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## INSIDE



# Moving the Goalpost

ABSTRACT & COMMENTARY

***Synopsis:*** *High-dose atorvastatin protects patients with acute coronary syndrome from death and major cardiovascular events better than usual dose pravastatin.*

**Source:** Cannon CP, et al. *N Engl J Med*. 2004;350:1495-1504.

In a head-to-head smackdown, Cannon and colleagues in the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial enrolled 4162 patients from around the world in a prospective, double-blinded, randomized, controlled trial of pravastatin (Pravachol®) 40 mg daily vs atorvastatin (Lipitor®) 80 mg daily. These doses were chosen because, on average, pravastatin (PRA) 40 mg is able to reduce low-density lipoprotein cholesterol (LDL-C) to approximately 100 mg/dL and atorvastatin (ATOR) 80 mg can drop it to 70 mg/dL, provided total cholesterol is in the neighborhood of 240 mg/dL.

These are the same drugs used in the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study[1] where patients taking ATOR had no progression, or in some cases regression, of atheroma, while patients taking PRA had progression. While these results are impressive, the PROVE IT researchers heeded the cry of physicians for primary, patient-oriented outcomes rather than secondary, disease-oriented end points. Adult patients who had been hospitalized within 10 days of either acute myocardial infarction or high-risk unstable angina were enrolled if they were in stable condition, if any planned percutaneous revascularization procedures had been completed, and if their total cholesterol levels were < 240 mg/dL. If they were already on lipid-lowering therapy, the cholesterol cut off was 200 mg/dL. There were multiple exclusion criteria.

For instance, life expectancy < 2 years, current use of 80 mg of any statin, current use of a fibric acid derivative or niacin that could not be discontinued before randomization, and use of drugs that inhibit cytochrome P-450 3A4 (ATOR's metabolic pathway) all would have eliminated candidates. Other exclusion criteria included having undergone a percutaneous coronary procedure within the last

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6 months or coronary bypass surgery within the last 2 months, and other conditions that would have precluded use of the study medications. All patients received aspirin and dietary education. Some received clopidogrel or warfarin. All other lipid-lowering drugs were discontinued. Patients were seen and blood samples obtained at randomization, 30 days, and 4 months, and every 4 months after that until the study ended. Average follow up was 24 months. Only 8 patients were lost to follow up. Primary end points were: death from any cause, myocardial infarction, unstable angina requiring hospitalization, coronary revascularization, and stroke.

The 2 groups were well matched. The patients on average were 58 years old, three-quarters male, and 90% white. Slightly better than one-sixth had diabetes, half suffered from hypertension, and more than one-third smoked. The only clinically and statistically difference between the 2 groups was the presence of peripheral vascular disease (6.6% in the PRA group, 5.0% in the ATOR group). At the start of the study, both groups had average LDL-C values of 106 mg/dL. As expected, the LDL-C values at the end of the study averaged 95 in the PRA group and 62 in the ATOR group. The average high-density lipoprotein cholesterol levels before the study were 39 in the PRA group and 38 in the ATOR group. At study's end they had risen 8.1% in the PRA group and 6.5% in the ATOR group (statistically significant). C-reactive protein reduction was significantly greater in the ATOR group.

More patients in the PRA group had a primary end point by the end of the study than ATOR patients (26.3% vs 22.4%). Except for stroke and death from any cause, there were similar reductions for the individual elements of the primary end point. There was no difference in the stroke rate and a statistically insignificant trend favoring ATOR for death from any cause. ATOR worked well in all groups, but especially in patients with LDL-C > 125 mg/dL. Discontinuation rates for both drugs were similar. Fewer patients taking PRA had liver enzyme levels > 3-time normal than patients taking ATOR (1.1% vs 3.3). Neither group experienced rhabdomyolysis.

## COMMENT BY ALLAN J. WILKE, MD

It wasn't that long ago (2002) that the National Cholesterol Education Program[2] set 100 mg/dL as the LDL-C goal for high-risk patients. The bar has been lowered. The atorvastatin pharmaceutical representatives will be visiting you soon (if they haven't already) and will spin these results as a 16% reduction in the hazard ratio. While they technically speak the truth, a better way to look at the results is the absolute reduction of 3.9%. This works out to a number-needed-to-treat of 25. If they push the issue, you can point out that the ATOR patients had a 300% increased risk of elevated liver enzymes (instead of an absolute increase of 2.2%, number-needed-to-harm 45)!

**This study raises more questions than it answers:**

1. How long will the beneficial effects last? What I found most impressive about this study was how soon (at 2 months) the 2 curves on the Kaplan-Meier graph began to separate. What would have happened if the study had been extended beyond the 2-year mark? Eventually, because death comes to us all, the curves have to meet again at the 100% point.
2. Was this a fair fight? In other words, could the

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pravastatin dose have been pushed to a level that would have achieved the same results as atorvastatin? As it turns out, the study was designed to allow a blinded increase in PRA to 80 mg daily, if the LDL-C didn't fall below 125 mg/dL. Only 8 patients ended up taking this dose, and there were no data presented on these patients. I suspect that an 8-patient group isn't large enough to do subgroup analysis.

3. Were these patients that you see? I think so, but it's a pretty small crowd. More importantly, can you extrapolate the findings to patients who don't make the inclusion or exclusion criteria?
4. Is there a point at which further reduction of LDL-C confers no additional benefit? How much LDL-C, if any, is necessary to maintain good health?
5. Does it matter how you get to a low LDL-C? The makers of the other statins (fluvastatin [Lescol®], lovastatin [Mevacor®], simvastatin [Zocor®]), ezetimibe (Zetia®), and (soon) torcetrapib*[3] hope you won't think so.

** The next new thing—an inhibitor of cholesteryl ester transfer protein*

6. Are the statins all the same? Some, like atorvastatin, are lipophilic, others, hydrophilic, like pravastatin. There is evidence,[4] based on simvastatin's ability to reduce coronary events even in patients with LDL-C < 100 mg/dL, that the statins' mechanism of action may be something more than LDL-C reduction.
7. Should we just put a statin in the water? Last year, Wald and Law[5] proposed the Polypill, a medication containing a statin, a thiazide, a ß-blocker, an ACE inhibitor, folic acid, and aspirin. They claimed it would prevent heart attacks and stroke if use by everyone over 55 years of age and those patients with existing heart disease.

You may be wondering about the "Infection" in PROVE IT. This study had a 2 × 2 factorial design where the patients also received gatafloxacin or placebo. The results of that study are yet to be published. Stay tuned. ■

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# Care, not Cure

ABSTRACT & COMMENTARY

***Synopsis:*** *This brief, individual CBT intervention, developed specifically to alter hypochondriacal thinking and restructure hypochondriacal beliefs, appears to have significant beneficial long-term effects on the symptoms of hypochondriasis.*


**Source:** Barsky AJ, Ahern DK. *JAMA*. 2004;291:1464-1470.


This study recruited 187 patients from 2 large academic medical centers and from advertisements announcing a study "for health anxiety and hypochondriasis." To be included in the study, candidates had to score 150 or greater on the Whiteley Index and Somatic Symptom Inventory, and not to have major medical morbidity expected to worsen significantly for the next 12 months. These subjects were randomized to either usual care or to the cognitive behavioral therapy (CBT) group, and the seniority and practice volume of their primary care physicians was taken into account in this randomization process. Each patient's primary physician received a letter explaining that the patient was in the study; the letter made 5 suggestions for medical management (quoted verbatim below):

1. Make improved coping with somatic symptoms rather than symptom elimination the goal of medical management;
2. Uncouple access to the physician from symptom status by scheduling regular appointments;
3. Provide only limited reassurance;
4. Explain the patient's symptoms using the model of cognitive and perceptual symptoms amplification;
5. Be conservative in medical diagnosis and treatment, within the bounds of appropriate medical practice.

For the active treatment group, treatment consisted of 6 CBT sessions. These sessions occurred weekly, and lasted for 90 minutes. Each session was "tightly scripted," and focused on 1 of these 5 factors: attention and bodily hypervigilance, beliefs about symptom etiology, circumstances and context, illness and sick role behaviors, and mood. There were 3 study therapists involved, and all had advanced degrees and prior CBT experience. Patients were followed up at 6 and at 12 months after treatment. Outcome variables were a readministration of the Whitely Index,[1] the Health Anxiety Inventory,[2] the Hypochondriacal Cognitions Questionnaire, and the Somatic Symptom Inventory,[3] and the Functional Status Questionnaire.[4]

Of the 187 total patients, 107 volunteered in response to the ad. These patients were "sicker" and more disabled than patients recruited from the physicians' offices. One hundred-two patients were randomized to the treatment arm and 85 to the control arm. These groups did not differ by any important variable. The subjects were mostly middle-aged women with at least a decade of hypochodriacal symptoms. Only abut two-thirds of the active treatment group completed all 6 sessions.

For the CBT group, there were statistically significant improvements on most measures at 6 and 12 months of follow-up. Specifically, CBT patients had significant improvement in levels of hypochondriacal symptoms, beliefs, and attitudes, as well as health-related anxiety compared with the controls. They also had improvement in social functioning and intermediate activities of daily living compared to the control group. At 6 months, 20 of the CBT and 10 of the control patients had initiated psychotropic medication or care with a mental health professional.

## COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

Hypochondria is "morbid concern about one's health especially when accompanied by delusions of physical disease."[5] Barsky and Ahern do not tell us what symptoms these patients suffered from, but typical symptoms reported by hypochondriacs include insomnia and pain of all sorts, including headache, GI distress, and chest pain. These symptoms can be quite distressing both to patients and to their physicians, because they can be markers of serious pathology and warrant serious investigation. Physicians can begin to suspect that they are dealing with a hypochondriac when the patient is disappointed, rather than relieved, that the workup is negative (unfortunately, however, we all know horror stories of tumors missed and metabolic disorders overlooked by conscientious clinicians). Hypochondriacs are prevalent in primary care,[6] and they are conspicuous consumers of health care resources.[7] Any treatment that improves hypochondriacs' ability to function and to cope with symptoms is likely to be cost effective. Thus, this paper is potentially quite significant, and it has already been widely discussed in the lay literature.

This paper interested me because, as a sleep specialist, I see many patients with difficulty sleeping. Although insomnia can be a manifestation of physical or psychiatric illness (and it is important to carefully address those issues) it is often a manifestation of hypochondriasis. For example, we know that women are much more likely to complain of sleeping problems than are men, even though objective measurement indicates that women actually sleep better than do men.[8-10] Further, peri- and postmenopausal women sleep better (by objective measurement) than do premenopausal women, even though they are less satisfied with their sleep.[11] For insomnia, it is likely that the response to the symptom, rather than the symptom itself, that is the major determinant of distress, quality of life, use of health care, and overall functioning. CBT aims to help the patient cope more effectively with sleeping problems; as the patient worries less about her inability to sleep, she does, in fact, often begin to sleep better. In the long run, CBT is at least as effective as are hypnotics for patients with insomnia.[12] Barsky and Ahern note that with CBT, hypochondriacal attitudes improved more than symptoms did. In other words CBT improves coping with symptoms rather than curing the symptoms themselves—hence, "care rather than cure."

There are many problems with the application of CBT to patients with insomnia and other kinds of hypochondriasis. First and foremost, many patients with insomnia do not appreciate referral for CBT, preferring to have a more "medical" treatment. In the paper at hand, only about 30% of those patients who were eligible consented to enroll in the trial. Another problem, of course, is that insurance rarely pays for CBT, which confers the message that it is not "real" treatment, and also causes a financial barrier to access. Finally, experienced, effective CBT practitioners are not readily available in many communities.

So, how can we apply the lessons from this paper to the practice of internal medicine? Rules 1-5 (listed above) could be very powerful, even as a stand alone tool for hypochondriacs. To my way of thinking, patients with somatic symptoms may need to hear that there is a "good news, bad news" aspect to their complaints. The good news is that their insomnia, headache, chronic pain—or whatever—is not a harbinger of life-threatening illness; the bad news is that it might not be curable. Somatization is distressing for patients and for their physicians; both want a medical, scientific solution, and both are distressed and disappointed when there isn't one. As physicians, we are sometimes frustrated with these patients, (and they with us!) and may dismiss their complaint, refer them to someone else, or order testing that we know is unnecessary instead of addressing the issue head on. In so doing, we may be missing the opportunity to care, even when we can't cure.

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# Diligent Dental Flossing May Help Prevent Stroke

ABSTRACT & COMMENTARY

***Synopsis:*** *These data provide further support that inflammation in general and periodontal disease more specifically are stroke risk factors.*

**Source:** Grau AJ, et al. *Stroke*. 2004;35:496-501.

Chronic inflammation is now a well-recognized cause of atherosclerotic vascular disease, including coronary artery disease and stroke. Asymptomatic individuals harboring the common bacterium *Chlamydia pneumoniae* have been shown to have an elevated incidence of plaque in both the coronary and carotid arteries. Elevations in C-reactive protein, a nonspecific marker of inflammation, have also been implicated as a stroke risk. Gingivitis and periodontitis have been previously associated with stroke, but these studies were limited by small sample sizes, limited dental data, and difficulties with confounding variables.

Grau and colleagues used a case-control methodology to analyze 303 patients hospitalized with an acute stroke and compared them to both community and other hospital controls. All study subjects underwent a complete clinical and radiographic dental examination. The primary outcome variable was the clinical attachment loss (CAL), a measure of periodontitis in which the "pocket" formed at the base of the tooth was probed. A particularly deep pocket (a CAL > 6 mm) was evidence of severe disease. Gingivitis was recorded based on gingival bleeding after a probe passing through the crevice between the teeth irritated the gums.

Grau et al found that severe periodontal disease was associated with a 4.3 times higher stroke risk. This finding also applied to gingivitis. Interestingly, the risk associated with periodontitis applied differently among stroke subtypes. The greatest association was with large artery atherosclerotic type, followed by cryptogenic type, and, to a lesser degree, cardioembolism. These data support the link between periodontitis and atherogenesis and also support the theory that periodontitis may create a prothrombotic state via a recurrent bacteremia and platelet activation.

In subgroup analysis, the risk of periodontitis applied to both first-ever and recurrent stroke. When the data were broken down by gender, the results were weaker and nonsignificant in women. When broken down by age, the results only applied to patients younger than 60.

**COMMENT BY ALAN Z. SEGAL, MD**

These data provide further support that inflammation in general and periodontal disease more specifically are stroke risk factors. More importantly, these data identify a stroke risk factor that is clearly modifiable.

This study has weaknesses; in particular, there is no obvious explanation as to why there was such a prominent gender bias. Further analysis, especially in young people where there may be fewer confounding variables, is clearly needed. In the meantime, don't forget to floss!

*Dr. Segal is Assistant Professor, Department of Neurology, Weill-Cornell Medical College, Attending Neurologist, New York Presbyterian Hospital, New York, NY.*

## *Pharmacology Update*

# Cinacalcet HCL (Sensipar) Tablets

*By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD*

The first of a class of calcimimetics has been approved by the FDA for the treatment of hyperparathyroidism associated with renal failure and in patients with parathyroid cancer.

This new class of drug inhibits parathyroid hormone secretion and reduces serum calcium levels.[1] Cinacalcet is a second-generation calcimimetic and

is marketed as Sensipar™ by Amgen.

**Indications**

Cinacalcet is indicated for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis (CKP) and for the treatment of hypercalcemia in patients with parathyroid carcinoma.[2]

**Dosage**

The recommended starting dose is 30 mg twice daily. The dose should be titrated at every 2-4 week intervals up to 90 mg 4 times a day as needed to normalize the serum calcium level. The sequence of dose titration should be 30 mg twice daily, 60 mg twice daily, 90 mg twice daily, and 90 mg 3 or 4 times daily. Tablets should be taken whole (ie, not divided). No dosage adjustment is required in patients with renal impairment.[2] Food increases the bioavailability of cinacalcet. Serum calcium should be measured within 1 week after starting therapy or after a dosage change. Monthly serum calcium levels, phosphorus levels, and intact parathyroid levels should be measured after a stable dose has been established. Intact parathyroid hormone should be measured 1 to 4 months after initiation or dose adjustment and every 1 to 3 months thereafter.[2] In patients with moderate to severe hepatic dysfunction laboratory parameters should be monitored closely.

Cinacalcet is available as 30 mg, 60 mg, and 90 mg tablets.

**Potential Advantages**

Cinacalcet is the first in a class of calcimimetics and has the ability to significantly reduce levels of circulating parathyroid hormone without causing hypercalcemia and hyperphosphatemia but rather improves calcium-phosphorus homeostasis.

**Potential Disadvantages**

Cinacalcet is a substrate of CYP3A4. Parathyroid hormone and calcium levels should be monitored if a strong inhibitor of CYP3A4 (eg, erythromycin, itraconazole, ketoconazole) is added, discontinued or given concomitantly.[2] Most common side effects are nausea (31% vs 19% for placebo) and vomiting (27% vs 15%). In clinical trials two-thirds of patients developed at least one serum calcium level of < 8.4 mg/dL.[2]

**Comments**

Cinacalcet is the first oral calcimimetic agent. It works by increasing the sensitivity of the calcium-sensing receptor on the parathyroid cells. This enhances sensitivity to circulating serum calcium levels and decreasing PTH secretion. The efficacy of cinacalcet was established in three 6-month, double-blind, placebo-controlled trials in patients with secondary hyperparathyroidism in patients with chronic kidney disease on dialysis.[2,3] A total of 665 patients were on drug and 471 on placebo. Most patients (93%) were on phosphorus binders and 66% were on vitamin D sterols (eg, calcitriol). The primary end point was intact parathyroid hormone (iPTH) ≤ 250 pg/mL and secondary end points were calcium × phosphorus ion product, serum calcium levels and phosphorus levels. The median dose of cinacalet was 90 mg. Thirty-five to 46% of patients achieved iPTH ≤ 250 pg/mL compared to 4-7% for placebo. About one-third (28-35%) of patients achieved iPTH ≤ 250 pg/mL and Ca × P ion product of < 55 $mg^2/dL^2$. Serum calcium was reduced by 6.8%, serum phosphorus by 8.4% and bone-specific alkaline phosphatase by a median of 35%.[3] Disease severity, duration of dialysis, and administration of vitamin D sterols did not appear to affect the efficacy of cinacalcet. CKD patients not on dialysis have not been adequately studied. The effects of cinacalcet therapy on clinical outcomes have not been evaluated. Cinacalcet appears to be well tolerated

A small number of patients (n = 10) with parathyroid carcinoma have been studies. None were able to achieve normal serum calcium levels.

The cost of cinacalcet is about $8 per 30 mg. A starting dose of 30 mg twice daily for a month would be about $500.

**Clinical Implications**

Secondary hyperparathyroidism is common in patients with chronic renal disease on dialysis. This can lead to metastatic calcification (eg, coronary arteries) and increased mortality risk.[4,5] Current therapy for secondary hyperparathyroidism due to chronic renal disease is dietary modification, phosphate binders, and vitamin D sterols. However this often leads to hypercalcemia and hyperphosphatemia. Cinacalcet reduces parathyroid hormone and improves calcium phosphorus homeostasis representing an important therapeutic addition. ■

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# CME Questions

**21. Choose the one correct answer. In the study comparing pravastatin 40 mg to atorvastatin 80mg:**

a. atorvastatin lowered HDL-C levels.
b. pravastatin did not reduce LDL-C levels to goal.
c. atorvastatin was associated with fewer myocardial infarctions.
d. pravastatin was associated with more strokes.
e. atorvastatin was associated with rhabdomyolysis.

**22. Cognitive Behavioral Therapy (CBT):**

a. works primarily by reducing symptoms.
b. is less effective in the long run for insomnia than are hypnotics.
c. improves hypochondriacal attitudes more than symptoms.
d. requires months of therapy to have a measurable effect.
e. is irrelevant for most patients encountered in a primary care practice.

**Answers:** 21 (c); 22 (c)

By Louis Kuritzky, MD

## Antihypertensive Treatment and Measurement at Home or in the Physician's Office

A NOT-INSUBSTANTIAL MINORITY OF persons carrying a diagnosis of hypertension (HTN) actually have stress-induced transient episodes of HTN in clinicians' offices, which we call "white coat hypertension" (w-HTN). Because w-HTN does not appear to translate into increased risk for cardiovascular events, it is generally agreed that when persons are suspected of w-HTN, ambulatory monitoring of blood pressure (the gold standard) should be performed. Persons with normal ambulatory blood pressure (ABP), despite office BP elevations, do not require treatment, unless there is evidence of target organ damage.

Because ambulatory blood pressure monitoring (ABPM) is moderately expensive (approximately $100 in our community of Gainesville, Fla) and requires specialized equipment, it would be desirable if some simpler method of BP acquisition, such as home monitoring of blood pressure (HBPM) would suffice.

This blinded, randomized, controlled trial followed patients (n = 400) from 56 primary care practices, who were followed by traditional office monitoring, ABPM, or HBPM.

Patients who used HBPM ended up with less intensive medication regimens, but this was at the expense of less overall long-term BP control. On the other hand, HBPM (compared with office measurement) resulted in almost twice as many persons discontinuing BP medication entirely due to restoration of normotension; ie, consistent HBPM ultimately determined that they were normotensive off medication. HBPM is complementary to office measurement, and may help discover w-HTN. Because there is no large data-set upon which to base the normal range of home BP, the authors suggest outcome studies to establish such BP boundaries. ■

*Staeesen JA, et al. JAMA. 2004;291: 955-964.*

## Inactivated Intranasal Influenza Vaccine and the Risk of Bell's Palsy

LATE IN 2000, THE SWISS DRUG Monitoring Center and others noted numerous reports of Bell's palsy in persons who had received NFLU. To better study the relationship between NFLU and Bell's palsy, a case-control study of 773 persons with Bell's palsy, compared with 2319 age-matched controls was performed.

More than 27% of patients with Bell's palsy had received NFLU, compared with 1.1% of controls, resulting in an odds ratio of 84.0. Even at the lowest end of the confidence interval, 13 excess cases of Bell's palsy would be seen for each 10,000 NFLU vaccinees within 3 months after vaccination.

From 2000-2001, Switzerland used an inactivated virosomal-subunit influenza vaccine (Nasalflu®), but this is no longer in clinical use. The USA has approved a different vaccine, utilizing a cold-adapted live attenuated vaccine. ■

*Mutsch M, et al. N Eng J Med. 2004; 350:896-903.*

## Topiramate for Migraine Prevention

SOME PATIENTS REMAIN DISSATISFIED with or intolerant of available migraine treatments. Early studies have found that topiramate (TOP), an antiepileptic agent, is efficacious for migraine prevention. Although there are numerous potential pathways that might explain the efficacy of TOP, such as inhibition of voltage-gated sodium channels, most recently it has been suggested that modulation of trigeminovascular signaling may be the primary mechanism of action in migraine.

Patients suffering migraine with or without aura (n = 483) were randomized to TOP 50 mg/d, 100 mg/d, or 200 mg/d or placebo and followed for 18 weeks. The primary end point was change in migraine headache frequency per month.

At baseline, patients suffered 5-6 headaches per month, which was statistically significantly reduced by 2-3 headaches per month. with 100 mg/d and 200 mg/d TOP (but not by the 50 mg/d dose) Similarly, the number of days per month with headache was cut by 2.5-3 days/month at doses of 100 mg/d or 200 mg/d.

The most common adverse events associated with topiramate were paresthesia (50%), fatigue (14%) and anorexia (13%), but these uncommonly led to drug discontinuation. There were no serious adverse events, and modest changes in serum bicarbonate and chloride as seen in previous populations were also seen here. These data are encouraging for the clinical applicability of topiramate in patients who are not suitable candidates for other migraine treatments. ■

*Brandes JL, et al. JAMA. 2004;291(8):965-973.*

**In Future Issues:** New Treatments Dramatically Raise HDL Cholesterol