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INSIDE

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The List of Potential Benefits of Statins Grows

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

Professor of Medicine, University of Kentucky; Director, Sleep Disorders Center, Samaritan Hospital, Lexington

Dr. Phillips reports no financial relationship to this field of study.

Synopsis: *Use of statins is associated with reduced rate of deterioration of lung function with aging, though the effect is reduced in those who continue to smoke.*

Source: Alexeeff SE, et al. Statin use reduces decline in lung function. *Am J Respir Crit Care Med.* 2007;176:742-747.

This paper is a secondary analysis ("data mining") of the Veteran's Administration (VA) Normative Aging Study. The authors analyzed data for 803 men whose mean age was about 71 years. In order to participate in the study, subjects had to be free of known chronic diseases at baseline. Those enrolled in the study filled out questionnaires and had physical examinations and pulmonary function testing every 3 years. About a fourth of the participants were statin users. For the cohort as a whole, those who used statins and those who did not were not different except for a slightly higher number of pack-years (30.9 vs 28.8) for the statin users. A majority were white, and about 30% were never-smokers.

Those who used statins had a rate of decline of Forced Expired Volume in 1 Second (FEV1) and Forced Vital Capacity (FVC) that was about half that of those who did not use statins. Repeat analysis controlling for smoking status yielded similar findings, except that the benefit in lung function was less dramatic for those who continued to actively smoke. For example, in terms of the net difference in rates of decline between statin nonusers and users, the recent quitters had the greatest difference for FEV1 (19.7 ml/yr) and long-time quitters had the greatest net difference for FVC (24.7 ml/yr). In terms of the fold-difference in rates of decline, the long-time quitter group had the highest difference for both FEV1 and FVC.

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COMMENTARY

This is the first study to investigate the effects of statin use on decline of pulmonary function by smoking status. That statins could protect lung function is biologically plausible, since they have anti-inflammatory and antioxidant effects1-3, and both inflammation and oxidative stress are considered central to the pathogenesis of COPD.4 In their discussion, the authors note several important caveats, including that this analysis is not a randomized controlled trial, and that those who adhere to statin use may have healthier behaviors in general. But it is an intriguing finding, since our armamentarium to reduce the rate of pulmonary function decline is quite small, and actually only includes smoking cessation at present.

This paper adds to the growing list of potential benefits of statins (in addition to reduced cardiovascular risk). Other possible benefits include improvement of rheumatoid arthritis,[5] prevention of colon cancer,[6] reduction in dementia risk,[7] and perhaps renal protection.8 All of these associations need confirmation with well-done clinical trials, but the preliminary findings are certainly exciting. ■

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Warfarin vs Aspirin for Atrial Fibrillation in the Elderly

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Professor of Medicine, Chief of Cardiology, University of California, San Francisco

Dr. Crawford is on the speaker's bureau for Pfizer.

Source: Mant J. et al. *Lancet.* 2007; 370:493-503.

Abstract originally printed in October, 2007 Clinical Cardiology Alert.

OVER HALF OF PATIENTS WITH ATRIAL FIBRILLATION are over age 75 years, yet there is concern about the risk of serious hemorrhage in these patients on warfarin. Thus, the results of the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study are of interest. BAFTA was a prospective randomized open label study with a blinded assessment of endpoints. The primary end-point was the frequency of stroke, intracranial hemorrhage or systemic emboli in patients with atrial fibrillation age 75 or greater who were randomized to aspirin 75 mg/day vs warfarin adjusted to an INR of 2-3, target 2.5. Secondary endpoints included death, other vascular events and hemorrhage requiring hospitalization. The 973 patients were enrolled in primary care practices over a 3 year period and were followed for an additional 2 years. Average follow up was 2.7 years. Compliance with warfarin was 67% in this intention to treat analysis. Their INR's were therapeutic 67% of the time (19% below, 14% above). There were fewer primary end points in those on warfarin vs those on aspirin (1.8% per year vs 3.8% per year, RR = 0.48, CI 0.28-0.80, number needed to treat 50). No subgroup emerged in which warfarin was not superior to aspirin. The risk of major hemorrhage was small with 50 events (2%) per year and was not different in the 2 treatment groups. Secondary end point analysis showed that all major vascular events com-

bined and strokes alone were less on warfarin. The authors concluded that in those age 75 or older with atrial fibrillation, warfarin is superior to aspirin for preventing embolic events including intracranial hemorrhage. However, about one third of the patients will decide the potential benefits are not worth the inconvenience of therapy with warfarin.

COMMENTARY

The ACC/AHA/ESC guidelines recommend warfarin for atrial fibrillation patients if they have 2 or more risk factors for stroke (CHADS) where age >75 years is one (A). On the other hand they caution that the risk of major hemorrhage is higher in the elderly, and caution that this risk needs to be considered. This is a mixed message that has resulted in a conservative approach by physicians and patients. Part of the problem is a lack of clinical trial data in patients over 75. Thus, this trial is of considerable interest.

The superiority of adjusted dose warfarin over low-dose aspirin in this study is predictable. The surprise was that the risk of major hemorrhage was equal in both groups. This is especially surprising since low dose aspirin was used. The authors discuss several reasons that may help understand these results. Older trials had shown a 2-fold increase in major hemorrhage with warfarin vs aspirin and that major hemorrhage was more frequent as age increased. So this could be an alpha error in this trial. Even if this is the case the frequency of major hemorrhage will not be 2-fold higher. Some older trials used higher INR targets (up to 4.5); this trial used 2-3 (average 2.4). Current warfarin use before study entry was 40%. Therefore, there may have been a selection bias towards patients who could tolerate warfarin. There were significant cross-overs in this intention to treat study design. One third assigned warfarin switched to aspirin and 17% of those assigned to aspirin converted to warfarin. The net effect of these cross-overs would be to decrease the apparent risk of warfarin, but would also decrease the observed benefit of warfarin and the latter was not seen. About 20% of identified patients were excluded because of some contraindication to warfarin, but this does not seem excessive. Finally this was more of a real world study because patients were recruited form primary care practices rather then from hospitalized patients as has been done in other studies. Thus, they may have been a healthier group with fewer co-morbidities. Whatever the reason for the surprising results, this study makes us rethink what is a contraindication to warfarin therapy. Clearly older age alone is not a contraindication.

Revascularization for Stable Coronary Artery Disease

ABSTRACT & COMMENTARY

By Jonathan Abrams, MD

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Dr. Abrams serves on the speaker's bureau for Merck, Pfizer, and Parke-Davis.

Abstract originally printed in November, 2007 Clinical Cardiology Alert.

Sources: Lin GA, et al. Cardiologist's use of percutaneous coronary interventions for stable coronary artery disease. *Arch Intern Med*. 2007;167:1604-1609; Moscucci M. Behavioral factors, bias, and practice guidelines in the decision to use percutaneous coronary interventions for stable coronary artery disease. *Arch Intern Med*. 2007;167:1573-1575; Boden WE, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356:1503-1516.

Exceptional attention has been paid to the recent publication of the COURAGE Trial (April 2007) regarding the efficacy of percutaneous coronary intervention (PCI) in stable coronary disease patients. Whereas in acute coronary syndromes, including STEMI and unstable angina, there is reasonable consensus as to an interventional approach in patients with either PCI or CABG as opposed to medical therapy, a highly visible dialogue is now taking place regarding the appropriate approach in stable CAD. This unusual study from University of California-San Francisco reports on a series of focus groups comprised of interventional and non-interventional cardiologists in California in an effort to assess their views of PCI in stable CAD patients vs high-quality medical therapy without revascularization.

The results of COURAGE confirm that PCI for stable coronary disease does not offer a mortality or MI benefit vs aggressive medical therapy. Previous studies and metaanalyses have also shown that PCI does not improve survival or non-fatal MI reduction with a PCI strategy in stable angina patients when compared with medical therapy. The data do support earlier and greater relief of angina for PCI compared to medical therapy, but after one or more years, chest pain symptoms tend to be comparable between the strategies of PCI or medical therapy. In the United States, there is considerable geographic variation in the use of angioplasty that suggests multiple factors other than coronary anatomy influence, whether an invasive approach is utilized. In order to explore reasons for the variation in decision making,

physicians from UCSF designed a qualitative study using 3 focus groups comprised of 4 to 9 cardiologists and asked the participants to discuss the issues regarding their decisions whether or not to utilize PCI in stable angina patients.

Overall, the physicians acknowledged that PCI has not been shown to reduce the hard end points of death or acute MI in chronic stable CAD patients. The "oculostenotic" reflex was cited by the physicians, who more often than not voted for PCI, even in asymptomatic patients. The 3 focus groups were similarly structured, with a moderator and 3 hypothetical case scenarios. The fictional patients all had stable CAD with either no symptoms or atypical complaints, and were felt by the study authors to represent individuals who clearly have not been shown to derive benefit from PCI. The focus groups lasted for 90 minutes and were comprised of invasive and noninvasive cardiologists, cardiology fellows, and individuals from both rural and urban environments. A systematic and detailed approach to discussion was used. New methods of triangulation were utilized to reduce bias. A summary of the major systematic discussions of each focus group was provided; the participants agreed with the summary record. Themes discussed were related to physician's medical-legal concerns and technical advances that relate to PCI. The majority believed that PCI "would benefit the patients described in our case scenarios by preventing cardiac events, even in asymptomatic patients." The participants did acknowledge that PCI was less likely than medical therapy to provide benefit in terms of preventing MI or death; however, they stressed the benefit of patients leaving the hospital with an open artery. It was also believed to be important to perform PCI for equivocal stress testing results or lesion-ischemic mismatch on stress test. Concern about not intervening on an obstructive lesion was common; the likelihood of a subsequent event was felt to be unacceptable. In general cardiologists believed that even in low-risk patients, complications due to catheterization would be more meaningful than the "potential consequences of not performing PCI". Decreased anxiety following a procedure in asymptomatic patients was commonly cited, especially in individuals who were self referred. Patients who reached the cath lab generally underwent PCI, regardless of why the patient was sent for the angiogram. Thus ". . .by the time one is this far along, the die is cast. The cath lab staff probably wouldn't leave the lab unless we did something with the lesion. . ." Medical-legal concerns were also an important motivation; not performing an intervention was believed by some to be a setup for a potential law suit after an event occurred.

Cardiologists agreed that available technological advances, such as electron beam CT and CT angiography, are and will be increasing the number of asymptomatic patients who are referred for studies. They believe that these patients should be treated aggressively, although no evidence is available that such an approach would prevent death or myocardial infarction. The availability of drug-eluting stents seems to have been important in supporting catheterization decisions. The authors comment, ". . .the current practice of cardiologists in our sample is to recommend PCI for almost all significant lesions seen at cardiac catheterization." The cardiologists believed that they were benefiting even asymptomatic patients by performing PCI." Emotional and psychological factors were important determinants of physician judgment, suggesting an overly positive belief in PCI efficacy. The authors discuss a variety of reasons why cardiologists favor an invasive approach more than being guideline driven. Physician and patient anxiety about abnormal test results, as well as the ease in doing PCI following a diagnostic catheterization "has made PCI almost inevitable in anything with a signi icant lesion."

The experience of the cardiologists was comparable whether they came from rural, suburban, or urban areas. The conclusion of the authors is that "cardiologists may believe they are benefiting their stable patients. . .but this belief (for PCI) appears to be based on emotional or psychological factors rather than on evidenced clinical benefits." Physicians need to find a "greater balance between emotion and beliefs and clinical evidence to provide the best treatment for patients."

In an accompanying editorial, Dr. Moscucci from the division of cardiology at the University of Michigan, discusses deviation from treatment guidelines and the potential impact of increased CT coronary angiogram availability, which will provide even more asymptomatic patients for a decision of PCI or not. Moscucci calls for the development of appropriate criteria and improved physician and patient communication.

COMMENTARY

It is likely that this subject will engender considerable comment, and hopefully, alterations in the way physicians deal with decision making. The increasing dialogue among health professionals, industry, and patients regarding invasive vs noninvasive procedures for patients with CAD hopefully will be helpful and informative for the thousands of individuals for whom deci-

sions for or against PCI hold great importance.

The results of the University of California focus groups in dealing with PCI are of considerable interest. While the database is quite small, the authors found that there was substantial agreement among the physicians regarding various factors pro and con for the role of PCI in stable CAD. A much larger and more specific study is needed; it is likely that providers and those working in health policy will be looking carefully into this matter with great interest. One needs to expand the hypothetical case scenarios made available to the participants; the cases appear to be somewhat simplistic, and perhaps, overly amenable to a quick decision of go vs no go. The more dialogue about this matter, the better it is for our patients, physicians, and healthcare providers. It is widely acknowledged that PCI rates are extremely disparate around the United States, with 2- to 3-fold differences in utilization of angioplasty among cities. Canadian use of angioplasty and PCI is lower than in the United States on a per capita basis, yet overall survival rates do not appear to be different.

One important area that is not discussed in these two articles is the current emphasis on noninvasive or conservative therapy. Thus, the COURAGE trial has recently caused somewhat of a furor because of the finding that individuals who had active ischemia on stress testing, and angina with stable symptoms, had comparable morbidity and mortality at 5 years to those randomized to PCI. The impact of this study indicates that aggressive medical therapy and lifestyle changes without PCI resulted in equal outcomes of MI or cardiac death in individuals randomized to no angiogram vs those randomized to PCI. Of note, in COURAGE, the large diabetic cohort showed no difference in cardiac death or myocardial infarction when compared to the non-diabetics, thus emphasizing the outstanding outcomes achievable with aggressive medical therapy. Other trials are also persuasive in that optimal medical therapy in stable patients may be appropriate, at least until symptoms arise or worsen, without jeopardizing the patient. Street talk suggests a current 10-20% decrease in recent cardiac catheterization since COURAGE was reported. The drug-eluting stent controversy regarding late thrombosis may have also had a dampening effect on performing PCI. It appears that an algorithm is taking shape that provides a better fit for the patient and cardiologist with respect to how to deal with significant CAD in stable individuals. ■

Can Clinical Empathy Be Taught?

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

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Dr. Ling reports no financial relationship to this field of study.

Abstract originally printed in November, 2007 OB/GYN Clinical Alert.

Synopsis: *collaborative efforts between faculties of medicine and theater can be effective in teaching clinical empathy.*

Source: Dow Alan W, et al. Using Theater to Teach Clinical Empathy: A Pilot Study. *Society of General Internal Medicine.* 2007;2007:1114-1118.

It is one thing to be empathetic, but it is something quite different to be able to convey empathy to the patient. This skill of becoming connected to the patient is what the investigators termed "clinical empathy" At Virginia Commonwealth University, a preliminary investigation included 20 internal medicine residents with 14 undergoing 6 hours of classroom instruction and workshop sessions with professors of theater. The curriculum was focused on increasing measurable clinical empathy in office encounters.

The intervention group showed significant improvement after the instruction in all 6 subscores ($p < .011$); and, when compared to the control group, it had better post-test scores in 5 of 6 subscores ($p < .01$). The 6 subgroup categories were: Empathy, Relating, Nonverbal, Verbal, Respect, and Overall Impression.

■ COMMENTARY

What?! How could this study possibly have any relevance to my practice? I'll bet that's what some of the readers are silently screaming as they peruse this. Give me a few minutes, and I'll explain. Since it is highly unlikely that another paper like this will be published soon, I felt it important that the topic be addressed when there was at least an article with data available. Admittedly the numbers are small, it is nonrandomized and nonblinded. As a result, the level of evidence is not strong. The importance of empathy in clinical medicine is, however, unquestioned.

As one of the 6 core competencies identified in 1994 by the Accreditation Council for Graduate Medical Education, "Interpersonal and Communication Skills" is still not taught in a uniform or rigorous fashion. Certainly those of us trained long before the development of the Core Competencies did not have

a formal curriculum in it, even though it was certainly discussed as part of the "art of medicine."

The authors hypothesized that clinical encounters are similar to interplay that goes on between actors who must pick up on the subtleties of relationships between themselves and their colleagues. Whereas clinical teachers are not trained to instruct on developing these interactive skills, theater faculty is so trained. Thus was born the concept of crossing over between the 2 fields.

Just listing the topics covered in the sessions will help the reader appreciate the potential issues that each of us faces whenever we work with our own patient population: insight into patient behavior, building patient trust, active listening, listening for subtext, listening for values and strengths, making links to one's own experiences, strategies for acknowledging the patient's feelings, skills in physical expressiveness, body language, eye contact, breathing rhythms, and time management.

As I read and re-read this article in preparation for presenting it in this forum, it struck me that each of us has the potential to address our doctor-patient relationships without the formal training … at least as a starting point. Whenever you're in the patient room, do you sit? Do you make eye contact? Do you give the impression that you care? Are you watching how the patient is positioned? Are you hearing the message of what she is saying or are you listening to just the words?

As Yogi Berra, the Hall of Fame catcher once said, "You can observe a lot just by watching." How true… and he never went to medical school.

The authors provide the following quotation from Francis Weld Peabody: "The secret of the care of the patient is caring for the patient." I think that statement can help carry each of us forward in our daily practices with each individual patient encounter. ■

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Pharmacology Update

Doripenem Injection (Doribax™)

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

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; Assistant Clinical Professor of Medicine, University of California, San Francisco; Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Chan and Elliott report no financial relationship to this field of study.

THE FDA HAS APPROVED A NEW ANTIMICROBIAL agent from the carbapenem class. Carbapenems are broad spectrum, beta lactam, antimicrobial agents. The class currently includes imipenem, meropenem, and ertapenem. The newest member, doripenem is manufactured by Shionogi & Co. Ltd in Japan and marketed by Ortho-McNeil Pharmaceuticals as Doribax.

Indications

Doripenem is indicated as a single agent for the treatment of complicated intra-abdominal infections caused by *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Bacteroides caccae, Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Streptococcus intermedius, Streptococcus constellatus*, and *Peptostreptococococcus micron*. It is also indicated for complicated urinary tract infections, including pyelonephritis, caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*.[1]

Dosage

The recommended adult dose is 500 mg every 8 hours given by intravenous infusion over one hour. The duration of treatment is 5-14 days for intra-abdominal infections. Appropriate oral therapy (eg, amoxicillin/clavulanate) should be considered after at least 3 days of parenteral therapy. The duration of therapy for complicated urinary tract infections is 10 days but can be extended to 14 days with concurrent bacterial infection. Dosage

CME Objectives

The objectives of *Internal Medicine Alert* are:

- to describe new findings in differential diagnosis and treatment of various diseases;
- to describe controversies, advantages, and disadvantages of those advances;
- to describe cost-effective treatment regimens;
- to describe the pros and cons of new screening procedures.

adjustment is required in patients with moderate or severe renal dysfunction. The recommended doses are 250 mg every 8 hours for patients with estimated creatinine clearance of 30 to 50 ml/min and 250 mg every 12 hours for >10 up to 30 ml/min.[1]

Doripenem is supplied as single-dose 500 mg vials.

Potential Advantages

Doripenem has improved *in vitro* activity against *Pseudomonas aeruginosa* compared to imipenem and meropenem.[2,3]

Potential Disadvantages

The most frequent adverse events are headache, nausea, diarrhea, rash, and phlebitis. Carbapenems in general may reduce serum concentrations of valproic acid and increase the risk of seizures. Levels of valproic acid should be monitored and alternative antibacterial or anticonvulsant therapy should be considered. Probenecid increases bioavailability of doripenem by interfering with active renal tubular excretion.[1]

COMMENTARY

Doripenem is the newest member of the carbapenem beta lactam antimicrobials to be approved. Its *in vitro* activity against aerobic bacteria is similar to meropenem against gram-negative bacteria and to imipenem against gram-positive bacteria.[4] Against anaerobic bacteria, doripenem is comparable or slightly less active than imipenem and meropenem.[5] Doripenem was approved-based on multinational, multicenter, double-blind, non-inferior trials compared to meropenem in complicated intra-abdominal infections and levofloxacin in complicated urinary tract infections.[1] In two studies of adults with intra-abdominal infections (n = 946), doripenem (500 mg every 8 hour) and meropenem (1 g every 8 hour) for 5-14 days), with the option of oral therapy after three days, showed comparable microbiological eradication. Patients were categorized as either microbiologically evaluable (ME) or microbiologically modified intent-to-treat (mMITT). ME was defined as those with susceptible pathogens at baseline with no protocol deviations and microbiological eradication assessed 25-45 days after completion of therapy. Those with baseline pathogens regardless of susceptibility were included in the mMITT analysis. Eradication rates for ME were 81.0% and 82.8% for doripenem and 82.1% and 85.9% for meropenem. For mMITT, rates were 71.9% and 73.7% and 74.2% and 78.0% for doripenem and meropenem respectively. Similarly, doripenem was found to be non-inferior to levofloxacin (250 mg every 24 hours) in complicated urinary tract infections (n = 1171). Adverse events appear to be similar to the comparator drugs. In a study presented in poster form, doripenem (500 mg every 8 hours) was similar to imipenem (500 mg every 6 hours or 1 g every 8 hours) in terms of overall cure rate in patients with ventilator-associated pneumonia (68.3% vs 64.8%).6 Cure rate was higher for doripenem against *P. aeruginosa* infections (65% vs 36%). The daily cost for doripenem (500 mg every 8 hours) is $230 compared to $177 for meropenem (1 g every 8 hours).

Clinical implications

Doripenem is a new carbapenem that has not demonstrated any clinical advantage over existing therapy for complicated intra-abdominal and complicated urinary tract infections. It should be used judiciously and only for infections caused by pathogens with known or strongly suspected susceptibility to the drug. ■

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CME Questions

55. Which of the following is true regarding beneficial effects of statins:

a. There are no benefits beyond reduction in cardiovascular risk.
b. Benefits in reducing dementia, colon cancer, and renal failure have been conclusively documented.
c. Preservation of lung function with aging occurs regardless of smoking status.
d. Randomized, placebo-controlled trials are necessary to confirm potential benefits.

56. Reasons given for preferring PCI to medical therapy for chronic stable angina, despite no evidence of its superiority, include:

a. oculostenotic reflex.
b. medical-legal concerns.
c. benefits of an open artery.
d. All of the above

Answers: 55 (d); 56 (d)

Clinical Briefs

By Louis Kuritzky, MD, *Clinical Assistant Professor, University of Florida, Gainesville*
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Benefits of Coronary Prevention: WOSCOPS

THE PREPONDERANCE OF EVIDENCE supporting lipid modulation for reduction of coronary heart disease (CHD) springs from secondary prevention trials comprised largely of mid-life individuals with prior history of diabetes, stroke, or MI. Much less evidence is available to confirm the benefits of primary prevention through lowering of LDL. The West of Scotland Coronary Prevention Study (WOSCOPS) enrolled a population (n=6,595) of men with elevated cholesterol who had NOT sustained an MI, and randomized them to pravastatin 40 mg/d (PRAV) or placebo for 5 years. Inclusion criteria required LDL at baseline to be at least 174 mg/dL. At the conclusion of the trial the composite endpoint (CHD death plus nonfatal MI) was reduced by 30% in the PRAV group compared with the placebo group. Whether the 5-year PRAV intervention might result in continued benefit beyond the initial clinical trial period was the subject of this report by Ford, et al.

After the WOSCOPS trial completion, the two arms of the trial started to look fairly similar: almost equal percentages of each were receiving a statin (PRAV group=38.7%, placebo group= 35.2%).

Endpoint ascertainment 10 years after close of the clinical trial still showed a big advantage for study subjects originally assigned to PRAV (ie, the endpoint of fatal + nonfatal MI was still a 37% relative risk reduction seen in the PRAV group (p=0.001)). Considering the high number of persons in the placebo group on statins in the post-trial interval, these long-term benefits of PRAV treatment may actually be an underestimate. ■

Ford I, et al. N Engl J Med. 2007;357(15):1477-1486

Topiramate for Alcohol Dependence

COMPLEX NEUROCHEMICAL MECHANISMS support the potential role of topiramate (TOP) for enhancing abstinence from alcohol (ABST). For instance, TOP has two different pathways by which it can reduce CNS dopamine release, thereby decreasing reinforcing aspects of alcohol ingestion. Indeed, favorable effects have already been seen in a short pilot trial.

The 14-week double-blind placebo controlled trial randomized 183 men to 300 mg/d TOP or placebo. Participants fulfilled DSM-IV criteria for alcohol dependence, and had at least 4 drinks/day (women) or 5 drinks/day (men). One drink was defined as 10 oz beer, 4 oz wine, or 1 oz of 100-proof liquor.

The primary efficacy endpoint was number of days of heavy drinking, defined as more than 5 drinks/d for men, or 4 drinks/d for women. Secondary outcomes included the percentage of days of successful total abstinence, and weekly average number of drinks.

At study endpoint, TOP was associated with a statistically significant reduction in the primary endpoint; the placebo group continued to engage in heavy drinking on 52% of days, vs 44% of days for TOP subjects. Similarly, the TOP group was over two times more likely to maintain at least 28 days of continuous abstinence than the placebo group. Differences between TOP and placebo were seen early (by 4 weeks), and were maintained throughout the trial. TOP seems a reasonable consideration to enhance alcohol abstinence. ■

Johnson BA, et al. JAMA 2007;98(14):1641-1651.

Job Strain and Recurrent CHD

ALTHOUGH THE EVIDENCE IS BY NO means incontrovertible, many clinicians concur with clinical trials which suggest job strain is a risk factor for and contributor to myocardial infarction (MI). Whether a second coronary event might also be related to job strain has been far less studied, and the trials addressing this question have been in very small populations.

Hospitals in Quebec, Canada, supplied study subjects for this large trial (n=1,191) of relatively young adults (age < 60) who had sustained an acute MI, and returned to work within 18 months after the index event. The primary outcome was incidence of new CHD events, including fatal and nonfatal MI, and angina. The Karasek Job Content Questionnaire, a validated metric for psychological demands of the work environment, was used.

After 2 years of followup, risk of a second cardiac event was more than twice as great amongst persons with the highest levels of job stress.

It is theorized that job strain induces sympathetic activation with subsequent enhanced thrombogenicity. Although less well supported, an additional theory about job stress is that persons under greater stress might be less adherent to medication and healthy lifestyle components. In any case, job strain does appear to exact a meaningful cardiovascular toll, which does not dissipate after the first event. ■

Aboa-Eboule C, et al. JAMA. 2007;298(14):1652-1660.

In Future Issues: Exploring the Substitution of Exenatide for Insulin