be inclined to accept the high-dose.

The high drop-out rate because of an adverse event, or the patient's preference, or "other reasons" is disturbing. This occurred despite patients' knowledge that they were at high risk of recurrence and death. Drop-outs would likely be higher still in primary care practice.

Pravastatin has the advantage of not being significantly metabolized by the P450 system in the liver. Thus, concerns about interactions between pravastatin and concomitantly administered drugs is much less than with atorvastatin, which is metabolized by the P450 system. RTJ

4-4 EFFECTS OF CONJUGATED EQUINE ESTROGEN IN POSTMENOPAUSAL WOMEN WITH HYSTERECTOMY

This study reports the conjugated equine estrogen (**CEE**)-alone phase of the Women's Health Initiative trial which was continued for 7 years.

The burden of incident disease events was equivalent in the CEE-alone and placebo groups. There was no significant difference in risks other than a slight increase in incidence of stroke. The absolute *excess* was 12 additional strokes per 10 000 person-years. And an absolute *reduction* of hip fracture of 6 per 10 000 person-years.

The estimated excess risk for all monitored events (CHD, stroke, pulmonary embolism, colorectal cancer, hip fracture, and deaths from other causes). was a non-significant 2 events per 10 000 person-years.

This differs importantly from the WHI trial of combined estrogen/progestin in which the risk of CHD was significantly elevated.

Women and their health-care professionals now have usable risk estimates for the benefit/harm ratio of CEE-alone in treatment of menopausal symptoms. "Women can be reassured that incidence of CHD and breast cancer is not increased at least for 6.8 years". But, the data reinforce that there is no overall benefit of CEE for chronic disease prevention.

Nevertheless, CEE-alone *cannot* be recommended for disease *prevention*. CEE should be used only for menopausal symptoms at the smallest effective dose for the shortest possible time.

The study reported a lower risk of breast caner in the CEE-alone group vs the placebo group. This is contrary to other observational studies in which risk of BC is increased. I believe clinicians should remain wary and should consider that HRT in any form increases risk of breast cancer.

I believe risks of CEE-alone as well as combined estrogen/progestin have been overemphasized, and that many women are being unnecessarily denied relief from their menopausal symptoms. RTJ

4-5 EFFECT OF VITAMIN D ON FALLS

This meta-analysis of randomized, controlled trials concludes that vitamin D supplementation reduces risk of falling in elderly persons. Based on 5 of the trials in over 1200 persons, vitamin D, was associated with a reduction in rate of falls by 22%.

In two studies, vitamin D plus calcium (compared with calcium alone) improved body sway by 9% within 2 months, and increased muscle function up to 11%.

What is a possible mechanism**?** 1,25-hydroxyvitamin D, the active metabolite, binds to a highly specific nuclear receptor in muscle tissue. This may mediate de novo protein synthesis through this specific nuclear receptor leading to an increase in the number, size and strength of muscle fibers. This benefit may occur within several months. (Too early to be attributed to increased bone strength.)

I considered this a weak study, but interesting. If indeed vitamin D strengthens muscle and thus prevents falls, its benefit/harm-cost ratio (which is already high.) will be substantially increased.

Vitamin D and calcium intake is generally too low in the US population. I believe that supplementation is warranted in persons of all ages to help maintain bone mass and strength. If muscles are strengthened, so much the better. RTJ

4-6 ALCOHOL INTAKE AND RISK OF INCIDENT GOUT IN MEN

Health Professionals Follow-up Study followed over 47 000 male subjects (mean age 55 at baseline) for 12 years. None had gout at baseline.

Compared with men who did not drink alcohol, the relative risk (RR) of incident gout increased linearly as consumption rose from 1 drink daily (RR compared with none = 1.3) to 2.5 in those imbibing 5 or more drinks daily.

Beer consumption showed the strongest independent association with risk of gout. The RR per each 12 ounce serving per day = 1.49 (Beer is the only alcoholic beverage that contains a large amount of purine.) Consumption of spirits was also associated with increased risk. (RR per each drink daily = 1.15.) Wine consumption was *not* associated. (RR = 1.04 for each 4-ounce serving daily.) The null association persisted regardless of the type of wine.

Risk of gout was greater in men with a body mass index (BMI) over 25 compared with a BMI under 25: In subjects with a BMI under 25, RR of gout was 2.5 in heavy drinkers. In subjects with BMI over 25, RR increased to 5.6.

"Prospective data indicate that alcohol intake is strongly associated with incidence of gout. The risk varies substantially with the type of alcoholic beverage. Beer confers the greatest risk, moderate wine drinking does not increase risk."

See Practical Pointers March 2004 3-10—an investigation by the same authors as the above study.

Both genetic and environmental factors play a part in the pathogenesis of gout. As with atherosclerotic disease, hypertension, obesity, and type II diabetes, gout can be considered a disease of "civilization"—part of the epidemic of overnutrition and sedentary lifestyles. Gout is associated with a high intake of meat and seafood, and low intake of dairy products.. Now this study reinforces the long-observed relation with alcohol.

As with obesity, gout is becoming more prevalent in developing countries as they become more "Westernized" .I have read that there are more obese persons in the world now than hungry persons. RTJ

4-7 SYSTEMATIC REVIEW OF TOPICAL CAPSAICIN FOR THE TREATMENT OF CHRONIC PAIN

Selected 6 randomized, double-blind, placebo controlled trials (656 patients) which compared topically applied capsaicin (0.075%) with placebo in adults with neuropathic conditions. And 3 trials (368 patients) of capsaicin (0.025%) in patients with musculoskeletal conditions. Capsaicin was applied 3 times daily

Patients had moderate or severe chronic pain.

Primary outcome = number of patients with at least 50% reduction in pain.

At 8 weeks, for those with neuropathic pain the relative benefit of capsaicin *vs* placebo was 1.4. NNT = 6. (Ie, one of 6 patients would achieve a reduction in pain of 50%.) At 4 weeks, for those with musculoskeletal pain, the relative benefit of capsaicin *vs* placebo was 1.5. NNT = 8.

There was a substantial response to placebo—25% to 42%.

Topical capsaicin maybe useful as an adjunct or sole therapy for a small number of patients who are unresponsive to, or intolerant of, other treatments.

"Systematic Review of Topical Rubifacients Containing Salicylates for the Treatment of Acute and Chronic Pain", a companion article in this issue of BMJ (pp 995-98), reports efficacy for musculoskeletal pain was moderate to poor. Adverse effects were rare. There was, however, a lack of good clinical trials.

I believe, in some patients topical applications may be helpful. No way to find out without trying. First inform the patient about possible benefits and harms. Over-the-counter availability is a plus. The placebo effect is an added benefit. RTJ

4-8 ABC OF SMOKING CESSATION: HARM REDUCTION

Smoking is primarily a nicotine-seeking behavior.

For individuals addicted to nicotine, cutting down, switching to "low tar" cigarettes, and switching to pipe or cigars do not reduce risk.

There is good evidence that use of smokeless tobacco is less risky than cigarettes.

The technology to develop safe, inhaled forms of nicotine that could provide a more satisfactory alternative to cigarettes is available. In the current regulatory framework, such products would not be licensed and therefore are not commercially available. "This imbalance in the regulation of nicotine needs to be redressed urgently in favor of public health."

Should primary care clinicians advocate their patients who are recalcitrant smokers to judiciously use nicotine replacement in conjunction with cigarette smoking? My PDR (specifically for Nicortol inhaler) states that patients should be urged to stop smoking completely while using this product. Adverse effects may occur due to high peak nicotine levels. I believe this statement by the drug manufacturer is primarily a defense against litigation.

Should we advise switching to snuff?

Would it be reasonable to encourage manufacture of very high-content nicotine cigarettes? This could easily be done.

These approaches open legal difficulties. We are still constrained by outside forces from applying the best medical care possible. RTJ

4-9 ASYMPTOMATIC PRIMARY HYPERPARATHYROIDISM

The diagnosis of AHP is made on the basis of a combination of elevated total serum calcium + an inappropriately elevated PTH.

Most patients with AHP who do not meet the criteria for surgery do well, with no evidence of progressive disease. In most patients, the average serum and parathyroid hormone levels do not change over 10 years. And BMD is typically stable. Hypercalciuria usually does not worsen. Younger patients (< age 50) are more likely to progress.

Criteria of parathyroid surgery (cutoff points):

Serum calcium	1.0 mg/dL above upper normal
24-hour calcium	> 400 mg
Reduction in creatinine clearance	30%
Bone mineral density	T score below -2.5 (Radius is particularly vulnerable)
Age	Under 50

Surgery is routinely warranted in patients with kidney stones.

Many patients with AHP will not require surgery. Patients who do not meet the criteria for surgery should be monitored periodically (serum calcium, creatinine clearance, and BMD) because about 25% of patients will progress.

To advise surgery or advise continued surveillance is a clinical call. It depends on patient preference and individual circumstances. If expert surgery is available, I would tilt toward surgery. This would relieve the patient of continuing concerns. RTJ

4-10 MINIMALLY INVASIVE PARATHYROIDECTOMY

The arrival of tecnitium-99m sestamibi scanning revolutionized preoperative localization of parathyroid glands. It accurately identifies the side and size of the adenoma in 9 out of 10 cases.

Patients with reliably localized single adenomas may be treated with a minimal access approach. This is achieved through a 2 cm incision. It can usually be done as a day case procedure in less than 20 minutes with local anesthesia. It has become the first line treatment in specialized units.

Primary care clinicians, if they practice long enough, will encounter patients with asymptomatic HPT. The advent of minimalist surgery further tilts the decision toward operating. RTJ

4-11 EFFECTS OF TOLVAPTAN, A VASOPRESSOR ANTAGONIST, IN PATIENTS HOSPITALIZED WITH WORSENING HEART FAILURE

Levels of arginine vasopressin (**AVP**; the water-retaining hormone secreted by the pituitary) are increased in heart failure (**HF**). Water retention and hyponatremia result.

Tolvaptan is a non-peptide, orally administered, once daily vasopressin *antagonist*. It binds predominantly with the AVP receptor in the kidney, resulting in decreased renal vascular resistance, increased renal blood flow, improved glomerular filtration rate, and loss of free water. Rather than being classified as a traditional diuretic, tolvaptan is more precisely characterized as an *aquaretic*.

This study assessed the clinical effectiveness of tolvaptan in patients hospitalized for HF.

Tolvaptan, given *in addition* to standard therapy (including diuretics) resulted in a greater net volume loss *vs* placebo. It produced a rapid and sustained increase of serum levels of sodium (due to loss of free water) in patients with hyponatremia.. It did not adversely affect BP, heart rate, electrolyte levels, or renal function

When I started to study medicine, the treatment of HF consisted of rest, digitalis pills, salt restriction, and the intramuscular mercury-containing diuretic, mercuhydrin. (How many out there remember mercuhydrin?)

Therapeutic advances have been remarkable—beta-blockers, ACE inhibitors and angiotensin II blockers, spirinolactone, and loop diuretics, as well as use of low-dose digoxin. Nevertheless, prognosis of patients with HF remains poor. These newer drugs are really "rear guard" therapies. It may well be that the main benefit of vaptans is symptomatic relief. Lessening dyspnea and edema may make patients more comfortable. Certainly, vaptans will make therapy easier by reducing worry about hyponatremia, hypokalemia, and renal dysfunction.

Note, the study assessed only systolic HF. The large issue of diastolic HF remains.

Primary care clinicians stay tuned. RTJ

4-12 COMPUTED TOMOGRAPHIC COLONOSCOPY (VIRTUAL COLONOSCOPY)

This study assessed the accuracy of CTC *vs* conventional colonoscopy in a large number of participants.

45% to 61% of the lesions were missed by CTC. (False negative tests.) 10% of the CTC patients were diagnosed falsely as having a 6 mm or larger lesion. (False positive tests)

Accuracy to CTC varied considerably between centers.

Patients expressed no clear preference for either technique.

CTC is not yet ready for widespread clinical application.

I abstracted this article mainly because enthusiasts in local communities are investing in costly scanners and advertising CTC to the general public as well as to professionals.

A study abstracted in Practical Pointers December 2003 (12-10) reported the experience of the Uniformed Services University of Health Sciences. This group has had considerable experience with CTC, and uses sophisticated equipment. They claimed that CTC detects polyps of 6 mm or larger as accurately as conventional colonoscopy. If a polyp of this size is detected, conventional colonoscopy is required to remove it.

A critical issue remains. Should all polyps detected be referred for conventional colonoscopy? If not, what is the cut-point size? How should smaller polyps be followed? Patients with smaller polyps (not removed) would be required to undergo screening at shorter intervals than patients whose polyps are removed.

As noted, the bowel-cleansing preparation is the same in both procedures. In observational studies, arrangements for immediate conventional colonoscopy can be made beforehand. In usual practice settings, many patients would require a second bowel cleansing.

I do not believe community-based primary care clinicians should advocate CTC at this time. RTJ

4-13 DUCTAL CARCINOMA IN SITU OF THE BREAST: Review Article

Prevalence of DCIS has markedly increased since screening mammography has become routine (one case detected for every 1300 screening mammograms).

DCIS consists of the clonal proliferation of cells that appear malignant and that accumulate within the lumens of mammary ducts. There is no evidence of invasion beyond the epithelial basement membrane into the adjacent breast stroma. It is a precursor of invasive ductal carcinoma.

The crucial task of pathological assessment is to distinguish DCIS from invasive cancer. Classification remains a challenge due to differing pathologic criteria, interobserver variability, and the heterogeneous nature of tumor growth.

The natural history of *untreated* low-grade DCIS has been defined in long-term, follow-up studies of women who underwent diagnostic biopsy in the era before widespread screening mammography. After 10 years of follow-up, 14 to 60 percent of the women had received a diagnosis of invasive cancer in the affected breast. Such a risk is widely thought to justify the present treatment approaches.

Simple mastectomy is highly effective—curing at least 98% of lesion—and is a potential treatment option for all patients.

Women with DCIS in one breast are at risk for a second tumor (either invasive or in situ) in the contralateral breast—about 0.5% to 1% per year. This warrants follow-up mammography in the opposite breast.

Women with DCIS have considerable deficits in their knowledge of the disease. Their levels of psychological distress and fear of recurrence and death are similar to those among women with invasive breast cancer.

Because incidence of DCIS is related to hormone replacement therapy, and is benefited by tamoxifen, I would guess that aromatase-inhibitor therapy would be efficacious. Undoubtedly, studies will be forthcoming.

The generally favorable prognosis should be emphasized. Women with DCIS should be repeatedly reassured. This is an important responsibility for primary care clinicians. RTJ

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Evidence Of Longer Term Symptomatic Improvement—Up To 24 Weeks

4-1 CORTICOSTEROID INJECTIONS FOR OSTEOARTHRITIS OF THE KNEE

Osteoarthritis **(OA)** is the single most common cause of disability in older adults. Ten percent of patients age 55 or more have painful disabling OA of the knee. Of these, ¼ are severely disabled. Treatment (other than knee replacement) is directed at pain relief and improving function.

Intra-articular corticosteroid injection is a common treatment. Clinical evidence suggests that benefit is short lived, usually one to four weeks. Some rheumatologists, however, report a sustained response.

Clinical trials usually report outcomes from only one injection given at a dose lower than recommended by the Am. Coll. of Rheumatologists (equivalent to 40 mg triamcinolone).

Concern has been expressed about possible joint destruction and tissue atrophy following repeated injections. Studies of cartilage damage, however, tend to suggest that changes are more likely due to the underlying disease than the steroid.

This is the first meta-analysis aimed to determine the efficacy of intra-articular corticosteroids. Are intra-articular injections of corticosteroids more efficacious than placebo in improving symptoms of OA of the knee? How long does the beneficial effect last?

Conclusion: Short term improvement (up to 2 weeks) occurs following injection. There is also evidence of longer term symptomatic improvement. .

STUDY

1. Systematic review found 10 controlled trials which compared efficacy of intra-articular injections (corticosteroid *vs* placebo).. The patients seemed to have mainly mild to moderate OA.
2. Terms of improvement were patient oriented: distinct improvement, subjective improvement, decreased pain, overall improvement, and response to an OA research scale.

RESULTS

1. The equivalent prednisone dose varied from 6 mg to 80 mg.
2. Six studies showed a significant improvement. The pooled relative benefit (steroid *vs* placebo injection) was 1.6 with the number needed to treat to obtain improvement in one patient = between 1.3 and 3.5. No important harms were reported other than transient redness and discomfort. Only one of the 6 studies investigated potential loss of joint space and found no difference between corticosteroid and placebo up to 2 years.
3. The pooled results of 2 high quality trials gave a relative benefit of 2.1 with a NNT to benefit one patient in 4.4 over 16 to 24 weeks.
4. The one study that investigated potential loss of joint space found no difference between corticosteroid and placebo up to 2 years. This study used higher dose triamcinolone (40 mg—equivalent to 50 mg prednisone) than most others studies and also gave repeated injections (every 3 months for 2 years).

DISCUSSION

1. "Intra-articular injections of corticosteroids improve symptoms of osteoarthritis." Most trials reported benefit up to two weeks. Two trials reported improvement up to 16 to 24 weeks. "This is the first review to show benefits of such injections in improvement of symptoms, which may extend beyond 16 weeks."
2. The dose of corticosteroid required to improve symptoms is not clear. Doses in the studies varied considerably. Higher doses may give longer benefit. A dose equivalent to 25 mg prednisone seems to be efficacious for pain control for 2 weeks. Only one study used 40 mg triamcinolone and found benefit at 24 months. It used multiple injections (every 3 months for 2 years). No difference in loss of joint space over 2 years.
3. "Currently, no evidence supports the promotion of disease progression by steroid injections.. Repeat injections seem to be safe over two years." This requires confirmation.

CONCLUSION

Evidence supports short term (up to two weeks) improvement in symptoms of OA of the knee after corticosteroid injections. Significant improvement was also shown in the only methodologically sound studies addressing longer term use. Multiple doses of the equivalent of 50 mg prednisone may be needed to show benefit at 16-24 weeks.

BMJ April 10, 2004; 328: 869-70 Meta-analysis, first author Bruce Arroll, University of Auckland, New Zealand.

The April 10 article was abridged, based on the unabridged version at doi:10.1136/bmj.38039.573970.7C

Comment:

The data regarding high doses of corticosteroid, repeated periodically, may encourage some clinicians to increase the dose. I believe many physicians are reluctant to recommend multiple high-dose injection for fear of further damaging the joint. The report that high-dose repeated injections over 2 years did not lead to further damage is interesting and reassuring. This is an important clinical point which urgently requires confirmation. I believe there is currently concern that joint damage does occur after repeated injections. If this is not the case, many patients would benefit from repeated injections of higher dose steroids, and would welcome a delay in the need for knee replacement RTJ

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Pop A Statin Along With Your Daily Aspirin

4-2 PHARMACOLOGIC LIPID-LOWERING THERAPY IN TYPE 2 DIABETES

Most adverse outcomes from diabetes are due to vascular complications, either micro-vascular or macro-vascular. Macro-vascular complications are more common and severe. Up to 80% of patients with type 2 diabetes **(DM2)** will develop or die of macrovascular disease. Associated costs are 10 times greater than for microvascular complications.

Although controlling hyperglycemia is beneficial, modifying cardiovascular risk by lipid-lowering and by treating hypertension is more clinically effective and cost effective.

This systematic review evaluated the effectiveness of pharmacologic lipid-lowering on outcomes in patients with DM2.

Conclusion: The great majority of patients with DM2 benefit from statin drugs.

STUDY

1. Selected randomized trials which evaluated clinical outcomes of lipid-lowering treatment in patients with diabetes.
   A. Meta-analysis of 6 primary prevention studies.
   B. Meta-analysis of 8 secondary prevention studies.

RESULTS

1. Primary prevention: Relative risk (RR) of cardiovascular events (treated *vs* control) = 0.78. Absolute risk reduction = 3%. Number needed to treat over 4 years to prevent one event = 35.
2. Secondary prevention (patients with established coronary disese); RR of cardiovascular events = 0.75. Absolute risk reduction = 7 %. NNT for 5 years to prevent one event = 14.
3. Most studies did not evaluate the effect of reaching a specific cholesterol level.
4. The benefit of a fixed dose of a statin appeared to be similar regardless of the baseline cholesterol level.

DISCUSSION

1. The foremost goal of therapy in type 2 diabetes should be prevention of cardiovascular disease through optimization of risk factors. This includes aggressive treatment of hypertension, lipid-controlling therapy, smoking cessation, and use of daily aspirin.
2. Current evidence suggests that lipid control leads to about a 25% reduction in major cardiovascular events.
3. Moderate doses of statin drugs are beneficial. (Eg, 40 mg simvastatin or 40 mg pravastatin.)
4. Only one of the primary prevention studies, however, showed statistically significant benefit. The observed benefits were quite small or absent in patients who had low baseline risks of cardiovascular disease. The authors recommend caution in extrapolating the average results in primary prevention to patients with lower than average risk (such as young patients who have no other major risk factors).[1]
5. “Given the absolute risk reductions observed, treatment will probably be cost-effective under most circumstances.”
6. “The appropriate target for LDL-cholesterol levels remains, at best, poorly defined.” The NCEP guidelines state that patients with diabetes should start therapy if LDL-c levels exceed 130 mg/dL. “Currently available clinical trial data do not firmly support this specific approach.” This suggests that empirical use of statins in persons with diabetes with average or above average cardiovascular risk is much more important than the

baseline or target LDL-c level. "It could be argued that there is no strict definition of hyperlipidemia in patients with type 2 diabetes, since nearly the entire population qualifies for lipid-lowering treatment."

7. Setting an LDL-c level of less than 100 mg/dL rather than simply recommending moderated doses of statins for most or all patients with type 2 diabetes is difficult to justify.
8. Statins have lipid-independent effects. They may modulate cardiovascular risk by stabilizing plaques and by improving endothelial function. Thus, widespread use of at least moderate doses of statins may be more beneficial than dose titration.
9. "We do not feel that the evidence is sufficient to make strong recommendations of *primary* prevention therapy for people with diabetes who have relatively low cardiovascular risk."
10. "Considering the safety of statin drugs, routine monitoring of liver or muscle function is *probably* [2] not warranted unless patients have symptoms, have liver enzyme abnormalities at baseline[3], or are taking drugs that interact with the statins.[4] "This simplifies and reduces the cost of treatment and would be similar, for example, to simply prescribing a daily aspirin for a patient with diabetes."
11. Given the markedly elevated risk for cardiovascular events in people with type 2 diabetes, aggressive management of lipids provides substantial benefit, at least to average patients. 'The use of statins should be nearly universal in this population."

CONCLUSION

In patients with type 2 diabetes, treatment with lipid-lowering agents reduces cardiovascular risk . Most patients, including those whose baseline LDL-c is below 115 mg/dL and possibly below 100, benefit. Moderate doses suffice.

Annals Int Med April 20, 2004; 140: 650-58 "Clinical Guidelines", review article, first author Sandeep Vijan, Veterans Affairs Health Services Research and Development, Ann Arbor, MI.

Comment:

This study presents a simplifying common- sense clinical approach. for primary care. We need more guidelines like this.

The UK has just released a low-dose of simvastatin for over the counter availability. RTJ

1 *Since DM2 is a lifetime disease, young patients without major risk factors will evolve into older patients with risk factors, and thus be candidates for therapy.*

2 *The word "probably" is not reassuring I wish authors would not use it.*

3 *Would this suggest that liver enzymes should be routinely determined at baseline for all patients?*

4 *Pravastatin has the advantage of not being metabolized by the liver P450 enzyme system Drug interactions may be less common with this drug. RTJ*

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Target LDL-Cholesterol Level May Be Lower Than That Recommended In The Current Guidelines."

4-3 INTENSIVE VERSUS MODERATE LIPID LOWERING WITH STATINS AFTER ACUTE CORONARY SYNDROMES

Lipid-lowering with statins reduces risk of cardiovascular events. Benefits in reducing risk of death and cardiovascular events range across a wide range of cholesterol levels, and whether or not patients have a history of coronary heart disease (**CHD**). Current guidelines recommend a target LDL-c of less than 100 mg/dL for patients with established CHD or diabetes.

This study asked—What is the optimal level of LDL-cholesterol (LDL-c) after an acute coronary event?

Conclusion: Intensive LDL-c lowering with statin therapy below current target levels provided greater protection

STUDY

1. Enrolled over 4000 patients (mean age 58) who had been hospitalized for an acute coronary syndrome (ACS) within the preceding 10 days. ACS defined as acute myocardial infarction (with or without ECG evidence of ST-elevation), or high risk unstable angina. (Ie, a secondary prevention trial in a select, very high risk group.)
2. Randomized to: 1) moderate-intensity treatment with 40 mg pravastatin (*Pravachol*), or 2) high-intensity treatment with 80 mg atorvastatin (*Lipitor*) daily.
3. All continued to receive standard medical and interventional treatment for ACS, including aspirin.
4. Primary endpoint = death from any cause, myocardial infarction, documented unstable angina requiring re-hospitalization, revascularization, and stroke.
5. Follow-up = a mean of 24 months.

RESULTS

1. Median LDL-c levels achieved: pravastatin – 95 mg/dL; atorvastatin 62 mg/dL.

2. Outcomes at 2 years:	Pravastatin	Atorvastatin	Absolute difference	NNT
Primary end-point	26.3%	22.4%	1.9%	53
Discontinued treatment [1]	33%	30.4%		
Liver enzymes > 3 times normal	1.1%	3.3%	2.2%	45 (harm)

DISCUSSION

1. Over 2 years, the more intensive LDL-c lowering regimen with atorvastatin resulted in a lower risk of death and major cardiovascular events as compared with the moderate pravastatin regimen.
2. "Although prior placebo-controlled studies have shown that a standard-dose statin is beneficial, we demonstrated that more intensive lipid-lowering significantly increases this clinical benefit."
3. Part of the benefit from statin therapy may be due to stabilization of vulnerable plaques in the coronary arteries. This would be a reason for early intensive administration. [2]

4. Atorvastatin is metabolized by cytochrome P450 in the liver. This must be considered when the patient is receiving other drugs metabolized by the same system. [3]
5. Although both drugs were "generally well tolerated", there were significantly more liver-related side effects with high-dose atorvastatin. Patients in clinical practice generally have more co-existing conditions, and they might not tolerate a high-dose statin.
6. "Our results suggest that after an acute coronary syndrome, the target LDL-cholesterol level may be lower than that recommended in the current guidelines."

CONCLUSION

In patients with a recent acute coronary artery syndrome, an intensive lipid-lowering with atorvastatin regimen provided greater protection against both death and major cardiovascular events than a standard regimen with pravastatin. Early and continued substantial lowering of LDL cholesterol may benefit these patients.

NEJM April 8, 2004; 350: 1495-504 Original investigation by the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators (PROVE IT-TIMI 22)
Study supported by Bristol-Myers Squibb and Sankyo

Comment:

This was a *secondary* prevention trial in a very high risk group. Benefits would be considerably less if high-dose atorvastatin were used in *primary* prevention. Certainly, these results cannot be extrapolated to *primary* prevention.

The authors suggest that the high-dose regimen "significantly" increased *clinical* benefit. Primary care clinicians must ask—is this "clinical" benefit applicable to every day practice? Patients with an acute coronary syndrome and their doctors must decide if one chance in 53 over 2 years is worth while, Note that harms (liver disturbance) were statistically significant (and, I believe, as *clinically* significant as the reported benefits) in the high-dose patients. Cost, adverse effects, and likelihood of discontinuation of treatment must be considered. Some patients, knowing they are at very high risk of death or recurrence, would be inclined to accept the high-dose.

1 The high drop-out rate because of an adverse event, or the patient's preference, or "other reasons" is disturbing. This occurred despite patients' knowledge that they were at high risk of recurrence and death. Drop-outs would likely be higher still in primary care practice.

2 Benefits did not begin to emerge until about 3 months of therapy.

3 Pravastatin has the advantage of *not* being significantly metabolized by the P450 system in the liver. Thus, concerns about interactions between pravastatin and concomitantly administered drugs is much less than with atorvastatin, which is metabolized by the P450 system.

Cost becomes an important issue especially in drugs continued long-term or indefinitely:

www.dugstore.com quotes:	Lipitor 80 mg	$3.06 each
	Pravachol 40 mg	$3.88 each
	Pravachol 80 mg	$3.86 each

Thus, a pill cutter would reduce the cost of a 40 mg daily dose in half. Statins have a very favorable therapeutic index. (Ie, even if the pill is not cut exactly in half, a slightly higher dose on day one and a slightly lower dose on day two would make no difference in safety or efficacy.) RTJ

==========

Estrogen-Alone Is Safer Than Combined Estrogen/Progestin

4-4 EFFECTS OF CONJUGATED EQUINE ESTROGEN IN POSTMENOPAUSAL WOMEN WITH HYSTERECTOMY

The Women's Health Initiative **(WHI)** combined estrogen/progestin trial was halted in July 2002 after a mean 5.2 years of follow-up because health risks exceeded benefits. Risk of coronary heart disease (**CHD**), stroke, and venous thromboembolic disease were increased in women assigned to treatment with estrogen/progestin *vs* placebo. Breast cancer was also increased, while colon cancer and fractures were reduced.

This study reports the conjugated equine estrogen (**CEE**)-alone phase of the trial which was continued for another 2 years.

Conclusion: The burden of incident disease events was equivalent in the CEE and placebo groups. There was no significant difference in risks other than a slight increase in incidence of stroke. CEE cannot be recommended for disease *prevention*.

STUDY

1. Randomized, double-blind, placebo-controlled trial enrolled over 10 500 mostly healthy postmenopausal women (age 50-79; mean = 63) to assess effects of CEE-alone on incidence of major disease. All had a prior hysterectomy which permitted use of estrogen alone.
2. Randomized to: 1) CEE 0.625 mg daily, or 2) placebo.
3. Primary outcome = incidence of CHD (non-fatal myocardial infarction or CHD death). Incidence of breast cancer (**BC**) was the primary safety outcome.
4. A global index of risks and benefits summarized overall effects (CHD, stroke, pulmonary embolism, colorectal cancer, hip fracture, and deaths from other causes).
5. In February 2004, the National Institutes of Health decided to terminate the CEE-alone phase prior to its scheduled termination because there was no evidence of benefit, and a slight *increase* in the risk of stroke.
6. Follow-up was for a mean of 6.8 years.

RESULTS

1. Estimated hazard ration (HRs) —CEE *vs* placebo:

Coronary heart disease	0.91
Breast cancer	0.77**
Stroke	1.39*
Pulmonary embolism	1.34
Colorectal cancer	1.08

Hip fracture	0.61*
Total cardiovascular disease	1.12*
Total cancer	0.93
Total fractures	0.70*
Total mortality	1.04
Global index	1.01

(* statistically significant)

(** This reported reduction in risk of BC is contrary to previous reports.)

2. There was an absolute *excess* risk of stroke of 12 additional strokes per 10 000 person-years. And an absolute *reduction* of hip fracture of 6 per 10 000 person-years.
3. CEE did not significantly affect total mortality rates or cause-specific mortality.
4. The estimated excess risk for all monitored events in the global index was a non-significant 2 events per 10 000 person-years.
5. CHD was the only outcome with a statistically significant trend of slightly *elevated* hazard ratio in the *early* follow-up period that *diminished* over time. [1]
6. What about the effect of age at baseline? HR of colorectal cancer was statistically associated with advancing age. HRs for CHD, invasive breast cancer, hip fracture, total deaths, and global index *favored* CEE at age 50-59.[2]

DISCUSSION

1. CEE increased risk for stroke, reduced risk of hip fracture, but did not significantly affect incidence of CHD over a period of 6.8 years. This differs importantly from the WHI trial of combined estrogen/progestin in which the risk of CHD was significantly elevated.
2. The trend toward a reduction in BC incidence was unexpected, and is opposite that of the WHI estrogen/progestin trial which reported a 24% increased risk. This is also contrary to the results of the results of the preponderance of observational studies. [3]
3. In the current study, a small non-significant *increase* in CHD was observed in the first year of CEE exposure, but the cumulative effect suggests a possible modest *benefit* with longer term use. [1]
4. The observed adverse effect on the risk of stroke is consistent with the risks reported in the WHI estrogen/progestin trials.
5. This study provides strong evidence that CEE reduces risk of hip, vertebral, and other fractures.
6. In preliminary subgroup analyses, the estimated HRs for CEE, including the global index, were *lower* for women age 50-59. While these results suggest that CEE may be somewhat more favorable in younger women than in older women, subgroup analyses must be interpreted with caution.
7. Women and their health-care professionals now have usable risk estimates for the benefit/harm ratio of CEE-alone in treatment of menopausal symptoms. “Women can be reassured that incidence of CHD and BC is not increased at least for 6.8 years”. But, the data reinforce that there is no overall benefit of CEE for chronic disease prevention.

8. CEE should be used only for menopausal symptoms at the smallest effective dose for the shortest possible time.

CONCLUSION

The use of conjugated estrogen-alone increased the risk of stroke, decreased the risk of hip fracture, and did not affect CHD incidence over an average of 6.8 years. The burden of incident disease events was equivalent in the CEE and placebo groups, indicating *no* overall benefit. CEE should not be recommended for prevention of chronic disease.

JAMA April 14, 2004; 291: 1701-12 Original investigation by the Women's Health Initiative, multiple investigators, correspondence to Garnet L Anderson, WHI Coordinating Center, Seattle, Washington. www.jama.com

Comment:

1 *This is consistent with reports that risks are higher in the first year of HRT treatment. Observational studies have reported that after the first, most risky, year of use is passed safely, risks gradually decrease with continued use, and actually become low enough to negate adverse effects. This leads eventually to a null effect of HRT risk.*

2 *HRT is safer in younger women.*

3 *Despite this observation, I believe the preponderance of evidence leads to the conclusion that HRT and estrogen-alone increase risk of breast cancer. Combined estrogen/progestin increases risk more than estrogen-alone. Estrogen-alone is safer.*

I believe risks of CEE-alone as well as combined estrogen/progestin have been overemphasized, and that many women are being unnecessarily denied relief from their menopausal symptoms. RTJ

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Vitamin D Supplementation Appeared To Reduce Risk Of Falls.

4-5 EFFECT OF VITAMIN D ON FALLS

Falls in elderly persons lead to substantial morbidity and mortality. Falls are an independent determination of functional decline and lead to many nursing home admissions.

Is vitamin D related to incidence of falls? A moderate protective effect has been reported, attributed primarily to improvement in bone mineral density.

Vitamin D may also directly improve muscle strength, thereby reducing risk of falls and fractures. Previous randomized trials reported that vitamin D reduced fractures within 12 weeks, a finding consistent with muscle-strength benefits.

This study assessed the role of vitamin D in preventing falls among elderly people.

Conclusion: Vitamin D supplementation appeared to reduce risk of falls.

STUDY

1. Systematic review found 10 double-bind, randomized trials of various forms of vitamin D in elderly persons (mean age 60) that examined falls resulting from low trauma. Persons with unstable health status were excluded.
2. Compared rates of falls in those taking vitamin D *vs* those taking placebo or calcium.

RESULTS

1. Based on 5 of the trials in over 1200 persons, vitamin D, was associated with a reduction in rate of falls by 22%.
2. The number needed to treat to prevent one person from falling = 15 [Treatment time varied from 7 months to 3 years.]
3. An analysis of 5 other trials involving 10 000 persons resulted in a smaller, but still significant, effect size. (Relative risk of falls in persons taking vitamin D *vs* those taking placebo = 0.87.)
4. Subgroup analysis suggested that the effect size was independent of calcium supplementation, type of vitamin D, duration of therapy, and sex.

DISCUSSION

1. What is the physiological explanation of this beneficial effect? 1,25-hydroxyvitamin D, the active metabolite, binds to a highly specific nuclear receptor in muscle tissue, leading to improved muscle function. In two studies, vitamin D plus calcium (compared with calcium alone) improved body sway by 9% within 2 months in elderly ambulatory women, and increased muscle function up to 11% in institutionalized women.
2. These effects may be mediated by de novo protein synthesis through the specific nuclear receptor for vitamin D expressed in muscle. In one study, vitamin D increased the relative number and size of muscle fibers in elderly women within 3 months of treatment.
3. Some studies reported that 800 IU daily was more beneficial than 400 IU.
4. The role of calcium and the amount necessary in combination with vitamin D could not be determined. Calcium combined with vitamin D, however, may be important.

CONCLUSION

Vitamin D supplementation appeared to reduce the risk of falling among older individuals with stable health by more than 20%.

JAMA April 29, 2004; 291: 1999-2006 Original investigation, first author Heike A Bischoff-Ferrari, Robert B Brigham Arthritis and Musculoskeletal Diseases Clinical Research Center, Harvard Medical School, Boston, Mass.

Comment:

I considered this a weak study, but interesting. If indeed vitamin D strengthens muscle and thus prevents falls, its benefit/harm-cost ratio (which is already high.) will be substantially increased

Vitamin D and calcium intake is generally too low in the US population. I believe that supplementation is warranted in persons of all ages to help maintain bone mass and strength. If muscles are strengthened, so much the better. RTJ

==========

Alcohol Intake Is Strongly Associated With An Increased Risk Of Gout

4-6 ALCOHOL INTAKE AND RISK OF INCIDENT GOUT IN MEN

The association between heavy alcohol intake and gout has been suspected since ancient times. Metabolic studies have shown that hyperuricemia, not gout per se, can be induced by alcohol loading. Conversely, hyperuricemia has been proposed as a marker for ethanol ingestion.

This study re-examined the issue, prospectively assessing the relation between total alcohol consumption and type of alcohol and risk of incident gout.

Conclusion: Alcohol intake is strongly associated with an increased risk of gout. Beer confers a lager risk than spirits. Moderate wine drinking was not associated.

STUDY

1. Health Professionals Follow-up Study followed over 47 000 male subjects (mean age 55 at baseline) for 12 years. None had gout at baseline
2. Assessed average daily alcohol consumption by a food-frequency questionnaire which included separate questions about wine, beer, and spirits.
3. A supplementary questionnaire determined cases of gout which met the Am. Coll. of Rheumatology criteria for gout.

RESULTS

1. Documented 730 incident cases of gout over the 12 years.
2. Compared with men who did not drink alcohol, the relative risk (RR) of gout:

Alcohol	None	1.00
	10 - 14.9 g/d	1.32
	15 – 29.9 g/d	1.49
	30 – 49.9 g/d	1.96
	50 and over g/d	2.53

3. Beer consumption showed the strongest independent association with risk of gout. The RR per each 12 ounce serving per day = 1.49
4. Consumption of spirits was also associated with increased risk. RR per each drink daily = 1.15
5. Wine consumption was *not* associated. (RR = 1.04 for each 4-ounce serving daily. The null association persisted regardless of the type of wine.
6. Risk of gout was greater in men with a body mass index (BMI) over 25 compared with a BMI under 25:

Relative risks:	Under 25	Over 25

Abstainers	1.00	2.8
Over 50 g/d	2.5	5.6

(RR increased linearly as BMI increased.)

DISCUSSION

1. There was a strong association between alcohol consumption and incident gout over 12 years.
2. The risk was increased with intake of as low as 10 – 15 g/day. Risk increased as intake increased.
3. The risks were independent of dietary and other purported risk factors.
4. What might the mechanism be for the association? Alcohol can induce hyperuricemia by decreasing excretion and by increased production. Alcohol is converted to lactic acid which reduces renal excretion by competitively inhibiting uric acid secretion by the proximal tubule. The confounding effect of fasting often associated with heavy drinking induces ketonuria which decreases excretion of uric acid. Alcohol also increases uric acid production by favoring formation of uric acid precursors.
5. Other provocative factors are present in heavy drinkers: concurrent trauma and hypothermia of the extremities.
6. Each serving of beer increased the risk of gout more than twice as much as each serving of spirits, even though the alcohol content of beer per serving is less than in a serving of spirits. Daily consumption of two 4-ounce glasses of wine was not associated with incident gout. Some non-alcoholic components that vary across these beverages may play an important role in the incidence of gout. Beer is the only alcoholic beverage that contains a large amount of purine.
7. These findings are most directly generalizable to men over age 40, the most gout-prevalent population.

CONCLUSION

Prospective data indicate that alcohol intake is strongly associated with incidence of gout. The risk varies substantially with the type of alcoholic beverage. Beer confers the greatest risk, moderate wine drinking does not increase risk.

Lancet April 17, 2004; 363: 1277-81 Original investigation, first author Hyon K Choi, Massachusetts General Hospital, Boston

Comment:

See Practical Pointers March 2004 3-10—an investigation by the same authors as the above study.

Both genetic and environmental factors play a part in the pathogenesis of gout. As with atherosclerotic disease, hypertension, obesity, and type II diabetes, gout can be considered a disease of "civilization"—part of the epidemic of overnutrition and sedentary lifestyles. Gout is associated with a high intake of meat and seafood, and low intake of dairy products.. Now this study reinforces the long-observed relation with alcohol. I am dubious, however, about the lack of association with wine .I believe that consumers of high quantities of wine (eg, a bottle a day—not all that uncommon) would be subject to gout.

As with obesity, gout is becoming more prevalent in developing countries as they become more "Westernized". I have read that there are more obese persons in the world now than hungry persons. RTJ

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Capsaicin May Be Useful In Some Patients As An Adjunct Or Sole Therapy.

4-7 SYSTEMATIC REVIEW OF TOPICAL CAPSAICIN FOR THE TREATMENT OF CHRONIC PAIN

Capsaicin, from chili peppers, binds to nocioceptors in the skin, causing excitation of the neurones and a period of enhanced sensitivity. Cutaneous vasodilation occurs. This is followed by a refractory period with reduced sensitivity and, after repeated applications, persistent desensitization.

Topical preparations are used to treat pain from postherpetic neuralgia, diabetic neuropathy, osteoarthritis , and rheumatoid arthritis.

Adverse effects are mainly burning, stinging, and erythema at the application site.

This meta-analysis determined the efficacy and safety of topical capsaicin for chronic pain from neuropathic and musculoskeletal disorders.

Conclusion: Capsaicin may be useful in some patients as an adjunct or as sole therapy.

STUDY

1. Selected 6 randomized, double-blind, placebo controlled trials (656 patients) which compared topically applied capsaicin (0.075%) with placebo in adults with neuropathic conditions. And 3 trials (368 patients) of capsaicin (0.025%) in patients with musculoskeletal conditions. The strength was three times greater in the neuropathic pain patients. Capsaicin was applied 3 times daily.
2. Patients had moderate or severe chronic pain. Some studies recruited patients who were not responsive to other treatments.
3. Both active and placebo treatments were rubbed on. This precluded any effect of rubbing.
4. Primary outcome = number of patients with at least a 50% reduction in pain.

RESULTS

1. At 8 weeks, for those with neuropathic pain, the relative benefit of capsaicin *vs* placebo was 1.4.
   NNT = 6. (Ie, one of 6 patients would achieve a reduction in pain of 50%.)
2. At 4 weeks, for those with musculoskeletal pain, the relative benefit of capsaicin *vs* placebo was 1.5.
   NNT = 8.
3. There was a substantial response to placebo—25% to 42%.
4. About one third of patients experienced local adverse effects. The number needed to harm one patient by a local adverse effect = 2.5. Adverse effects led to withdrawal in 13%.

DISCUSSION

1. Topical capsaicin is better than topical placebo in the treatment of chronic pain from neuropathic and musculoskeletal pain.
2. The large placebo responses are comparable with placebo responses for oral analgesics and topical NSAIDs.

3. About one in three patients treated with capsaicin will experience a local adverse event. For every 10 patients treated with capsaicin, one will withdraw due to an adverse event.
4. A study in healthy volunteers showed that epidermal nerve fibers significantly degenerated within a few days of capsaicin 0.075%. Once discontinued, reinnervation occurs, and is almost complete in 6 weeks.
5. For patients with chronic moderate or severe pain, even a small reduction in pain can be beneficial.

CONCLUSION

Topical capsaicin maybe useful as an adjunct or sole therapy for a small number of patients who are unresponsive to or intolerant of other treatments.

BMJ April 24, 2004; 991-94 Original investigation, first author Lorna Mason, University of Oxford, Radcliffe Hospital, Oxford, UK.

"Systematic Review of Topical Rubifacients Containing Salicylates for the Treatment of Acute and Chronic Pain", a companion article in this issue of BMJ (pp 995-98), reports efficacy for musculoskeletal pain was moderate to poor. Adverse effects were rare. There was, however, a lack of good clinical trials.

An editorial by Martin R Tramer Geneva University, Switzerland (p 998) comments: topical capsaicin is unlikely to be a first choice for neuropathic pain. There is simply not enough analgesia, and there is too much harm. It may serve as an adjuvant for some patients. And may serve as a last resort when everything else has failed. Topical salicylates are safe and may be used as first line treatment in, for instance, sports injuries.

Topical analgesics remain popular among patients, but do not have a good reputation among doctors. Why? Perhaps because of the unreliability of existing evidence.

Comment: I believe, in some patients topical applications may be helpful. No way to find out without trying. First inform the patient about possible benefits and harms. Over-the-counter availability is a plus. The placebo effect is an added benefit. RTJ

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"The Imbalance In The Regulation Of Nicotine Needs To Be Redressed Urgently In Favor Of Public Health."

4-8 ABC OF SMOKING CESSATION: HARM REDUCTION

A substantial proportion of smokers either do not want to quit, or have been unable to do so despite many attempts. Harm-reduction strategies aimed at reducing the adverse effects of tobacco may help these individuals. This review article discusses various strategies used.

Cutting down: A common strategy. No evidence exists, however, that major health risks are reduced by this strategy. Smoking is primarily a nicotine-seeking behavior. Patients who attempt to cut down tend to compensate by taking more and deeper puffs. This results in a much smaller reduction in the intake of nicotine and associated toxins than the reduction in number of cigarettes smoked suggests. Cutting down, in conjunction with the use of

nicotine replacement therapy **(NRT),** is a more promising strategy. (Although this strategy may result in sustained reductions of intake of toxins, no strong evidence exists for health benefits.)

Switching to "low tar" cigarettes: Low tar means low nicotine. As in cutting down, smokers tend to compensate by changing their smoking pattern. Very little reduction in tar results. (The nicotine and tar content of cigarettes proceed in tandem.)

Switching to cigars or pipes: The risks of regular smoking of pipes and cigars for smokers who have never been regular cigarette smokers are indeed lower because they tend not to inhale. Cigarette smokers who switch, however, continue to inhale and are therefore likely to gain little or no health benefits.

Switching to smokeless tobacco: Health risks of snuff and chewing tobacco are considerably lower than for those associated with cigarettes. In Sweden, use of oral moist snuff ("snus") is common. In relation to cigarettes, the health risks seem to be extremely low. The overall use of snus as an alternative to cigarettes contributes to the low overall prevalence of smoking and smoking-related disease in Sweden. Use of similar products could provide a viable alternative for many smokers.

Switching to pharmaceutical nicotine: Use of NRT is standard practice in managing smoking cessation. These products are not licensed for long term use as alternatives to smoking. Compared with cigarettes, risks are much lower. Thus, *long-term* use is a rational harm-reduction strategy. Most smokers, however, do not find NRT to be as satisfying as cigarettes, and the viability of these products as long-term substitutes is limited. The technology to develop safe, inhaled forms of nicotine that could provide a more satisfactory alternative to cigarettes is available. In the current regulatory framework, such products would not be licensed and therefore are not commercially available. "This imbalance in the regulation of nicotine needs to be redressed urgently in favor of public health."

BMJ April 10, 2004; 328: 88 5-87 "Clinical Review" by Ann McNeill, St George's Hospital Medical School, London, UK

Comment:

Should primary care clinicians advocate their patients who are recalcitrant smokers to judiciously use nicotine replacement in conjunction with cigarette smoking? My PDR (specifically for Nicortol inhaler) states that patients should be urged to stop smoking completely while using this product. Adverse effects may occur due to high peak nicotine levels. I believe this statement by the drug manufacturer is primarily a defense against litigation.

Should we advise switching to snuff?

Would it be reasonable to encourage manufacture of very high-content nicotine cigarettes? This could easily be done.

These approaches open legal difficulties. We are still constrained by outside forces from applying the best medical care possible. RTJ

==========

"In Most Patients, The Average Serum Calcium And Parathyroid Hormone Levels Do Not Change Over 10 Years."

4-9 ASYMPTOMATIC PRIMARY HYPERPARATHYROIDISM

The advent of multichannel biochemical screening ushered in the era of asymptomatic primary hyperparathyroidism. **(AHP).** The prevalence of AHP increased by a factor of five.

In these patients, the serum calcium is elevated, but usually by only 1 mg/dL above the upper limit of normal (10.2 mg/dL). The parathyroid hormone **(PTH)** level is usually 1.5 to 2.0 times the upper limit of normal (65 pg/mL). [*Paradoxical elevation. The normal feedback mechanism leads to a lowering of the hormone.*] The 24-hour calcium excretion tends to be near the upper limit of normal.

Radiography almost never shows skeletal involvement. Bone mineral densitometry **(BMD)** measurement does. The greatest reduction is in the distal radius, a site composed predominantly of cortical bone vulnerable to the catabolic actions of PTH. The hip and lumbar spine show smaller reductions. The pattern differs from the usual pattern of the early postmenopausal years. Actually, in postmenopausal women with AHP, BMD in the lumbar spine is generally well preserved, emphasizing a protective effect of PTH against the loss of cancellous bone.

About 20% of patients are symptomatic, with kidney stones and overt bone disease.. There is debate regarding symptoms of weakness, easy fatigability, and depression. These symptoms are nonspecific, and hard to attribute to AHP.

Diagnosis: Although there are advantages to measuring ionized calcium (*technically difficult*) rather than total calcium, most experts rely on the total calcium corrected for the albumin concentration. (Add 0.8 mg per dL for every 1 g per dL below an albumin concentration of 4 g per dL. The diagnosis of AHP is made on the basis of a combination of elevated total serum calcium + an elevated (*inappropriately*) PTH.

Natural history without surgery: Most patients with AHP who do not meet the criteria for surgery do well, with no evidence of progressive disease. In most patients, the average serum calcium and parathyroid hormone levels do not change over 10 years. And BMD is typically stable. Hypercalciuria usually does not worsen Younger patients (< age 50) are more likely to progress.

Criteria of parathyroid surgery (cutoff points):

Serum calcium	1.0 mg/dL above upper normal
24-hour calcium	> 400 mg
Reduction in creatinine clearance	30%
Bone mineral density	T score below -2.5 (Radius is particularly vulnerable)
Age	Under 50

Surgery is routinely warranted in patients with kidney stones.

Surgery and outcomes after surgery: 80% or more patients have a single benign adenoma; 20% have hyperplasia of all 4 glands. Success rate by expert surgeons approaches 90%. Localization of the adenoma is possible by several different imaging techniques. Technetium-labeled sestamibi [1] is a preferred method.

Preoperative parathyroid imaging is required for all patients undergoing minimally invasive parathyroidectomy. (*See following abstract*.)

After successful surgery, serum and urinary calcium concentrations return to normal. Kidney stone recurrence is greatly reduced, and BMD gradually improves.

Medical therapy: Many patients with AHP will not require surgery. Patients who do not meet the criteria for surgery should be monitored periodically (serum calcium, creatinine clearance, and BMD) because about 25% of patients will progress.

Postmenopausal estrogen reduces serum calcium by 0.5 to 1.0 mg/dL, stabilizes parathyroid hormone levels, and increases BMD. Raloxifene (*Evista*, a selective estrogen receptor modulator [SERM]) may be a safer alternative. Bisphosphonates are another option. Alendronate (*Fosamax*) has resulted in significant increases in BMD, although serum and urine calcium levels do not change. Calcium and vitamin D: it is prudent to refrain from excess intake of calcium (over 1500 mg daily), it is also important not to restrict intake too much (under 750 mg daily). Calcium-poor diets may lead to increased PTH secretion. Many patients with AHP have lower levels of 25-hydroxy vitamin D. Supplementation with 400 IU daily is reasonable. Caution against high doses which may lead to increased levels of serum calcium. Maintain an adequate intake of calcium and vitamin D—not too low (*as in many persons in the USA*) but also not too high. Advise patients to maintain adequate fluid intake.

NEJM April 22, 2004; 350: 1746-51 "Clinical Practice", review article, first author John P Belezikian, College of Physicians and Surgeons, Columbia University, New York.

Comment:

I enjoy review articles. They are informative. They condense information about a particular disease. Abstracting them fully, however, is not practical. They are usually too long.

In abstracting chosen reviews, I select points which I consider important and interesting, and others I never knew or had forgotten.

1 *I searched Google for Technetium-labeled sestamibi. Sestamibi is a nitrate compound--a lipophilic monovalent cation. It enters cells via passive diffusion. Tc-S has also been used to scan myocardium.*

To advise surgery or advise continued surveillance is a clinical call. It depends on patient preference and individual circumstances. If expert surgery is available, I would tilt toward surgery. This would relieve the patient of continuing concerns. RTJ

==========

"A New Era In The Treatment Of Primary Hyperparathyroidism"

4-10 MINIMALLY INVASIVE PARATHYROIDECTOMY

"Parathyroidectomy is the treatment of choice in *symptomatic* primary hyperparathyroidism. It cures fatigue, and the bone, abdominal, urological, and mental symptoms associated with hypercalcemia." It also results in a quantifiable improvement in health-related quality-of-life.

Additionally, a 25 year follow-up of patients with untreated "asymptomatic disease" showed a notable increase in cardiovascular deaths. "Support for an operative approach is further provided by lack of an effective medical treatment and the cost and doctor hours involved in the follow up of conservatively managed patients."

The arrival of tecnitium-99m sestamibi scanning revolutionized preoperative localization of parathyroid glands. It accurately identifies the side and size of the adenoma in 9 out of 10 cases.

Patients with reliably localized single adenomas may be treated with a minimal access approach. This is achieved through a 2 cm incision. It can usually be done as a day-case procedure in less than 20 minutes with local anesthesia.

Minimally invasive surgery is possible only in patients with an accurately localized single adenoma. It has become the first line treatment in specialized units. Its value lies particularly in providing treatment of elderly patients who so often have comorbid conditions.

BMJ April 10, 2004; 328: 849-50 Editorial, first author F Fausto Palazzo, John Radcliffe Hospital, Oxford UK**.**

Comment:

Primary care clinicians, if they practice long enough, will encounter patients with asymptomatic HPT. The advent of minimalist surgery further tilts the decision toward operating. RTJ

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Introducing "Vaptans" For Treatment Of Heart Failure

4-11 EFFECTS OF TOLVAPTAN, A VASOPRESSOR ANTAGONIST, IN PATIENTS HOSPITALIZED WITH WORSENING HEART FAILURE

Patients with heart failure (**HF)** have progressive fluid retention manifested by an increase in weight. Worsening symptoms often lead to hospitalization.

Pharmacologic treatment of HF is often inadequate. Readmission rates for HF are high. Use of diuretics is often associated with hypotension, electrolyte abnormalities, worsening renal function, and possibly increased mortality.

Levels of arginine vasopressin (**AVP**; the water-retaining hormone secreted by the pituitary) are increased in HF. Water retention and hyponatremia result.

Antagonists to AVP may prevent progression of HF. In contrast to ACE-inhibitors and beta-blockers, they may quickly improve congestion and hyponatremia.

Tolvaptan is a non-peptide, orally administered, vasopressin *antagonist*. It has no intrinsic agonist properties. In addition to standard therapy, it may result in a reduction in weight without worsening renal function or causing hypokalemia.

This study assessed the clinical effectiveness of tolvaptan in patients hospitalized for HF.

Conclusion: Administered in addition to standard therapy, tolvaptan holds therapeutic promise.

STUDY

1. A phase-2 (hypothesis generating) multicenter, randomized, double-blind, placebo-controlled trial entered over 300 patients (mean age 62) hospitalized for HF. All had an ejection fraction less than 40% *(mean ejection fraction = 24%; ie, "systolic" HF).* All had persistent signs and symptoms of systemic congestion despite continuation of standard therapy, including diuretics.
2. Randomized to: 1) varying doses of tolvaptan given daily, or 2) placebo. Therapy continued for 60 days.
3. Main outcome measures = change in bodyweight at 24 hours; and worsening HF (death, hospitalization, or unscheduled visits for HF after discharge).
4. Follow-up = 60 days.

RESULTS

1. Weight at 24 hours decreased by ~ 2 kg *vs* 0.6 kg for placebo. At discharge from hospital, the mean 24-hour urine volume was greater in the tolvaptan group; dyspnea was less, and jugular venous distention was reduced.
2. There were no changes in heart rate or BP in the tolvaptan group. None developed hypokalemia or worsening renal function.
3. The risk of death, hospitalization, or unscheduled visits for HF (worsening HF) after 60 days of tolvaptan therapy was similar to that of placebo (25% vs 27%). There was, however, a trend toward lower mortality in the tolvaptan group in patients with high BUN levels and severe systemic congestion. (This requires confirmation.)

DISCUSSION

1. Patients with systolic dysfunction often have elevated levels of AVP leading to water retention and hyponatremia.
2. Tolvaptan binds predominantly with the AVP receptor in the kidney, resulting in decreased renal vascular resistance, increased renal blood flow, and improved glomerular filtration rate.
3. Tolvaptan, given in addition to standard therapy (including diuretics) resulted in a greater net volume loss *vs* placebo.
4. Tolvaptan produced a rapid and sustained increase of serum levels of sodium (due to loss of free water) in patients with hyponatremia.
5. Diuretics are the mainstay of therapy for systemic congestion in HF. Their use is associated with hyponatremia, hypokalemia, and hypomagnesemia; and worsening renal function. They also cause hyperglycemia, hyperuricemia, and increased sensitivity to digoxin. In this study, all patients received diuretics. Thus, the comparative effects of tolvaptan *vs* diuretics could not be assessed. In another study, however, tolvaptan used without a diuretic reduced weight and edema without adverse changes in electrolyte levels. It has also been reported to increase and normalize sodium levels in patients with hyponatremia due to liver cirrhosis, and the syndrome of inappropriate antidiuretic hormone secretion.

CONCLUSION

Tolvaptan, in addition to standard therapy, including diuretics, increased water loss and resulted in loss of body water more rapidly and effectively than standard therapy in patients hospitalized with heart failure. It did not adversely affect BP, heart rate, electrolyte levels, or renal function. It improved serum sodium levels in patients with hyponatremia. "It holds promise for management of systemic congestion..."

JAMA April 28, 2004; 291: 1963-71 Original investigation by the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIF in CHF) Investigators, first author Mihai Gheorghiade, Northwestern Feinberg School of Medicine, Chicago.

An editorial in this issue (pp 12017-18, first author Gary S Francis, Cleveland Clinic Foundation, Ohio comments and expands on the study:

Many patients with acute congestive decompensation have hypervolemia and hyponatremia that is poorly responsive to conventional loop diuretics.

The antidiuretic hormone arginine vasopressin (*I believe better termed the "water-retaining hormone". RTJ*) modulates (*reduces*) free water transport in the kidney. Antagonists (eg, tolvaptan) block this effect. Rather than being classified as a traditional diuretic, tolvaptan is more precisely characterized as an *aquaretic*.

The increase in circulating levels of AVP in HF has been known for years, although the exact mechanism for the increase is still not known. The clinical effects of treatment with AVP antagonists are only recently being studied. A long-term phase 3 efficacy trial is being conducted.

Comment:

When I started to study medicine, the treatment of HF consisted of rest, digitalis pills, salt restriction, and the intramuscular mercury-containing diuretic, mercuhydrin. (How many out there remember mercuhydrin?)

Therapeutic advances have been remarkable—beta-blockers, ACE inhibitors and angiotensin II blockers, spirinolactone, and loop diuretics, as well as use of low-dose digoxin. Nevertheless, prognosis of patients with HF remains poor. These newer drugs are really "rear guard" therapies. It may well be that the main benefit of vaptans is symptomatic relief. Lessening dyspnea and edema may make patients more comfortable. Certainly, vaptans will make therapy easier by reducing worry about hyponatremia, hypokalemia, and renal dysfunction.

Note, the study assessed only systolic HF. The large issue of diastolic HF remains.

Primary care clinicians stay tuned. RTJ

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CTC Is Not Yet Ready For Widespread Clinical Application.

4-12 COMPUTED TOMOGRAPHIC COLONOSCOPY (VIRTUAL COLONOSCOPY)

In studies performed at expert centers, computed tomographic colonoscopy (**CTC**) has been reported to be reasonably accurate in the diagnosis of colorectal neoplasia.

This study assessed the accuracy of CTC *vs* conventional colonoscopy in a large number of participants.

Conclusion: CTC is not yet ready for widespread clinical application. Too many false negative tests.

STUDY

1. Non-randomized multicenter study entered over 600 patients, age over 50, who were referred for routine, clinically-indicated colonoscopy in 2000 and 2001.
2. The CTC was performed using multislice scanners. A conventional colonoscopy immediately followed.
3. Determined the sensitivity and specificity of CTC in detecting lesions sized at least 6 mm. (Conventional colonoscopy was the "gold standard".)

RESULTS

1. A total of 827 lesions were detected in 308 of 600 participants who underwent both procedures.

   Sensitivity of the tests = percentage of true positive tests (Ie, % of lesions detected in patients who had a lesion.)

	CTC	Colonoscopy *
At least 6 mm	39% ***	99% **
At least 10 mm	55% ***	100%

   * Conventional colonoscopy was considered the "gold standard".

   ** The use of colonoscopy as the "gold standard" may be criticized because it cannot claim complete accuracy, even in expert hands. Rarely, a lesion was missed by colonoscopy and was detected by CTC.)

   *** 45% to 61% of the lesions were missed by CTC. False negatives test.

2. A total of 496 patients did *not* have any lesions of 6 mm or more.

   Specificity of the tests = percentage of true negative test;. (Ie, % of negative findings in patients who did not have a lesion):

	CTC	Colonoscopy
At least 6 mm	90% *	100%

   * 10% of the CTC patients were diagnosed falsely as having a 6 mm or larger lesion. False positive tests.

3. CTC missed 2 of 8 cancers.
4. Accuracy to CTC varied considerably between centers.
5. Patients expressed no clear preference for either technique.

DISCUSSION

1. In this study, the low sensitivity of CTC in detecting lesions contrasts with some other studies. This was despite the author's consideration that the radiologists in the study were considered sufficiently experienced.
3. In one center with the greatest experience with CTC, the sensitivity of CTC was 82%. (Still about 20% were missed.) The sensitivity of all other centers combined was only 24%.
4. There was no evidence of a "learning curve". (Ie, no correlation between increasing experience and accuracy.)
5. Patients expressed no distinct preference for CTC over standard colonoscopy. CTC requires the same bowel preparation as conventional colonoscopy. Many patients consider this the worst part of the procedure.
6. Many patients may opt for conventional colonoscopy knowing that there is approximately a 20% chance that colonoscopy will be needed if a lesion is discovered on CTC.

7. “Even if the results of CTC continue to be good in the hands of experts, it has yet to be proven that this expertise can be taught and disseminated reliably into daily practice.” But, CTC technology is evolving and becoming more sophisticated.

CONCLUSION

CTC is not yet ready for widespread clinical application.

JAMA April 14, 2004; 291: 1713-19 Original investigation, first author Peter B Cotton, Medical University of South Carolina, Charleston www.jama.com

Comment:

I abstracted this article mainly because enthusiasts in local communities are investing in costly scanners and advertising CTC to the general public as well as to professionals.

A study abstracted in Practical Pointers December 2003 (12-10) reported the experience of the Uniformed Services University of Health Sciences. This group has had considerable experience with CTC, and uses sophisticated equipment. They claimed that CTC detects polyps of 6 mm or larger as accurately as conventional colonoscopy. If a polyp of this size is detected, conventional colonoscopy is required to remove it.

A critical issue remains. Should all polyps detected be referred for conventional colonoscopy? If not, what is the cut-point size? How should smaller polyps be followed? Patients with smaller polyps (not removed) would be required to undergo screening at shorter screening intervals than patients whose polyps are removed.

As noted, the bowel-cleansing preparation is the same in both procedures. In observational studies, arrangements for immediate conventional colonoscopy can be made beforehand. In usual practice settings, many patients would require a second bowel cleansing.

I do not believe community-based primary care clinicians should advocate CTC. RTJ

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Prognosis Following Mastectomy Is Favorable.

4-13 DUCTAL CARCINOMA IN SITU OF THE BREAST; Review Article

DCIS consists of the clonal proliferation of cells that appear malignant and that accumulate within the lumens of mammary ducts. There is no evidence of invasion beyond the epithelial basement membrane into the adjacent breast stroma. It is a precursor of invasive ductal carcinoma. Following the widespread use of screening mammography, the prevalence of DCIS has risen dramatically.

Biological characteristics:

DCIS and synchronous adjacent invasive cancers share chromosomal changes. This demonstrates their clonal, evolutionary relationship. Chromosomal imbalances occur, with gain or loss at multiple loci, as hyperplastic lesions progress through DCIS to invasive breast cancer **(BC**). As genetic changes occur, there is a progression from normal ductal lumen to benign proliferative changes to atypical hyperplasia to DCIS, and to invasive carcinoma. Data suggest that DCIS represents a stage in the development of BC in which most of the molecular changes that characterize invasive BC are already present, though the lesion has not assumed a fully malignant phenotype.

Clinical and pathological features:

DCIS accounts for nearly 20% of all breast cancers detected by screening (one case detected for every 1300 screening mammograms).

Postmenopausal hormone replacement therapy may increase risk of DCIS.

Because of mammography, nearly 90% of DCIS are diagnosed while they are clinically occult.

Microcalcifications occur in about 75%; soft tissue densities in about 10%; both occur in about 15%.

Calcification patterns are only moderately correlated with pathological types of DCIS.

The crucial task of pathological assessment is to distinguish DCIS from invasive cancer. Classification remains a challenge due to differing pathologic criteria, interobserver variability, and the heterogeneous nature of tumor growth.

DCIS originates in a single glandular structure. It may spread within the breast through the ductal system. Most patients with low-to-intermediate grade DCIS have multifocal disease, characterized by discontinuous intraductal growth, with gaps of up to 1 cm between tumor foci. High grade lesions tend to be continuous.

The natural history of untreated low-grade DCIS has been defined in long-term, follow-up studies of women who underwent diagnostic biopsy in the era before widespread screening mammography. After 10 years of follow-up, 14 to 60 percent of the women had received a diagnosis of invasive cancer in the affected breast. Such a risk is widely thought to justify the present treatment approaches.

Treatment

The goal is prevention of local recurrence—in particular invasive BC. Options for surgical treatment include simple mastectomy, or breast conserving surgery (often called lumpectomy, although in most cases there is no lump). Death from BC after surgery for DCIS occurs in only 1% to 2% of all patients within 10 years. Simple mastectomy is highly effective—curing at least 98% of lesion—and is a potential treatment option for all patients. BC recurs in 1% to 2% of patients with DCIS who have undergone mastectomy due to the presence of occult invasive disease at the time of diagnosis, or to recurrence of DCIS in residual breast tissue, or to contralateral breast disease.

Women with DCIS in one breast are at risk for a second tumor (either invasive of in situ) in the contralateral breast - about 0.5% to 1% per year. In two large studies rates of recurrence were 16% and 19% at 15 years.

Tamoxifen as adjuvant therapy reduced the likelihood of local recurrence in post-surgery patients by an absolute 3% and reduced risk of a tumor in the opposite breast. Reduction in risk occurred only in the lesions which were estrogen-receptor positive.

"There is no role for chemotherapy in the treatment of DCIS." Neither dissection of axillary nodes nor mapping of sentinel nodes is routinely warranted owing to the very low incidence of axillary metastases. Radiotherapy is not indicated after mastectomy. It is routinely administered after breast conserving surgery to reduce risk of ipsilateral recurrence.

Patients with recurrent DCIS have an excellent prognosis, with a less than 1% recurrence after salvage mastectomy.

Women with DCIS have considerable deficits in their knowledge of the disease. Their levels of psychological distress and fear of recurrence and death are similar to those among women with invasive breast cancer.

Because DCIS is a precursor to invasive cancer and shares many biological features of invasive disease, it is increasingly recognized as a target for *primary* preventive measures. In women at high risk for breast cancer because of age, family history, or prior benign breast disease, tamoxifen reduced the risk of DCIS by 50% to 70%.

Summary:

DCIS is a preinvasive breast tumor commonly detected by screening mammography.
It is a heterogeneous tumor with a spectrum of biologic and clinical features affecting the likelihood of transformation to invasive BC and recurrence within the affected breast. The goal of treatment is to reduce the risk of recurrent disease, particularly invasive cancer.

NEJM April 1, 2004; 350: 1430-41 "Medical Progress", review article, first author Harold J Burstein, Brigham and Women's Hospital, Harvard Medical School. Boston.

Comment:

Because incidence of DCIS is related to hormone replacement therapy, and is benefited by tamoxifen, I would guess that aromatase-inhibitor therapy would be efficacious. Undoubtedly, studies will be forthcoming.

The generally favorable prognosis should be emphasized. Women with DCIS should be repeatedly reassured. This is an important responsibility for primary care clinicians. RTJ

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