

# **PRACTICAL POINTERS**

## **FOR PRIMARY CARE**

**ABSTRACTED MONTHLY FROM THE JOURNALS**

**JUNE 2004**

**STATIN THERAPY IMPROVES OUTCOMES OF ACUTE CORONARY SYNDROMES**

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## HIGHLIGHTS and EDITORIAL COMMENTS JUNE 2004

### 6-1 ASSOCIATION OF STATIN THERAPY WITH OUTCOMES OF ACUTE CORONARY SYNDROMES: The GRACE Study

Statin drugs may have effects in addition to their effect on lipids. These include modulation of inflammation, inhibition of platelet function and thrombosis, and enhancement of endothelial function. The ability of statins to *immediately* affect basic pathophysiologic mechanisms has increased interest in their potential role in acute coronary syndromes. (ACS)

This study examined the association between previous and early in-hospital statin therapy and outcomes of ACS.

Patients who presented with an ACS who were already taking statins were less likely to present with ST-segment elevation MI, experience a large infarct, and have important clinical complications, or die.

Much of the observed effect was lost if statin therapy was not continued during hospitalization. Such patients had death rates similar to patients who had never received statins. Withdrawal of statins reduces the protective effect of statin pretreatment.

In statin-naïve patients, early statin therapy was associated with an improvement in outcomes.

*Should primary care clinicians act on these conclusions? Primary care clinicians often act on inconclusive evidence if the putative benefit/harm-cost ratio of the intervention is high. Although the outcomes of the study require confirmation and further experience, I believe the benefit/harm-cost ratio of immediate statin therapy (as of immediate aspirin therapy) for patients with ACS is potentially high. The benefit is potentially life-saving.*

*The harm and cost of short-term therapy is very low. I would give a high-dose statin immediately on presentation of a patient with presumed ACS.*

*Those on statins long-term should be continued on statins when admitted for ACS. Those not on statins should start them immediately. And, of course, continue after discharge.*

*A study "Lipid-Lowering Therapy And In-Hospital Mortality Following Major Non-Cardiac Surgery" (See Practical Pointers May 2004) also presents evidence of immediate protective effects of statins given within the first 2 days after major surgery. RTJ*

### 6-2 THE SEARCH FOR THE "HOLY GRAIL" OF CLINICALLY SIGNIFICANT CORONARY ATHEROSCLEROSIS.

In some individuals, coronary atherosclerosis (CA) is stable for years, and in others it is very unstable, with rapidly progressive lesions that result in sudden death or an acute coronary syndrome. The diagnostic "Holy Grail" of coronary atherosclerosis is *not* to be able to identify coronary atherosclerosis (which almost all Americans have eventually) but to identify individuals with *unstable* coronary atherosclerotic lesions.

The editorialist describes the evolution of our understanding the pathophysiology of CA—from the concept of a gradual process that over decades narrows the arteries, to silent CA diagnosed by treadmill exercise testing, to coronary angiography, and finally to efforts to detect unstable plaques.

More myocardial infarctions occur in the larger sub-population with negative results on a treadmill test than in those with positive results. More myocardial infarctions are caused by hemodynamically insignificant lesions than from high grade stenosis.

*This editorial was written in response to a meta-analysis in this issue of Archives (pp 1285-92) which concluded that the coronary artery calcium score detected by electron-beam computed tomography is an independent predictor of coronary events.*

*The point of the editorial was to state that the clinical utility of fast computed tomography is not ready for prime time. While scanning may reveal calcification, individuals with unstable coronary disease are not always identified. A patient with potentially unstable coronary atherosclerotic lesions may have mildly calcified or non-calcified arteries. Patients with stable and unstable coronary atherosclerosis may have similar calcium scores.*

*Prevention of an essentially universal disease must be universal. Must we wait for screening tests to detect “higher risk”, and only then encourage patients to change his or her lifestyles?*

### **6-3 NATURAL HISTORY OF EARLY, LOCALIZED PROSTATE CANCER**

Even without any initial treatment, only a small proportion of patients diagnosed with PC at an early stage die of the disease within 10 to 15 years following diagnosis.

This observational study of the long-term natural history of localized PC (diagnosed at a mean age 72) assessed disease progression and mortality over years of watchful waiting.

Over 21 years, most patients died, mainly of causes other than PC. Only 9% survived.

Poor differentiation (in only 4% of the cohort) was a strong predictor of cancer-specific death. This became evident within the first 5 years.

Further follow-up *after* 15 years revealed a substantial worsening of the cancer. The cause-specific mortality from PC increased by 3-fold during years 15 to 20 after diagnosis. .

“If our data reflect a real phenomenon, they would imply that the probability of progression from localized and indolent to metastatic and mortal disease increases markedly after long-term follow-up.”

This would support radical treatment, notably among patients with an estimated life expectancy of over 15 years.

*This would argue for greater screening of younger men; less aggressive screening in older men. Long-term follow-up may be necessary to observe the full benefits of early diagnosis and definitive treatment in younger men. Older men likely die of other causes.*

*According to these data, even if your PC is highly differentiated, you still run a risk of about 2 in 100 of developing metastatic disease each year, and about 1 to 2 chances in 100 of dying of PC each year. If you survive over 15 years, these chances are increased by 300%.*

*Prostate cancer is never cured spontaneously.*

*If you live long enough and are not treated, your chance of developing metastatic disease (requiring orchiectomy or estrogen therapy) and fatal PC is high, even if you have a highly differentiated PC. If you have a poorly differentiated grade PC and are not treated, you will likely die of it within 5 years.*

*No doubt some lives are saved by radical treatment. Who to treat and when to treat remains a dilemma. RTJ*

#### **6-4 ABSENCE OF AN EFFECT OF LIPOSUCTION ON INSULIN ACTION AND RISK FACTORS FOR CORONARY HEART DISEASE.**

Abdominal obesity (increased abdominal subcutaneous fat, and increased visceral fat) is associated with insulin resistance and other risk factors for coronary heart disease (**CHD**).

This study asked: Which of these fat deposits is associated with insulin resistance and increased risk of CHD?

Liposuction in 15 grossly obese women reduced volume of subcutaneous abdominal fat by 44%. Weight loss = 10 kg; total body fat decreased by 18%. Liposuction did not significantly alter insulin sensitivity (assessed by stimulation of glucose uptake in muscle); did not suppress glucose production by the liver; and did not suppress lipolysis of adipose tissue.

Levels of C-reactive protein and other indicators of inflammation did not change.

Other risk factors for CHD were unchanged (BP, plasma glucose, insulin, and lipid concentrations).

Large-volume reduction in subcutaneous abdominal fat mass did not have any beneficial metabolic effects despite a considerable decrease in body weight, waist circumference, and plasma leptin concentrations

This provides insight into the mechanism by which conventional weight loss improves insulin sensitivity. Induction of a negative energy balance, not simply a decrease in the mass of fat tissue, is critical for achieving the metabolic benefits of weight loss. Even small amounts of weight loss induced by a negative energy balance affect many variables pertaining to body-fat composition and lipid metabolism—variables that contribute to metabolic abnormalities associated with obesity. Conventional weight loss decreases visceral fat mass, intrahepatic fat, fat-cell size, and the rate of release of fatty acids from intra-abdominal adipose tissue. Liposuction does not.

Adipose tissue is now recognized as an important endocrine organ that produces several bioactive proteins. Fat loss by conventional obesity treatment decreases plasma concentrations of C-reactive protein, interleukin-6, and tumor necrosis factor. It improves insulin sensitivity and inhibits vascular inflammation.

*I abstracted this article mainly to point out the risks associated with intra-abdominal fat accumulation.*

*Visceral fat drains directly into the portal circulation and into the liver; subcutaneous fat drains into the general circulation. There is a vast metabolic difference. RTJ*

#### **6-5 THERMODYNAMICS, LIPOSUCTION, AND METABOLISM**

Hyperglycemia improves *rapidly* during caloric restriction. It outpaces the rate of weight loss. About half of the improvements in glycemic control are achieved during the first week of a negative energy balance, although the actual fat loss is typically quite small. Substantial proportions of the early benefits of weight loss on insulin resistance and hyperglycemia in type 2 diabetes may be attributed to a negative energy balance.

Similar observations have been made concerning hypertension. Much of the decrease in BP occurs fairly rapidly in response to a negative energy balance. There is, however, a return toward hypertensive levels once weight has reached a plateau.

Visceral adiposity is strongly associated with insulin resistance. In animals, surgical resection of visceral fat tissue yields marked and nearly immediate reduction in insulin resistance. The removal of an equivalent amount

of subcutaneous fat has little effect. The relation may be related, at least in part, to the release of fatty acids into the portal circulation.

Adipose tissue has endocrine functions—synthesizing leptin, adiponectin, and cytokines such as tumor necrosis factor, interleukin-6, and C-reactive protein.

*During World War II type 2 diabetes practically disappeared in the Netherlands. This was related to the near starvation conditions produced by the invasion by Germany. RTJ*

## **6-6 COMPARISON OF SURGERY AND COMPRESSION WITH COMPRESSION ALONE IN CHRONIC VENOUS ULCERATION (ESCHAR study)**

Multilayered elastic compression bandaging, leg elevation, and exercise achieve healing in up to 80% at 24 weeks. However, despite continued use of elastic compression stockings, the 12-month recurrence rate is high.

Simple superficial venous surgery (saphenous vein ablation) theoretically removes the underlying venous incompetence in legs in patients with isolated superficial reflux.

This randomized study reported that healing over 24 weeks was similar between groups. Recurrence of the ulcer within 1 year was much less likely in the surgery group. [NNT = 6]

*The investigators state that about a quarter of patients with venous ulcers will refuse surgery. Primary care clinicians then deal with these individuals as best they can. RTJ*

## **6-7 FREQUENCY OF SYMPTOMS OF OVARIAN CANCER IN WOMEN PRESENTING TO PRIMARY CARE CLINICS.**

Ovarian cancer (OC) has been called the “silent killer” because symptoms are thought not to develop until advanced stages when chance of cure is poor. Standard textbooks state that symptoms do not occur until the disease is advanced. However, several retrospective studies have indicated that the majority of patients with OC do have early symptoms, although not necessarily gynecologic in nature.

Identification of early symptoms may have important clinical implications because the 5-year survival for early stage disease is 70% to 90% compared with 20% to 30% for advanced-stage disease.

This study compared the frequency, severity, and duration of symptoms typically associated with OC vs typical symptoms of women attending primary care clinics.

Women with OC described differences in symptoms compared with the typical women presenting for care. Symptoms in patients with OC were more frequent, more severe, and more often had an onset within 6 months. Patients were much more likely to have a combination of abdominal bloating, increased abdominal size, and urinary urgency.

These symptoms warrant further diagnostic intervention because they are more likely to be associated with ovarian tumors.

*This requires the patient to carefully recall and describe her symptoms. And requires the physician to be especially alert about fully understanding the onset, severity, and duration of the symptoms. Clarity may be achieved only after several visits.*

*Physicians should ask women presenting with relatively new-onset symptoms specifically about bloating, abdominal size and urinary symptoms. RTJ*

## **6-8 EFFECT OF LIFESTYLE CHANGES ON ERECTILE DYSFUNCTION IN OBESE MEN**

Erectile dysfunction (**ED**) is common, even in young men. Several modifiable lifestyle factors are associated with maintenance of erectile function. Men with a body mass index over 28 have a 30% higher risk of ED. The prevalence of overweight and obesity in men reporting ED may be as high as 79%, although vascular factors associated with obesity may play an important role.

This study of obese men with ED determined if a long-term reduction in BMI and an increase in physical activity would positively affect erectile functions.

At 2 years an intensive dietary-fitness program led to over 10% loss of body weight and an increase in physical fitness. About 1/3 of the men regained erectile function.

For many patients, ED is a manifestation of more generalized pathology. Hypertension, hyperglycemia, and dyslipidemia are common co-morbidities. Endothelial dysfunction is likely a pathogenic mechanism common to these co-morbid states, risk of cardiovascular disease, and ED. The study demonstrated improvements in endothelial function related to weight loss..

*This is not, however, a practical application. Few patients in primary care practice would be able to complete such a program*

*The main message is—maintain a healthy lifestyle, don't wait to repair damage until after it is done. RTJ*

## **6-9 WAITING FOR PLAN B—THE FDA AND NONPRESCRIPTION ON EMERGENCY CONTRACEPTION**

The proposal to switch to levonorgestrel emergency contraception (EC; *Plan B*) to over-the-counter status is in limbo. In May, the FDA rejected the application for non-prescription sales. The acting director wrote that the company had “not provided adequate data to support a conclusion that *Plan B* can be used safely by young adolescent women for emergency contraception without the professional supervision of a practitioner licensed by law to administer the drug”. In rejecting the application, the FDA also rejected the advice of its medical review-staff. (A vote of 23 to 4 in favor of nonprescription status.)

*I would be willing to wager that this decision will be reversed. RTJ*

## **6-10 FONDAPARINUX OR ENOXAPARIN FOR THE INITIAL TREATMENT OF SYMPTOMATIC DEEP VEIN THROMBOSIS**

Fondaparinux is a selective inhibitor of activated factor X (Xa). Once-daily injections produce a predictable anticoagulant effect.

This randomized, double-blind multicenter study entered over 2200 patients (mean age 61) with established acute symptomatic DVT of the lower extremity. Randomized to fondaparinux once-daily, or the low-molecular-weight heparin enoxaparin twice-daily. Many received injections at home. All were started on oral anticoagulant therapy within 72 hours.

Double-blind subcutaneous injections were continued for at least 5 days, or until the warfarin-induced INR reached 2.0 or greater. Oral therapy was continued for 3 months

Over 3 months, outcomes were very similar between groups: recurrent thromboembolic events, pulmonary embolism, recurrent DVT, major bleeding, and death.

“This study adds to the growing body of evidence that inhibitors of activated factor X are effective, safe, and easy-to-use antithrombotics.”

*There are several cautions about at-home treatment with either LMWH or fondaparinux: 1) concern about undertreatment of DVT and resultant pulmonary embolism, and 2) the need for careful laboratory monitoring of oral anticoagulation status during the first days of treatment.*

*Should fondaparinux be considered a “me too” drug? For a new drug to be adopted into primary care practice to replace an old effective drug, important attributes must be established—must be established as just as effective, or more effective; must be established as just as safe or safer; must be more convenient to administer and require fewer doses; must be less costly.*

*Study sponsored by Sanofi-Synthelabo and MV Organon. I always look for “spin” in drug-company sponsored studies. This study looks straightforward. We look for confirmation. RTJ*

## **6-11 LONG TERM DONEPEZIL (*Aricept*) TREATMENT IN 565 PATIENTS WITH ALZHEIMER’S DISEASE (AD 2000)**

All three available cholinesterase inhibitors produce small improvements in cognitive and global assessments in selected patients mild-to-moderate AD over 3-12 months. Little is known about long-term effectiveness, or their usefulness in patients with severe AD. Nonetheless, the demand from clinicians and patients remains strong.

This study asked whether the cholinesterase inhibitor donepezil (*Aricept*) is cost effective and produces worthwhile clinical and social improvements.

In absolute terms, donepezil group achieved a slightly higher score on the mini-mental-examination within the first 36 weeks (about 1 point above baseline on a 30-point scale). Thereafter, scores deteriorated back to baseline at 48 weeks and to minus 4 points at 112 weeks. The placebo group lost points continuously during the 112 weeks.

Comparatively, over 112 weeks, donepezil group (compared with placebo) maintained a slightly better score (a fraction of one point) despite declining in absolute terms.

Donepezil was associated with *no* improvement in activities-of-daily living scale *at any time* up to 2 years, although, compared with placebo, decline in ADL score was slightly slower.

No significant benefits were seen *vs* placebo in institutionalization, progression of disability, behavioral and psychological symptoms, psychopathology of carers, formal care costs, adverse events, or deaths.

No evidence that costs of caring for patients with Alzheimer’s disease in the community are reduced by donepezil. Any effect of donepezil on informal caregiver time is likely to be small.

Benefits of the acetylcholinesterase inhibitor, donepezil, are “below minimally relevant thresholds”. It is not cost effective “The disappointingly little overall benefit from donepezil cannot be taken lightly.” Clinicians can

validly question whether other uses of scarce resources allocated for dementia would provide better value than routine prescription of cholinesterase inhibitors.

*I believe many patients are continuing to receive CIs far beyond the time of any hope of benefit.*

*COST: about \$1600 per year quoted by drugstore.com. As is often the case, the 10 mg dose costs just a few dollars more per year than the 5 mg dose. A pill cutter may cut cost in half. There is no statistically significant difference in effects of 10 mg vs 5 mg. Adverse effects (eg, gastrointestinal) are greater with the 10 mg dose. RTJ*

## **6-12 AD 2000: DONEPEZIL IN ALZHEIMER'S DISEASE**

Patients seen in everyday practice differ from those selected for inclusion in drug-company-sponsored trials. Drug companies use highly refined selection criteria; often include specialized tests to aid diagnosis; restrict allowable comorbidity and concomitant medications; and the extent of behavioral or functional impairment. They pay for all protocol-related care, including medications. "Typical selection criteria for industry sponsored trials would exclude over 90% of out-patients with mild-to-moderate Alzheimer's disease in California who would otherwise be eligible to receive treatment. The controversy about effectiveness, costs, and the clinical meaning of trial results has been fueled by the use of participants who do not represent typical patients."

In the trial, donepezil and placebo were both associated with a worsening over time. The mean differences on the MMSE and activities of daily living scale represent a delay in symptom-worsening of about 3 months.

*This commentary presents a clinically important point. It emphasizes the gulf which may separate results of randomized controlled trials from benefits evident in primary care practice. There may be a large difference between results reported by a clinical trial for AD and clinical benefits for Mr. Jones, whose family brings him into your office because of memory loss. A practical office-based, "real world" trial is more meaningful and convincing. Beware of "spin".*

## **6-13 TACKLING THE NEXT INFLUENZA PANDEMIC**

"We must now hasten the preparations for another inevitable influenza pandemic."

A recent systemic review concluded that the prophylactic use of neuraminidase inhibitors (NIs) could lead to a reduction of 70-90% in risk of symptomatic flu. These drugs have shown efficacy in preventing transmission of influenza in institutions and community setting. The availability of a highly effective supplement to vaccination opens to debate the appropriate role of NIs and other antiviral drugs in the control of pandemic influenza.

What might be an alternative strategy? It is known that "ring" vaccination, which has been used in the past, will quell smallpox outbreaks. The strategy entails post-exposure vaccination of close contacts. For smallpox, this approach has provided a wide safety net of prevention, while focusing vaccination where it was needed most. Ring prophylaxis may be applicable to the initial management of an influenza pandemic. NI treatment of influenza cases with the infection and prophylactic use for their contacts may decrease attack rates substantially. It limits usage of the drug to where it is needed most.

Antiviral ring prophylaxis for flu has proved to be effective in family settings. It requires only short term daily treatment for a period of 5-10 days, and targets a relatively limited proportion of the population. Used in this way, NIs may be dispensed more rapidly and require less of a stockpile.

*COST: Tamiflu, 75 mg cost about \$6 each capsule— \$60 for a treatment course; \$42 for 7-day prophylaxis. I believe most patients would consider this a bargain.*

*Healthcare workers should be the first in line to receive “ring” prophylaxis, and to continue it until assured that the current vaccine is effective.*

*Primary care clinicians will likely use NIs freely to unvaccinated family members during an epidemic of flu.*  
RTJ

#### **6-14 DANGERS OF ROSUVASTATIN (*Crestor*) IDENTIFIED BEFORE AND AFTER FDA APPROVAL**

The lipid-lowering drug rosuvastatin (*Crestor*; Astra-Zeneca) is currently in the midst of the most heavily financed launch of a prescription drug *ever*.

The correspondent presents available pre-marketing and post-marketing evidence of the adverse effects of the drug. The preapproval document stated that 80 mg is associated with a high frequency of creatine kinase elevations (CK 10 times upper normal). *Crestor* was approved with the belief that lower doses would be much safer. The 80 mg dose was subsequently discontinued.

Since marketing of rosuvastatin, there have been 18 additional cases of rhabdomyolysis. Two patients were using 40 mg; five using 20 mg; 11 using 10 mg.

The 10, 20, and 40 mg doses have been associated with a risk of renal toxicity. There have been 8 reported cases of acute renal failure and 4 of renal insufficiency since marketing began. Nine were using 10 mg; two using 40 mg. “By now, the number of reported cases of rhabdomyolysis and renal insufficiency or renal failure—20 of which have occurred in people using 10 mg—is certain to have increased substantially from the number filed by April 13, 2004.”

A statistical review of comparative efficacy found no significant difference in LDL-cholesterol lowering between 5, 10, and 20 mg of rosuvastatin and 20, 40 and 80 mg of atorvastatin. (*This surrogate laboratory finding does not indicate comparative clinical effectiveness.*)

#### **Comment:**

*These letters raise an important clinical point. When should primary care clinicians add a new drug to their practice?*

*Is Crestor a unique and important addition to therapeutics? Or is it just a “me-too” drug? Should primary care clinicians prescribe it at the present time?*

- 1. Is Crestor more effective in lowering LDL? No. Other statins lower LDL just as much, although they might require a higher dose. Remember, this is a laboratory endpoint, not a clinical endpoint. Clinical efficacy has not been established.*
- 2. Is Crestor as safe as other statins? This is the dispute. That the 80 mg dose has been withdrawn because of toxicity raises caution. It will take several years of general use in the USA for the FDA to determine toxicity. Certainly, Crestor is not safer.*
- 3. Is Crestor more convenient to administer. Does it require fewer doses? No*

4. Is Crestor less costly? No. Costs are comparable.

*The first letter may raise an entirely unwarranted red flag. I do not know. I abstracted these letters mainly to reinforce the long-honored and oft-repeated admonishment to primary care clinicians not to be the first to prescribe a new drug, no matter how highly touted, unless it is known to be safe and carry unique and important benefits. Regardless of the question of toxicity, I do not believe the benefits of Crestor are unique or comparatively important.*

*I would not prescribe Crestor at this time. If it proves equally or less toxic, maintains its reported comparative efficacy in reducing LDL-c, and has a significant cost benefit, I would consider prescribing it.*

*I have faced (as have most older clinicians) the embarrassment of having a drug I had prescribed suddenly withdrawn from the market. The patient will ask for an explanation. RTJ*

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***Statin drugs may have important benefits if given immediately for acute coronary syndrome***

**6-1 ASSOCIATION OF STATIN THERAPY WITH OUTCOMES OF ACUTE CORONARY**

**SYNDROMES: The GRACE Study**

Statin drugs may have effects in addition to their effect on lipids. These include modulation of inflammation, inhibition of platelet function and thrombosis, and enhancement of endothelial function. The ability of statins to *immediately* affect basic pathophysiologic mechanisms has increased interest in their potential role in acute coronary syndromes. (ACS)

This study examined the association between previous and early in-hospital statin therapy and outcomes of ACS.

Conclusion: Statin therapy can modulate early pathophysiologic processes in patients with ACS.

**STUDY**

1. Multicountry observational study enrolled over 19 500 patients with ACS from 1999 to 2002.
2. All had symptoms of acute ischemia, and at least one of the following: ECG changes consistent with ACS, serial increases in biochemical markers of myocardial necrosis, documentation of coronary artery disease.
3. Treatments were defined as: no statin use; long-term use at home and within 7 days of the presenting event (but not in hospital); use in hospital only (not before hospitalization); and use both before and during hospitalization.
4. Determined hospital complications, and hospital deaths related to statin use. The composite end-point included death, in-hospital MI, and stroke.

**RESULTS**

1. 21% (4056) of the patients with ACS were already taking statins when they presented to the hospitals. Patients who were already taking statins when they presented to the hospital were less likely to have ST-segment elevation. (Odds ratio = 0.79); myocardial infarction (OR = 0.78); and other complications.
2. Incidence of hospital outcomes according to previous statin therapy:

	Long-term use (%)	No long term use (%)
Creatine phosphokinase > 2 times normal	28	45
MI after 24 hours or recurrent MI	7	10
Congestive heart failure	12	15
Cardiogenic shock	2	5
Cardiac arrest	3	6
Death	3	7
Final diagnosis:		
ST-elevation MI	18	38
Non-ST-elevation MI	30	30
Unstable angina	52	32

### 3. Hospital outcomes according to statin groups (%):

	No statin	Long-term only	In hospital only	Long-term and hospital
Cardiogenic shock	6.5	8.7	2.5	1.6
Cardiac arrest	7.5	8.2	3.4	1.9
Ventricular tachycardia or fibrillation	5	6.2	4.1	2.8
Death	9.9	11.6	2.1	2.1
Death, stroke, or in-hospital MI	17.9	17.3	15.3	9.2

*(Note that the 2 groups receiving statins in hospital had better outcomes than those who received no statins or received them long-term and discontinued on admission.)*

## DISCUSSION

1. Results suggest that previous statin therapy significantly affects severity of hospital presentation and hospital outcomes. Patients who presented with an ACS who were already taking statins were less likely to present with ST-segment elevation MI, experience a large infarct, and have important clinical complications, or die.
2. Much of the observed effect was lost if statin therapy was not continued during hospitalization. Such patients had death rates similar to patients who had never received statins. Withdrawal of statins reduces the protective effect of statin pretreatment
3. Previous studies have reported that statins (eg, atorvastatin) results in early (within 48 hours) decrease in C-reactive protein and augmentation of endothelium-dependent blood flow. Discontinuation in the hospital after admission for an ACS may cause a rebound phenomenon in which the protective pathophysiologic mechanisms are rapidly reversed.
4. “These findings are similar to the results of studies that have examined the effects of previous aspirin therapy on acute coronary syndrome presentation.” No reason why aspirin, beta-blockers, and ACE inhibitors cannot be used concomitantly with statins.
5. Some data suggests that initiation of lipid-lowering therapy during hospitalization in patients with acute MI is associated with long-term adherence and better post-discharge outcomes.
6. The authors state that their observational study cannot exclude possible multiple confounding factors.

## CONCLUSION

This large observational study suggests that patients who are taking statins when they present with an ACS have less severe presentations, fewer in-hospital complications, and lower hospital death rates.

The observed beneficial effect on outcomes is less apparent in those who did not continue statins during hospitalization.

In statin-naïve patients, early statin therapy was associated with an improvement in outcomes.

Annals Int Med June 1, 2004; 140: 857-66 Original investigation by the GRACE (Global Registry of Acute Coronary Events) investigators, first author Frederick A Spencer, University of Massachusetts Medical School, Worcester.

Comment:

*Should primary care clinicians act on these conclusions? Primary care clinicians often act on inconclusive evidence if the putative benefit/harm-cost ratio of the intervention is high. Although the outcomes of the study require confirmation and further experience, I believe the benefit/harm-cost ratio of immediate statin therapy (as of immediate aspirin therapy) for patients with ACS is potentially high. The benefit is potentially life-saving. The harm and cost of short-term therapy is very low. I would give a high-dose statin immediately on presentation of a patient with presumed ACS.*

*Those on statins long-term should be continued on statins when admitted for ACS. Those not on statins should start them immediately.*

*A study "Lipid-Lowering Therapy And In-Hospital Mortality Following Major Non-Cardiac Surgery" (See Practical Pointers May 2004 ) also presents evidence of immediate protective effects of statins given within the first 2 days after major surgery. RTJ*

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***More myocardial infarctions are caused by hemodynamically insignificant lesions than from high grade stenosis.***

## **6-2 THE SEARCH FOR THE "HOLY GRAIL" OF CLINICALLY SIGNIFICANT CORONARY ATHEROSCLEROSIS.**

In some individuals, coronary atherosclerosis is stable for years, and in others it is very unstable, with rapidly progressive lesions that result in sudden death or an acute coronary syndrome. The diagnostic "Holy Grail" of coronary atherosclerosis is *not* to be able to identify coronary atherosclerosis (which almost all Americans have eventually) but to identify individuals with *unstable* coronary atherosclerotic lesions.

Shortly after World War II, it became apparent that the greatest threat to the lives of Americans was not from without, but from within. Our greatest threat was cardiovascular disease, with 50% of Americans dying from it.

The medical profession's initial concept was that coronary atherosclerosis was characterized by a process that gradually, over decades, narrows the coronary arteries. We systematically looked for silent coronary disease with "executive physicals" that emphasized the treadmill exercise test. We were surprised to find that more myocardial infarctions occurred in the larger sub-population with negative results than in those with positive results.

These observations led to the era of coronary angiography, during which we assumed that angiography was the gold standard for identifying clinically significant coronary artery disease. Again, we found that, although a high grade coronary lesion was more likely to occlude, more myocardial infarctions were caused by hemodynamically insignificant lesions than from high grade stenosis. And there were many more of the hemodynamically insignificant lesions. When plaques in hemodynamically insignificant lesions ruptured, coronary artery thrombosis might occur with subsequent sudden death or an acute coronary syndrome. Most often the rupture is clinically silent. An estimated one in 100 plaque ruptures actually results in an acute coronary syndrome. The healing process leads to progressive coronary stenosis.

More recently, coronary intravascular ultrasound demonstrated that early atherosclerosis often results in "positive remodeling" of the coronary artery and does not narrow the lumen until the process is far advanced. As a

result, minimal lesions detected by coronary angiography may reflect advanced disease. These minimal lesions, if unstable, can result in plaque rupture and major acute coronary events.

How can we identify these unstable plaques? They are characterized by inflammation. The inflammatory cells produce cytokines that stimulate the liver to produce C-reactive proteins (CRP) and other acute phase reactants. High-sensitivity CRP appears to be a marker for more unstable coronary disease. Increasing levels of high-sensitivity CRP and an increasing ratio of total cholesterol to high density lipoprotein cholesterol can identify increased risk.

Scanning the coronary arteries for calcium, and assuming that one is identifying unstable coronary disease, or the risk for developing unstable coronary disease, is like scanning an egg and trying to assess the composition and stability of the yoke by the amount of calcium in the shell. Unstable coronary atherosclerosis undoubtedly develops before calcification.

The search for the “Holy Grail”, a fail-safe method for detecting clinically significant coronary atherosclerotic disease, must continue.

Archives Int Med June 28, 2004; 164: 1266-67 Editorial by Gordon A Ewy, University of Arizona, Tucson.

Comment:

*This editorial was written in response to a meta-analysis in this issue of Archives (pp 1285-92) which concluded that the coronary artery calcium score detected by electron-beam computed tomography is an independent predictor of coronary events.*

*The point of the editorial was to state that the clinical utility of fast computed tomography is not ready for prime time. While scanning may reveal calcification, individuals with unstable coronary disease are not always identified. A patient with potentially unstable coronary atherosclerotic lesions may have mildly calcified or non-calcified arteries. Patients with stable and unstable coronary atherosclerosis may have similar calcium scores.*

*Prevention of an essentially universal disease must be universal. Must we wait for screening tests to detect “higher risk”, and only then encourage patients to change lifestyles? RTJ*

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***“The probability of progression from localized to metastatic increases markedly after long-term follow-up.”***

### **6-3 NATURAL HISTORY OF EARLY, LOCALIZED PROSTATE CANCER**

The challenge of prostate cancer (PC) is to maximize the possibilities of survival without extensive over-treatment. Even without any initial treatment, only a small proportion of patients diagnosed at an early stage die from PC within 10 to 15 years following diagnosis.

No study has hitherto adequately analyzed whether patients who escaped metastases and death without treatment during 10 to 15 years after diagnosis continue to have an indolent, nonfatal disease course, or whether in the long-term tumor progression takes a more aggressive turn.

Because it takes several years after operation for any benefit to emerge, age at diagnosis, comorbidity, and long-term natural history will determine the potential advantage from radical primary treatment.

This observational study of the long-term natural history of PC assessed disease progression and mortality after years of watchful waiting.

Conclusion: Although most PCs diagnosed at an early stage have an indolent course, local recurrence and aggressive metastatic disease may occur in the long term.

## STUDY

1. Population-based cohort study followed 223 untreated patients (age range at diagnosis 41-91; mean = 72) with PC over a mean of 21 years. All had early stage PC: T1, T2; NX; M0.  
[T1-T2 = PC confined within gland; T1 = nodule surrounded by normal tissue, not palpable; T2 = palpable disease with a large nodule or multiple nodules; NX (no nodes involved); M0 (no metastases).]
2. The great majority of PCs were highly differentiated; only 4% were poorly differentiated.
3. None received a PSA determination. The test was not available when the study began. About half were diagnosed by histopathologic examinations of specimens obtained at operation for suspected benign prostatic hyperplasia.
4. All were followed up from diagnosis until death, or until September 2001, when the study was terminated. All were followed by clinical examinations, laboratory tests, and bone scans. If the PC progressed to symptomatic disease, estrogens or orchiectomy were prescribed. Local progression was defined as tumor growth through the prostate capsule (T3) as judged by digital rectal examination. Development to metastases (M1) was classified as generalized disease.
5. Main outcome = progression-free, cause-specific, and overall survival.

## RESULTS

1. Over the 21 years, most patients died (mainly of causes other than PC) Only 9% survived.
2. Poor differentiation was a strong predictor of cancer-specific death. This became evident within the first 5 years.
3. Most cancers had an indolent course during the first 10 to 15 years. Cancer progression and mortality remained fairly constant during the first 15 years following diagnosis. Progression to metastatic disease was 18 per 1000 person-years; PC mortality rate = 15 per 1000 person-years. In contrast, after 15 years, an approximately 3-fold higher rate occurred in both progression and mortality.
4. During the entire 21-year observation, PC was considered the cause of death in 16%. Among patients *under* age 70 at diagnosis, 22% died from PC. At higher ages at diagnosis, the mortality from PC decreased markedly.
5. Further follow-up after 15 years (n = 49 patients) revealed a substantial worsening of the cancer. Progression-free survival decreased from 45% to 36%; survival without metastases from 77% to 51%; and prostate cancer specific survival from 79% to 54%. PC mortality rate increased from 15 per 1000 person-years during the first 15 years to 44 per 1000 beyond 15 years.

## DISCUSSION

1. This study revealed an unexpected change in prognostic outlook after 15 years of observation. The cause-specific mortality from PC increased by 3-fold after this time as compared with the first 15 years.

2. The increase occurred consistently across stage and grade except for poorly differentiated cancers in which excess mortality became manifest during the first 5 years.
3. Mortality rates were mirrored closely by rates of disease progression to metastatic disease.
4. "If our data reflect a real phenomenon, they would imply that the probability of progression from localized and indolent to metastatic and mortal disease increases markedly after long-term follow-up."
5. PC mortality was slightly higher among patients whose cancer was diagnosed at age 70 or younger.

## CONCLUSION

Most PCs diagnosed at an early stage have an indolent course. Local tumor progression and aggressive metastatic disease may develop long-term (after 15 years). This would support radical treatment, notably among patients with an estimated life-expectancy of over 15 years.

JAMA June 9, 2002; 291: 2713-19 Original investigation, first author Jan-Erik Johansson, Orebro University Hospital, Orebro Sweden.

Comment:

*The study is unique. It will never be repeated.*

*This would argue for greater screening of younger men; less aggressive screening in older men. Long term follow-up may be necessary to observe the full benefits of early diagnosis and treatment in younger men.*

*According to these data, even if your PC is highly differentiated, you still run a risk of about 2 in 100 of developing metastatic disease each year, and about 1 to 2 chances in 100 of dying of PC each year. If you survive over 15 years, these chances are increased by 300%.*

*Prostate cancer is never cured spontaneously.*

*If you live long enough and are not treated, your chance of eventually developing metastatic disease (requiring orchiectomy or estrogen therapy) and fatal PC is high, even if you have a highly differentiated PC.*

*If you have a poorly differentiated grade PC and are not treated, you will likely die of it within 5 years.*

*No doubt some lives are saved by radical treatment. Which ones? RTJ*

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***Adipose tissue is an important endocrine organ that produces several bioactive proteins***

## **6-4 ABSENCE OF AN EFFECT OF LIPOSUCTION ON INSULIN ACTION AND RISK FACTORS FOR CORONARY HEART DISEASE.**

Abdominal obesity (increased abdominal subcutaneous fat, and increased visceral fat) is associated with insulin resistance and other risk factors for coronary heart disease (**CHD**).

This study asked: Which of these fat deposits is associated with insulin resistance and increased risk of CHD?

Conclusion: Removal of subcutaneous abdominal fat does not alleviate insulin resistance.

## STUDY

1. Followed 15 sedentary obese women (mean age 42) with increased abdominal circumference (mean = 108 cm; mean body mass index = 38). All had been scheduled for abdominal liposuction for cosmetic reasons.
2. Evaluated insulin sensitivity of liver, skeletal muscle and adipose tissue with a euglycemic-hyperinsulinemic clamp procedure (*see text*) before and after liposuction.
3. Also determined levels of inflammatory mediators and other risk factors for CHD.

## RESULTS

1. Liposuction reduced volume of subcutaneous abdominal fat by 44%. Weight loss = 10 kg; total body fat decreased by 18%.
2. Liposuction did not significantly alter insulin sensitivity (assessed by stimulation of glucose uptake in muscle); did not suppress glucose production by the liver; and did not suppress lipolysis of adipose tissue.
3. Levels of C-reactive protein and other indicators of inflammation did not change.
4. Other risk factors for CHD were unchanged (BP, plasma glucose, insulin, and lipid concentrations).

## DISCUSSION

1. Large-volume reduction in subcutaneous abdominal fat mass did not have any beneficial metabolic effects despite a considerable decrease in body weight, waist circumference, and plasma leptin concentrations.
2. The amount of fat removed was equivalent to weight loss achieved by optimal behavioral and pharmacological treatments. (about 12% of body weight). This amount of weight loss by these methods usually results in marked improvements in the metabolic abnormalities associated with obesity (insulin sensitivity, BP, and lipids), and reduces levels of circulating markers of inflammation.
3. “It is striking that the amount of fat loss achieved by liposuction...did *not* improve any of these metabolic variables.”
4. This provides insight into the mechanism by which conventional weight loss improves insulin sensitivity. Induction of a negative energy balance, not simply a decrease in the mass of fat tissue, is critical for achieving the metabolic benefits of weight loss. Even small amounts of weight loss induced by a negative energy balance affect many variables pertaining to body-fat composition and lipid metabolism—variables that contribute to metabolic abnormalities associated with obesity. Weight loss decreases visceral fat mass, intrahepatic fat, fat-cell size, and the rate of release of fatty acids from adipose tissue. Liposuction does not.
5. Adipose tissue is an important endocrine organ that produces several bioactive proteins, including interleukin-6, tumor necrosis factor, and adiponectin. Interleukin-6 and tumor necrosis factor can cause insulin resistance and atherosclerosis by impairing insulin signaling, stimulating lipolysis and fatty acid release, increasing hepatic synthesis of C-reactive protein, and increasing systemic inflammation, whereas the production of adiponectin by adipose tissue can *improve* insulin sensitivity and inhibit vascular inflammation. Fat loss by conventional obesity treatment decreases concentrations of C-reactive protein, interleukin-6, and tumor necrosis factor. Conversely, it *increases* concentration of adiponectin. .
6. Liposuction did decrease plasma leptin concentrations, a marker of adipose-tissue mass.
7. Liposuction may have cosmetic benefits, but no other.

8. “The effects of a negative energy balance on specific endogenous triglyceride depots and inflammation, which are not altered by liposuction, may be necessary to achieve the clinical benefits of therapy for obesity.”

## CONCLUSION

Abdominal liposuction does not improve obesity-associated metabolic abnormalities. It does not achieve the metabolic benefits of conventional weight loss.

NEJM June 17, 2004; 350: 2549-57 Original investigation, first author Samuel Klein, Washington University School of Medicine, St. Louis, MO.

Comment:

*I abstracted this article mainly to point out the risks associated with intra-abdominal fat accumulation. Visceral fat depots drain directly into the portal circulation and into the liver; subcutaneous fat depots drain into the general circulation. There is a vast metabolic difference.*

*I suspect the investigators really did not believe subcutaneous abdominal liposuction would improve metabolic functions. It is important, nevertheless, to have objective data.*

*C- reactive protein is a favored marker of inflammation because a high-sensitivity determination is available at modest cost.*

*Liposuction is the most common aesthetic procedure performed in the USA. New techniques make it possible to remove considerable amounts of subcutaneous fat tissue. RTJ*

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### ***Some adipose tissue has endocrine functions***

## **6-5 THERMODYNAMICS, LIPOSUCTION, AND METABOLISM**

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

The regulation of body weight adheres to the principle of thermodynamics: a positive energy balance causes weight gain, and a negative balance weight loss. (*Calories still count.*) There is good evidence that a moderate amount of weight loss plus increased physical activity reduces the likelihood of progression from impaired glucose tolerance to type 2 diabetes.

The editorialist comments on two important metabolic benefits that are directly related to effect of a negative energy balance: 1) rapid improvement in hyperglycemia, and hypertension, and 2) benefits on metabolic risk factors related to loss of visceral adiposity.

1) Hyperglycemia improves *rapidly* during caloric restriction. It outpaces the rate of weight loss. About half of the improvements in glycemic control are achieved during the first week of a negative energy balance, although the actual fat loss is typically quite small during short periods of caloric restriction. Substantial proportions of the early benefits of weight loss on insulin resistance and hyperglycemia in type 2 diabetes may be attributed to a negative energy balance.

Similar observations have been made concerning hypertension. Much of the decrease in BP occurs fairly rapidly in response to a negative energy balance. There is, however, a return toward hypertensive levels once weight has reached a plateau.

Weight loss by liposuction has no comparable beneficial effects.

2) Visceral adiposity is strongly associated with insulin resistance. In animals, surgical resection of visceral fat tissue yields marked and nearly immediate improvement in insulin resistance. The removal of an equivalent amount of subcutaneous fat has little effect.

The relation may be related, at least in part, to the release of fatty acids into the portal circulation.

Adipose tissue has endocrine functions—synthesizing leptin, and cytokines such as tumor necrosis factor, interleukin-6, and C-reactive protein.

It may well be that a negative energy balance permits a rapid improvement in fat content within liver and muscle, depots of stored energy that affect the severity of insulin resistance.

NEJM June 17, 2004; 350: 2542-44 Editorial by David E Kelley. University of Pittsburgh, PA.

Comment:

*During World War II type 2 diabetes practically disappeared in the Netherlands. This was related to the near starvation conditions produced by the invasion by Germany. RTJ*

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### ***Surgery prevents recurrence***

## **6-6 COMPARISON OF SURGERY AND COMPRESSION WITH COMPRESSION ALONE IN CHRONIC VENOUS ULCERATION (ESCHAR study)**

Chronic venous ulceration affects 1-2% of the population. It usually has a protracted course of healing and can recur many times.

Multilayered elastic compression bandaging, leg elevation, and exercise achieve healing in up to 80% at 24 weeks. However, despite continued use of elastic compression stockings, the 12-month recurrence rate is 25% or higher.

Conservative measures do little to address the underlying abnormal venous function. About 50% of patients with ulceration have reflux in the superficial system of veins alone; about 40% in the superficial and deep venous systems; and about 10% reflux in the deep system alone.

Simple superficial venous surgery (saphenous vein ablation) theoretically removes the underlying venous incompetence in legs in patients with isolated superficial reflux. Surgery to correct venous reflux in the deep veins is complex and of unproven value.

This study assessed the effect of surgery + compression vs compression alone on healing and recurrence of ulcers.

Conclusion: Surgery reduced 12-month recurrence. It did not hasten healing.

### **STUDY**

1. Performed venous Doppler ultrasound imaging of ulcerated or recently healed legs in 500 consecutive patients (mean age 73).
2. Randomized those with isolated superficial venous reflux and mixed superficial-deep reflux to:
  - 1) Compression alone, or 2) Compression + surgery of superficial veins.

3. Compression consisted of multilayer compression bandaging every week until healing occurred. Then continued compression with below-knee support stockings.
4. Primary endpoints = 24-week healing rates and 12-month recurrence rates.

## RESULTS

1. Healing rates over 24 weeks were similar between groups

	Surgery-compression	Compression alone
Isolated superficial	65%	66%
Superficial and segmental deep	56%	57%

2. Twelve month ulcer recurrence was significantly reduced in the surgery + compression group (12% vs 28%).

	Surgery-compression	Compression alone	NNT
Isolated superficial	12%	28%	6
Superficial and segmental deep	9%	25%	6

3. Adverse events: few surgical patients developed deep vein thrombosis, wound infection, hematoma, and phlebitis.

## DISCUSSION

1. Postoperative ultrasound has shown that segmental reflux in the deep veins is reversed in about 50% of cases by ablative superficial venous surgery.
2. Healing is not enhanced at 24 weeks by superficial vein surgery. This is probably because the hemodynamic benefits of compression are as great as surgery.
3. Superficial vein surgery significantly reduced recurrence of ulcer at one year.

## CONCLUSION

Surgical correction of superficial venous reflux reduced 12-month recurrence of leg ulcers. It did not hasten healing.

Lancet June 5, 2004; 363: 1854-59 Original investigation, first author Jamie R Barwell, Cheltenham General Hospital, Cheltenham, UK

ESCHAR Effect of Surgery and Compression on Healing And Recurrence

Comment:

*The investigators state that about a quarter of patients with venous ulcers will refuse surgery. Primary care clinicians then deal with these individuals as best they can. RTJ*

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***“Ovarian cancer is not a silent disease.”***

**6-7 FREQUENCY OF SYMPTOMS OF OVARIAN CANCER IN WOMEN PRESENTING TO PRIMARY CARE CLINICS.**

Ovarian cancer (OC) has been called the “silent killer” because symptoms are thought not to develop until advanced stages when chance of cure is poor. Standard textbooks state that symptoms do not occur until the disease is advanced. However, several retrospective studies have indicated that the majority of patients with OC do have early symptoms, although not necessarily gynecologic in nature.

Identification of early symptoms may have important clinical implications because the 5-year survival for early stage disease is 70% to 90% compared with 20% to 30% for advanced-stage disease.

Distinguishing symptoms of OC from those that typically occur in women seeking medical advice remains problematic.

This study compared the frequency, severity, and duration of symptoms associated with OC with symptoms in a typical population of women presenting to primary care clinics.

Conclusion: Suspicion of OC may be increased if symptoms occur more frequently, are more severe, and have begun within the past 6 months. Combined abdominal bloating, increased abdominal size, and urinary symptoms occur much more frequently in OC patients. .

## STUDY

1. Prospective case-control study of women attending primary care clinics. All voluntarily completed a survey of symptoms experienced over the past year. Symptoms severity was rated on a 5-point scale. Duration was recorded, and frequency indicated as the number of episodes per month.
  - A. Cases: 128 women with a pelvic mass who were about to undergo surgery (84 benign; 44 malignant). (Median age of OC patients = 55)
  - B. Controls: Over 1700 women (median age 45) actively seeking medical care who visited a clinic for a total of about 12 000 times.
2. Participants were given a list of 20 symptoms that had been reported to be associated with OC. These included pain, eating difficulties, abdominal symptoms, bladder symptoms, bowel symptoms, menstrual and sexual intercourse symptoms, and constitutional symptoms.
3. Main outcome measures: comparison of self-reported symptoms between OC patients (the “cases”) and the other clinic visitors.(the “controls”).

## RESULTS

1. Women with OC described differences in symptoms:
  - A. Frequency: Women with OC typically experienced more frequent occurrence of symptoms—20 to 30 times a month (almost daily). Clinic patients typically reported symptoms which occurred 2 to 3 times per month. In younger women, symptoms often appeared with menses.
  - B. Severity: Symptoms in OC patients were in general more severe. (Controls typically 2 to 3 on a scale of 1-5: OC patients typically 4 or 5.
  - C. Onset: New symptoms in OC patients were of more recent onset: 60% within 3 months; only 14% started over 1 year ago. Women with OC in general had symptoms of significantly shorter duration—6 months

or less. For women with irritable bowel syndrome and controls the median duration of symptoms was typically 12 to 24 months.

D. Median number of symptoms: OC eight different symptoms, 4 recurring; controls 4 different symptoms, and 2 recurring.

E. Type of symptom:

OC patients described several symptoms more frequently than controls:

	Odds ratio cases vs controls
Increased abdominal size	7.4
Bloating	3.6
Urinary urgency	2.5
Pelvic pain	2.2

2. The combination of bloating, increased abdominal size, and urinary symptoms was found in 43% of those with OC, but only in 8% of controls, and in 13% of women with irritable bowel syndrome (**IBS**). Women with IBS may present more difficulty in differential diagnosis. There are differences. Women with IBS were significantly more likely to have fatigue, gastrointestinal complaints, and abdominal pain. . Duration of their symptoms is longer.

3. All symptoms in controls were less common as age increased except for urinary tract symptoms which increased in severity with age. *(Be especially alert when an older woman presents a changing symptom pattern as described above.)*

4. Any ovarian mass (benign, borderline or malignant) has a high likelihood of producing symptoms. Most women with benign ovarian masses had complaints similar to those of OC.

## DISCUSSION

1. No screening test or surveillance strategy has been shown to reduce ovarian cancer mortality. Screening the general population is not effective.

2. It is important to understand the symptoms of OC so that the diagnosis can be made as soon as possible.

3. Theoretically, early diagnosis would lead to greater chance of cure. Optimal cytoreduction of the tumor is associated with cure in up to 40% and median survival of more than 50 months vs 20% and 36 months for suboptimal cytoreduction.

4. Symptoms typical of OC should not be attributed to the aging process.

5. "Ovarian cancer is not a silent disease."

## CONCLUSION

Symptoms that are more severe and frequent than expected and of more recent onset warrant further diagnostic intervention because they are more likely to be associated with ovarian tumors, both benign and malignant.

JAMA June 9, 2004; 291: 2705-12 Original investigation, first author Barbara A Goff, University of Washington School of Medicine, Seattle. www.jama.com

An editorial in this issue of JAMA (pp 2755-56, first author Mary B Daly, Fox Chase Cancer Center, Philadelphia PA comments:

Detected early, cure rates approach 90%. The majority of OC is unfortunately detected too late. Since an acceptable screening approach is not available, we must rely on symptom identification for early diagnosis.

“There is no way to avoid the conclusion that early diagnosis of ovarian cancer must rely on the elusive practice of clinical judgment, a skill that involves careful analysis of the characteristics of the presenting symptom set within the context of thoughtful dialogue.” “The importance of this study is not the validation of a symptom cluster, . . . but rather the reinforcement of the need for an ongoing process of communication between patients and their physicians.”

Comment:

*This requires the patient to carefully recall and describe her symptoms. And requires the physician to be especially alert about eliciting the time of onset, severity, and duration, of the symptoms. Clarity may be achieved only after several visits.*

*Physicians should ask specifically about bloating, abdominal size and urinary symptoms.*

*The authors did not describe outcomes for the 44 patients with OC who underwent surgery. RTJ*

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### ***About 1/3 of obese men regained erectile function while losing over 10% of their weight***

#### **6-8 EFFECT OF LIFESTYLE CHANGES ON ERECTILE DYSFUNCTION IN OBESE MEN**

Erectile dysfunction (**ED**) is common, even in younger men. Several modifiable lifestyle factors are associated with maintenance of erectile function. Men with a body mass index over 28 have a 30% higher risk of ED. The prevalence of overweight and obesity in men reporting ED may be as high as 79%, although vascular factors associated with obesity may play an important role.

ED and endothelial dysfunction may have some shared pathways through a defect in nitric oxide activity, production of which may be inhibited through age-, disease-, and behavioral-related pathways.

This study of obese men with ED aimed to determine if a long-term reduction in BMI and an increase in physical activity positively affected erectile functions.

Conclusion: The lifestyle changes were associated with improvement in erectile function.

#### **STUDY**

1. Randomized trial followed 110 obese sedentary, otherwise healthy, men<sup>1</sup> (Mean body mass index = 36; mean age 43) who had ED determined by the *International Index of Erectile Function*.<sup>2</sup> ED was defined by a score of 21 or less (out of a possible 25) on the index.
2. None had diabetes, hypertension, impaired renal function, or hyperlipidemia.<sup>1</sup>
3. Randomized to: 1) intervention group received detailed advice about how to achieve a loss of 10% or more in body weight by reducing caloric intake and increasing physical activity, or 2) a control group given general information about healthy food choices and exercise.
4. Main outcome = erectile function score and endothelial function assessed by response to L-arginine.<sup>3</sup>

5. Follow-up = 2 years.

## RESULTS

1. In the treated group, over 2 years, total energy and saturated fat intake decreased considerably. Intake of mono- and poly-unsaturated fat, and omega-3 fats increased.

2. Mean changes at 2 years:	Treated (n = 55)		Control (n = 55)	
	Baseline	2 years	Baseline	2 years
Weight (kg)	103	88	101	99
Body mass index	37	31	36.4	35.7
Physical activity (min/wk)	48	195	51	84
IIEF score	14	17	14	14
Men with IIEF score of 22 or higher		17		3

*(Note that about 1/3 of men regained function while losing over 10% of their weight, despite remaining obese. RTJ)*

3. There was also evidence in the treated group of improved endothelial function by responses of platelet aggregation and BP to L-arginine.

4. C-reactive protein levels decreased in the treated group.

## DISCUSSION

1. Healthy lifestyles are associated with maintenance of good erectile function.

2. Obese men with ED have evidence of abnormal endothelial function.

3. This study provides evidence that weight loss achieved by lifestyle changes can improve erectile function in obese men with ED.

4. Nitric oxide appears to play an important role in the pathogenesis of ED. Improved NO availability associated with weight loss may be implicated in improving erectile function.

5. The investigators state that the intervention in the treatment group was intensive, and involved frequent contact with the study team.

## CONCLUSION

Lifestyle changes (diet, exercise, and weight loss) in obese men with ED were associated with improvements in erectile function.

JAMA June 23/30 2004; 291: 2978-84 Original investigation , first author Katherine Esposito, Second University of Naples, Italy. [www.jama.com](http://www.jama.com)

1 Grossly obese sedentary men of this age who are otherwise healthy must be rare indeed. I would wager that most, if not all, had the metabolic syndrome

2 I had not encountered this index before. It consists of 5 questions about sexual functioning, each divided into a score of 1 to 5 depending on the difficulty experienced. Possible scores range from 5 to 25, the lower number

indicating a higher degree of dysfunction. (See description p 2979) Can be accessed at: Google “international index erectile function”

- 3 Erectile and endothelial dysfunction may have some shared pathways through a defect in nitric acid activity. Endothelial function was measured by response of BP and platelet aggregation to an intravenous bolus of L-arginine, a natural precursor of nitric oxide. See text and references.

An editorial in this issue of JAMA by Christopher S Saigal, University of California, Los Angeles, comments and expands on the study:

The introduction of *Viagra* in 1998 unleashed a tidal wave of interest in treatment of ED. The heavy direct-to-consumer marketing campaign contributed to a new, open discussion in popular culture about this very common condition. ED was suddenly fair game for late night comics. Within 2 years, a billion dollar industry developed. Physician office visits for ED increased.

For many patients, ED is a manifestation of more generalized pathology. Hypertension, hyperglycemia, and dyslipidemia are common co-morbidities. Endothelial dysfunction is likely a pathogenic mechanism common to these co-morbid states, risk of cardiovascular disease, and ED. Weight loss in these obese patients was associated with reduction in serum concentrations of markers of inflammation such as C-reactive protein. This is further evidence of improved endothelial function.

Regular physical exercise can have a modifying effect on risk of developing ED. One study of men age 40 to 70 without ED reported the future risk of developing ED was much lower in those who started a physical activity program vs those who remained sedentary.

The benefits of this intensive program are not limited by any means to improvement in ED. Lowering risk of cardiovascular disease is, for many, more important.

Comment:

*I congratulate the investigators, and especially the patients, on maintenance of a very rigid treatment program. This is not, however, a practical application. Few patients in primary care practice would be able to complete such a program*

*The main message is—maintain a healthy lifestyle, don't wait to repair damage until after it is done. RTJ*

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***“Unwanted pregnancy remains a major personal and public health issue”***

## **6-9 WAITING FOR PLAN B—THE FDA AND NONPRESCRIPTION ON EMERGENCY CONTRACEPTION**

The proposal to switch to levonorgestrel emergency contraception (EC; *Plan B*) to over-the-counter status is in limbo. In May, the FDA rejected the application of Barr Pharmaceuticals for non-prescription sales. Dr. Steven Galson, the acting director, wrote that the company had “not provided adequate data to support a conclusion that *Plan B* can be used safely by young adolescent women for emergency contraception without the professional supervision of a practitioner licensed by law to administer the drug”. In rejecting the application, the FDA also rejected the advice of its medical review-staff. (A vote of 23 to 4 in favor of nonprescription status.)

It is uncertain whether—or when—a revised application might be approved.

*Plan B*, approved for prescription use in 1990, consists of two 0.75 mg pills of the synthetic progestogen, levonorgestrel. (A component of many birth control pills.) It should be taken as soon as possible and within 72 hours of unprotected intercourse. Taken in the first 24 hours, the rate of pregnancy is reduced to 0.4%, and to 2.7% when taken within 72 hours.

Rates of pregnancies and induced abortions have decreased in the US, particularly among adolescents, primarily because contraceptive use has improved and because girls have been starting to have intercourse at older ages. Nonetheless, unwanted pregnancy remains a major personal and public health issue. Commonly cited estimates are that half of all pregnancies are unintended, that one of every two girls and women between 15 and 44 years has had at least one unintended pregnancy, and that in 2000, as many as 51 000 abortions were averted by use of EC pills.

Nonprescription use of EC would, according to Dr Galson. “dramatically increase access to oral contraception and will represent an important step forward in availability of these products”. Dr Galson stated that he himself “made the decision” not to approve on the basis of scientific data. His signing the “Not Approvable” letter was a very unusual action.

There is extensive data about the safety and effectiveness of Plan B. There have been only isolated findings of increased rates of intercourse, unprotected intercourse, or intercourse without appropriate contraceptive methods in association with its availability.

The FDA medical review committee voted unanimously that “the data demonstrate that Plan B is safe for use in the non-prescription setting” and that there is no evidence that over-the-counter “availability of Plan B leads to substitution of emergency contraception for the regular use of other methods of contraception”. Concerns about young teenagers were discussed, but these were not the focus of the deliberation. Committee members were not asked to vote on whether girls younger than 16 years could use nonprescription Plan B safely. FDA staff members also recommended the approval of the application. As part of the “questions and answers” document, the agency asked itself, “Did the FDA bow to political pressure in making this decision?”, and answered “No”.

The president of the American College of Obstetricians and Gynecologists(ACOG) said the FDA’s action was “morally repugnant”.

Young teenagers account for only a tiny fraction of the potential users of EC. Side effects and costs of nonprescription pills would be powerful deterrents to repeated use. Dr. Elizabeth Raymond of Family Health International, stated that “The FDA’s fixation on young adolescents is simply unjustified”. Research “shows that they can use the pills correctly and safely”.

Children may purchase acetaminophen, aspirin, and NSAIDs without a prescription and without an age check. The FDA has never required specific data on the safe and correct use of these or other medications in children and adolescents, although their improper use is harmful and potentially lethal.

The ACOG urges all obstetrician-gynecologists to provide prescriptions for EC to all women of reproductive age at every office visit.

Comment:

*I would be willing to wager that this decision will be reversed. RTJ*

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***“As effective and as safe as enoxaparin.”***

## **6-10 FONDAPARINUX OR ENOXAPARIN FOR THE INITIAL TREATMENT OF SYMPTOMATIC DEEP VENOUS THROMBOSIS**

Low-molecular-weight heparin (**LMWH**) is standard initial for treatment of deep venous thrombosis (DVT). It consists of once- or twice-daily subcutaneous injections of a dose adjusted only for bodyweight. Treating suitable patients at home, often with self-injection, is effective and safe.

Fondaparinux is a selective inhibitor of activated factor X (Xa). Once-daily injections produce a predictable anticoagulant effect. It has an advantage of not cross reacting with heparin-induced antibodies. Platelet monitoring may no longer be needed.

This study asks—is fondaparinux safe and effective therapy for established DVT? How does it compare with LMWH?

Conclusion: Once-daily fondaparinux was as effective and as safe as the LMWH enoxaparin.

### STUDY

1. Randomized, double-blind multicenter study entered over 2200 patients (mean age 61) with established acute symptomatic DVT of the lower extremity. All were judged to require antithrombotic therapy. None had symptomatic pulmonary embolism.
2. Randomized to: 1) fondaparinux (*Axistra*) subcutaneously once-daily—5 to 7.5 to 10 mg according to weight, or 2) enoxaparin (*Lovenox*) 1 mg/kg body weight twice-daily.
3. All were started on oral anticoagulant therapy within 72 hours. (Choice according to hospital practice to maintain an INR of 2.0 to 3.0.)
4. Double-blind subcutaneous injections were continued for at least 5 days, or until the warfarin-induced INR reached 2.0 or greater. Oral therapy was continued for 3 months.
5. Primary efficacy outcome was 3-month incidence of recurrent symptomatic DVT.

### RESULTS

1. Outcomes at 3 months	Fondaparinux	Enoxaparin
Recurrent thromboembolic events	3.9%	4.1%
Pulmonary embolism		
Fatal	5 patients	5 patients
Nonfatal	20 patients	12 patients
Recurrent DVT	18 patients	26 patients
Major bleeding		
During initial treatment	1.1%	1.2%

During entire study	2.6%	2.4%
Death during entire study	3.8%	3.0%

## DISCUSSION

1. The study demonstrated that fondaparinux is as safe and as effective as enoxaparin (or, in commonly used parlance, is “non-inferior”<sup>1</sup>).
2. Prefilling syringes with 7.5 mg fondaparinux (the most commonly used dose) makes treatment feasible for outpatient therapy. About 1/3 of the patients received treatment partially or entirely at home.
3. Home treatment with self-administered LMWH is increasingly used, but is subject to dosing errors when bodyweight, dosage, or dosing intervals are uncertain, and when patients have limited capability to titrate prefilled syringes, or withdraw dosage from multidose vials.
4. Fondaparinux does not have a specific antidote.
5. Primary efficacy outcome = 3-month incidence of recurrent DVT.

## CONCLUSION

Once-daily subcutaneous fondaparinux was at least as safe and effective (not inferior<sup>1</sup>) as twice-daily enoxaparin in the initial treatment of DVT.

Annals Int Med June 1, 2004; 140: 867-73 Original investigation, first author Harry R Buller, University of Amsterdam, the Netherlands.

An editorial in this issue of the Annals (pp 925-26) by Paolo Prandoni, University of Padua, Italy comments:

There are several cautions about at-home treatment with either LMWH or fondaparinux:

1) Concern about undertreatment of DVT and resultant pulmonary embolism, and 2) the need for careful laboratory monitoring of oral anticoagulation status during the first days of treatment. This is indispensable to guarantee the correct overlap between subcutaneous drugs and warfarin.

Fondaparinux has a possible advantage over LMWH in that it does not bind to platelet factor 4. This makes the development of immune thrombocytopenia extremely unlikely (although it is rare during treatment with LMWH).

Fondaparinux has been approved for prophylaxis of VTE after major orthopedic surgery. Once daily fondaparinux 2.5 mg reduced VTE risk by more than 50% in comparison with enoxaparin.

Other anticoagulant drugs are in the offing—ximelagatran, a selective antithrombin, and idraparinux, which can be administered in fixed doses once weekly.

Comment:

- 1 *The term “non-inferior” appears frequently in conclusions of current studies comparing one drug with another. I wonder why this (negative) terminology is used in favor of the positive “just as effective and safe”. Should fondaparinux be considered a “me too” drug? For a new drug to be adopted into primary care practice to replace an old effective drug, important attributes must be established. Comparing (a) Xa inhibitor to (b) LMWH:*

1. (a) must be established as just as effective, or more effective.
2. (a) must be established as just as safe or safer.
3. (a) must be more convenient to administer and require fewer doses.
4. (a) must be less costly.

*The study presents evidence that 1. and 2. are likely. Confirmation and more experience are required.*

*3. does seem likely. 4. is to be determined.*

*Study sponsored by Sanofi-Synthelabo and MV Organon. I hesitate to say it, but I always look for “spin” in drug-company sponsored studies. This study looks straight forward. We look for confirmation. RTJ*

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**“Benefits are below minimally relevant thresholds”**

**6-11 LONG TERM DONEPEZIL (*Aricept*) TREATMENT IN 565 PATIENTS WITH ALZHEIMER’S DISEASE (AD 2000)**

Degeneration in cholinergic forebrain neurons innervating the cortex is believed to contribute to cognitive defects seen in Alzheimer’s disease (**AD**). This concept triggered development of cholinesterase inhibitors (**CI**s) which raise acetylcholine levels by blocking the enzymes that metabolize acetylcholine.

All three available CIs produce small improvements in cognitive and global assessments in selected patients with mild-to-moderate AD over 3-12 months. Little is known about long-term effectiveness, or their usefulness in patients with severe AD. Nonetheless, the demand from clinicians and patients remains strong.

CIs (vs placebo) produce on average a small advantage on simple cognitive tests (eg, 3-points on the 70 point Alzheimer’s Disease Assessment Scale [ADAS-cog] ). Is this small benefit worthwhile?

This study asked whether the cholinesterase inhibitor donepezil (*Aricept*) is cost effective and produces worthwhile clinical and social improvements.

Conclusion: Benefits of donepezil are below minimally relevant thresholds. It is not cost effective.

**STUDY**

1. Randomized, double-blind trial entered 565 (and followed 486) community-resident patients (mean age 70-79). The patients had been referred from memory clinics. They were diagnosed as having AD (with or without vascular dementia) by DSM IV criteria. About half were judged to have mild AD; half to moderate AD by the Mini-mental-state examination.(MMSE)<sup>1</sup> The doctors involved were substantially uncertain whether donepezil would produce worthwhile benefits.<sup>2</sup>
2. Randomized to: 1) Donepezil (5 or 10 mg daily), or 2) Placebo.
3. Followed patients as long as judged appropriate.
4. Primary endpoints = entry into institutional care and progression of disability defined by an activity of daily living scale.

**RESULTS**

1. Effects on MMSE:
  - A. Donepezil group:

In absolute terms, donepezil group achieved a slightly higher score within the first 36 weeks (about one point above baseline on a 30-point scale). Thereafter, scores deteriorated back to baseline at 48 weeks and to minus 4 points at 112 weeks.

B. Placebo group:

In absolute terms, the placebo group continuously lost points during the 110 weeks.

C. Comparing A. with B.

Comparatively, over 112 weeks, donepezil group maintained a slightly better score (a fraction of one point) despite its continuing decline in absolute terms.

*(See figure 6 p 2111)*

*[Advocates can point to a slight improvement in MMSE over 36 weeks. The general course over 112 weeks was downward. RTJ]*

2. Effects on an ADL scale:

A. Donepezil group: *at no time* improved. Scores on the scale gradually deteriorated over 112 weeks to reach about 9 points lower than baseline.

B. Placebo group: compared with the donepezil group, ADL scores deteriorated over each time period at a slightly greater rate. (Scores about 1 point lower at each time period.)

*(See figure 4 p 2110)*

*[Although the donepezil group continued to deteriorate by both measures, advocates can state that the deterioration was slowed by a small margin.. Many clinicians would consider the difference inconsequential. RTJ]*

2. No significant benefits were seen vs placebo in institutionalization, progression of disability, behavioral and psychological symptoms, psychopathology of carers, formal care costs, adverse events, or deaths.

3. No difference between the 5 mg and the 10 mg dose.

## DISCUSSION

1. AD 2000 is one of the largest trials in terms of numbers of patients randomized, and the largest in person-years of placebo-controlled treatment.

2. Donepezil was associated with *no* improvement in activities-of-daily living scale *at any time up to 2 years*. Compared with placebo, decline in ADL score was slightly slower. *(Figure 4 p 2110)*

3. Donepezil was associated with a slight improvement in MMSE (about 1 point out of a possible score of 30) over 6 months. Thereafter, scores deteriorated. Scores in the donepezil group remained slightly higher than placebo scores at each time period over 2 years. *(Figure 6 p 2111)*

4. Donepezil produced no measurable reduction in rate of institutionalization or progress of disability. (These are the key determinants of overall cost-effectiveness.)

5. No evidence that costs of caring for patients with Alzheimer's disease in the community were reduced by donepezil.

6. Any effect of donepezil on informal caregiver time is likely to be small.

7. Do the (*statically*) significant but small improvements in cognition (*vs* placebo) seen over 2 years lead to a worthwhile clinical improvement in health-related quality-of-life? The US FDA has suggested that a reversal of the natural history of cognitive decline by 6 months constitutes a clinically important difference. This change equates to an annual decline of 1.4 MMSE points in treated patients *vs* a mean annual decline of 2.8 points in untreated patients (difference = 1.4 points). (Cognition declines both groups—only at a slightly slower rate in the donepezil group.) A large survey of clinicians revealed that 45% judged a 3-point change as the minimum benchmark.
8. A subset of patients could derive selective benefit from CIs. This assumption underlies government guidance. (*And leads family members to hope their loved-one may be an outlier, and achieve significant benefit. RTJ*) The study did not identify any variables that might predict treatment response. Apparently good responses are more likely to be chance fluctuations in the disease.
9. Donepezil is not cost-effective. It does not delay institutionalization. “The disappointingly little overall benefit from donepezil cannot be taken lightly.” Clinicians can validly question whether other uses of scarce resources allocated to dementia would provide better value than routine prescription of cholinesterase inhibitors.
9. Future studies need to achieve high compliance and complete follow-up to avoid bias from differential dropout rates.

## CONCLUSION

Benefits of the acetylcholinesterase inhibitor, donepezil, are below minimally relevant thresholds. It is not cost effective

Lancet June 16, 2004; 363: 2105-15 Original investigation by the AD 2000 Collaborative Group, correspondence to AD 2000 group, University of Birmingham UK.

Comment:

1 *Mild—MMSE score = 18 to 26 points; moderate = 10-18 points (on a 30 point scale).*

*MMSE available at [www.mja.com.au/public/mentalhealth/articles/yellowlees/yelbox4.html](http://www.mja.com.au/public/mentalhealth/articles/yellowlees/yelbox4.html)*

2 *Otherwise, the placebo-controlled trial would have been unethical*

*This is a complicated and long report. I believe I have abstracted the main points.*

*The authors make the remarkable statement that pharmaceutical companies opposed this trial. The trial was supported (non-commercially) by the UK National Health Service*

*I believe many patients are continuing to receive CIs far beyond the time of any hope of benefit.*

*COST: about \$1600 per year quoted by [drugstore.com](http://drugstore.com). As is often the case, the 10 mg dose costs just a few dollars more per year than the 5 mg dose. A pill cutter may cut cost in half. There is no statistically significant difference in effects of 10 mg *vs* 5 mg. Adverse effects (eg, gastrointestinal) are greater with the 10 mg dose RTJ*

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***Trials use participants who do not represent typical patients.***

**6-12 AD 2000: DONEPEZIL IN ALZHEIMER'S DISEASE**

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

Many published randomized trials of cholinesterase inhibitors (**ChIs**) have shown efficacy<sup>1</sup> for the treatment of AD. Approval by regulatory agencies has been world-wide. Nonetheless, effectiveness<sup>1</sup> remains controversial. Many clinicians, while acknowledging measurable and consistent cognitive effects, question the overall practical effectiveness<sup>1</sup> of these drugs. Many others are staunch advocates of their broad and long-term use.

Patients seen in everyday practice differ from those selected for inclusion in drug-company-sponsored trials. Drug companies use highly refined selection criteria; often include specialized tests to aid diagnosis; restrict allowable comorbidity and concomitant medications; and the extent of behavioral or functional impairment. They pay for all protocol-related care, including medications. “Typical selection criteria for industry sponsored trials would exclude over 90% of out-patients with mild-to-moderate Alzheimer’s disease in California who would otherwise be eligible to receive treatment. The controversy about effectiveness, costs, and the clinical meaning of trial results has been fueled by the use of participants who do not represent typical patients.”

In the trial, donepezil and placebo were both associated with a worsening over time. The mean differences on the MMSE and activities of daily living (**ADL**) scale represent a delay in symptom-worsening of about 3 months. The rather broad confidence intervals around primary endpoints are compatible with both a 30 to 45% increase and up to a 30% decrease in risks with donepezil.<sup>2</sup>

AD 2000 undermines the assumption that improvement in cognition and ADL scores generalize to maintenance of function, cost savings, or delay in institutionalization. “Results are incompatible with many drug-company-sponsored studies claiming remarkable effects for cholinesterase inhibitors.”

Lancet June 26, 2004; 363: 2100-01 “Commentary” an essay by Lon S Schneider, University of Southern California, Los Angeles.

Comment:

**1** *The editorialist uses these two terms carefully. “Efficacy” relates to conclusions of trials; “Effectiveness” relates to outcomes in the “real world” of practice.*

**2** *Families hope that their loved one may be among the outliers who receive greater benefit. I believe this hope leads to more willingness to begin and to continue using the ChIs.*

*This commentary presents a clinically important point. It emphasizes the gulf which may separate results of randomized controlled trials from benefits evident in primary care practice. There may be a large difference between results reported by a clinical trial for AD and clinical benefits for Mr. Jones, whose family brings him into your office because of memory loss. A practical office-based, “real world” trial is more meaningful and convincing. Beware of “spin”.*

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***“Ring” prophylaxis during the next inevitable pandemic of flu.***

## **6-13 TACKLING THE NEXT INFLUENZA PANDEMIC**

“We must now hasten the preparations for another inevitable influenza pandemic.” Currently, contingency plans are based largely on rapid vaccination of susceptible populations. Other measures, such as treatment with

antiviral drugs, serve only as adjuncts. Technical constraints on vaccine production and the time required to initiate mass vaccine production during a pandemic will limit effectiveness of this measure.

A recent systemic review concluded that the prophylactic use of neuraminidase inhibitors (NIs) could lead to a reduction of 70-90% in risk of symptomatic flu. These drugs have shown efficacy in preventing transmission of influenza in institutions and community setting. The availability of a highly effective supplement to vaccination opens to debate the appropriate role of NIs and other antiviral drugs in the control of pandemic influenza.

Challenges to this approach include the need for long-term, large scale, continuous prophylaxis; inadequate compliance with prolonged daily use; emergence of resistant viral strains; as well as insufficient supplies and limited manufacturing ability. "Stockpiling of antiviral drugs is therefore necessary, but the cost of stockpiling in such magnitude looks prohibitively expensive."

What might be an alternative strategy? It is known that "ring" vaccination, which has been used in the past, will quell smallpox outbreaks. The strategy entails post-exposure vaccination of close contacts. For smallpox, this approach has provided a wide safety net of prevention, while focusing vaccination where it was needed most. Ring prophylaxis may be applicable to the initial management of an influenza pandemic. NI treatment of influenza cases with the infection and prophylactic use for their contacts may decrease attack rates substantially. It limits usage of the drug to where it is needed most.

Influenza differs considerably for small pox. It has a shorter incubation period, a higher attack rate, and a lack of specific symptoms. These characteristics may impose difficulties in accurately identifying and rapidly treating contacts. Still, this policy, in conjunction with isolation and quarantine, can be expected to slow down dissemination of the disease, providing valuable time for production and distribution of a vaccine.

Antiviral ring prophylaxis for flu has proved to be effective in family settings. It requires only short term daily treatment for a period of 5-10 days, and targets a relatively limited proportion of the population. Used in this way, NIs may be dispensed more rapidly and require less of a stockpile.

Contacts receiving antiviral prophylaxis may form protective antibodies due to subclinical infection, rendering them immune for the duration of the pandemic.

Chemoprophylaxis will not suffice as a sole preventive measure in case of a pandemic. It must be accompanied by quarantine, isolation, and prevention of mass congregation as well as vaccination.

BMJ June 12, 2004; 328: 1391-92 Editorial, first author Ran D Balicer, Israeli Working Group on Influenza Pandemic Preparedness, Ramat-gan Israel.

Comment:

*COST: Tamiflu, 75 mg cost about \$6 each capsule— \$60 for a treatment course; \$42 for prophylaxis. I believe most patients would consider this a bargain.*

*Healthcare workers should be the first in line to receive "ring" prophylaxis, and to continue it until assured that the current vaccine is effective.*

*There are two NIs: 1) Oseltamivir (Tamiflu) for oral use, and zanamivir (Relenza) for inhalation. Both are effective for treatment and prophylaxis of flu.*

*For treatment, Tamiflu should be started within 40 hours of onset of symptoms, and continued for 5 days. The dose for adults is 75 mg twice daily. Children are given a lower dose—30, 40, or 60 mg twice daily depending on weight (available as a suspension).*

*For prophylaxis, adults are given 75 mg once daily for at least 7 days. Duration of protection lasts as long as the drug is given. It has been used up to 42 days in nursing homes. Drug resistance due to mutations of the virus has been reported.*

*Primary care clinicians will likely use NIs freely to unvaccinated family members during an epidemic of flu.*  
RTJ

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#### **6-14 DANGERS OF ROSUVASTATIN (*Crestor*) IDENTIFIED BEFORE AND AFTER FDA APPROVAL**

A letter to the editor from Sidney M Wolfe, Public Citizen's Health Research Group, Washington DC. *Lancet* June 26, 2004; 363: 2189-90 comments:

The lipid-lowering drug rosuvastatin (*Crestor*; Astra-Zeneca) is currently in the midst of the most heavily financed launch of a prescription drug *ever*.

The correspondent presents available pre-marketing and post-marketing evidence of the adverse effects of the drug.

*Pre-marketing:*

Documents included a acknowledgement of a risk of severe myopathy and rhabdomyolysis which clearly increased at the highest dose (80 mg). The preapproval document also stated that 80 mg is associated with a high frequency of creatine kinase elevations (CK 10 times upper normal). *Crestor* was approved with the belief that lower doses would be much safer. The 80 mg dose was subsequently discontinued.

*Post-marketing:*

Myopathy: Since marketing of rosuvastatin, there have been 18 additional cases of rhabdomyolysis. Two patients were using 40 mg; five using 20 mg; 11 using 10 mg.

Renal toxicity: Rosuvastatin is associated with renal abnormalities.

A small percentage exposed primarily to 80 mg had increased frequency of persistent proteinuria and hematuria, and, in some patients, an increase in serum creatinine. There is a reported dose-associated risk.. The 10, 20, and 40 mg doses have been associated with increasing risk up to 1% of patients. In individuals who develop ++ proteinuria or more, the percentage with an increase of creatinine of over 30% rose incrementally with dose—from 14% in the 5 mg daily dose to 33% in the 40 mg dose.

There have been 8 reported cases of acute renal failure and 4 of renal insufficiency since marketing began. Nine were using 10 mg.

Other “currently approved statins do not have similar renal effects”.

“By now, the number of reported cases of rhabdomyolysis and renal insufficiency or renal failure—20 of which have occurred in people using 10 mg—is certain to have increased substantially from the number filed by April 13, 2004.”

*Efficacy:*

A statistical review of comparative efficacy found no significant difference in LDL-cholesterol lowering between 5, 10, and 20 mg of rosuvastatin and 20, 40 and 80 mg of atorvastatin. (*This surrogate laboratory finding does not indicate comparative clinical effectiveness.*)

“The renal toxicity, high rate of cases of rhabdomyolysis compared with other statins, and lack of unique benefits are compelling reasons to remove rosuvastatin from the market before additional patients are injured or killed.” The correspondent recalls that cerivastatin (*Baychol*) was removed from the market because of increased risk of myopathy.

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A letter to the editor July 10, 2004; 364: 135 from Gunnar O Olsson, Astra-Zeneca, Molindal, Sweden offers a rebuttal:

*Crestor* has a safety profile comparable to those of other marketed statins. (The US FDA has reviewed post-marketing safety data and has supported this conclusion.)

*Crestor* was the most extensively studied statin ever submitted for regulatory review. More than 60 countries have approved it on the basis of an excellent benefit/risk profile. “More than 80% of patients can reach their LDL cholesterol goal on the usual start dose of 10 mg.”

The reported rate of rhabdomyolysis has remained very low (< 1 in 10 000) is consistent with the rates of all currently marketed statins.

Proteinuria has been associated with *Crestor*, but is transient, and often resolves on continued treatment. It is not predictive of acute or progressive renal disease.

Astra-Zeneca is surprised that The Lancet published a letter containing inappropriate comparisons that serve to cause undue alarm. “The letter, which is a rehash of misinformation presented by Public Citizen in the past includes reference to a non-marketed dose (80 mg) and is “highly speculative”.

“Rosuvastatin has an excellent benefit-risk profile compared with other marketed statins, having a better efficacy lowering LDL cholesterol and raising HDL cholesterol and a safety profile comparable to those of other marketed statins.”

Comment:

*These letters raise an important clinical point. When should primary care clinicians add a new drug to their practice?*

*Is Crestor a unique and important addition to therapeutics? Or is it just a “me-too” drug? Should primary care clinicians prescribe it at the present time?*

- 1. Is Crestor more effective in lowering LDL? No. Other statins lower LDL just as much, although they might require a higher dose. Remember, this is a laboratory endpoint, not a clinical endpoint. Clinical efficacy has not been established.*
- 2. Is Crestor as safe as other statins? This is the dispute. That the 80 mg dose has been withdrawn because of toxicity raises caution. It will take several years of general use in the USA for the FDA to determine toxicity. Certainly, Crestor is not safer.*
- 3. Is Crestor more convenient to administer. Does it require fewer doses? No*

*4. Is Crestor less costly? No. Costs are comparable.*

*The first letter may raise an entirely unwarranted red flag. I do not know. I abstracted these letters mainly to reinforce the long-honored and oft-repeated admonishment to primary care clinicians not to be the first to prescribe a new drug, no matter how highly touted, unless it is known to be safe and carry unique and important benefits. Regardless of the question of toxicity, I do not believe the benefits of Crestor are unique or comparatively important.*

*I would not prescribe Crestor at this time. If it proves equally or less toxic, maintains its reported comparative efficacy in reducing LDL-c, and has a significant cost benefit, I would consider prescribing it.*

*I have faced (as have most older clinicians) the embarrassment of having a drug I had prescribed suddenly withdrawn from the market. The patient will ask for an explanation. RTJ*