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Death Be Not Proud

ABSTRACT & COMMENTARY

Synopsis: *Many patients with terminal cancer support policies that would allow them access to euthanasia or physician-assisted suicide.*

Source: Wilson KG, et al. *Arch Intern Med* 2000;160:2454-2460.

Wilson and associates carefully recruited a group of patients who were dying of cancer. Because many of the potential patients for this study were too ill or died before they could be interviewed, they were able to offer participation to 150 subjects, 80 of whom declined to be interviewed. Their final sample was 70 patients. This group of 70 had a mean age of 64.5 years, consisted of 32 men, and was highly educated. A total of 41% were Roman Catholic, 41% were Protestant, and 17% were "none" or "other." As would be expected, the leading kind of cancer was lung (21%), followed by GU (19%), female breast (13%), gastrointestinal (13%), and head and neck (10%). The mean survival of this group was 44.5 days after the interview; only 15% lived as long as six months.

The interviews were audiotaped for later content analysis, and were conducted by clinical psychologists, doctoral students in psychology, or research associates in palliative care. Interviewers solicited participants' views about euthanasia and physician-assisted suicide (PAS), both in general, and with regard to the subject's personal situation. Euthanasia was defined as a situation in which "a medical doctor gives an overdose of medication to purposely end a patient's life. This is only done with patients who have asked their doctor to help them die in this way. Usually, the patients involved are very ill with a life-threatening disease." PAS was defined as an action in which "a medical doctor provides drugs and advice, so that a patient could commit suicide. The doctor does not actually inject the drugs, but rather gives the patient the means to end his or her own life."

Seventy-three percent of the patients believed that euthanasia or PAS should be legalized, with pain and the individual's right to choose as the main reason. Those who thought these actions should not be legalized cited religious or moral reasons. Fifty-eight percent of the participants said that they might personally request such a procedure if it were legal, particularly if pain or physical symptoms became intol-

Volume 22 • Number 22 • November 29, 2000 • Pages 169-176

INSIDE

erable. Eight of the 70 participants would have made such a request at the time of the interview: four of these had major depression, two had comorbid anxiety disorders, and one had major depression in remission.

Of those who would consider asking for hastened death, euthanasia was preferred to assisted suicide.

COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

Like it or not, this is a hot topic. I found 4812 articles in the National Library of Medicine published since 1966 using the key word "euthanasia," limited to human subjects. I found 487 web sites using the keyword "euthanasia." Euthanasia and PAS are legal in The Netherlands, the Australian Northern Territory, and Oregon. In a recent national telephone survey, 15.8% of 56 oncologists had performed euthanasia or PAS.[1] In six of the patients involved in this report, the patient did not participate in the decision, and in only about one-third of cases did the physicians adhere to all three of the proposed safeguards: 1) having the patient initiate and repeat the request for euthanasia or PAS; 2) ensuring the patient was experiencing extreme physical pain or suffering (although all the patients were receiving narcotic analgesia); and 3) consulting with a colleague. In a mail questionnaire of 1902 physicians, Meier and colleagues found that 11% were willing to hasten a patient's death even with the current legal constraints, and 18.3% reported having received a request for assistance with suicide from a patient.[2] Approximately 3.3% reported writing at least one prescription and 4.7% reported administering at least one lethal injection.

In the current report, patients reported the following reasons that there should be at least limited legal access to euthanasia or PAS: individual's right to choose, pain, diminished quality of life, suffering, hopeless situation, mental symptoms, burden for others, physical symptoms other than pain, and knowledge of others' experiences.

In previous reports, pain has been a significant negative factor in studies of end-of-life care.[3-5] Bereaved family members cite inadequate pain control (and access to physician's time!) as significant problems with end-of-life care.[4] However, neither a specific nurse intervention[3] nor patient empowerment and feedback[5] improved pain control in clinical trials. I suspect that sometimes physicians balk at giving adequate pain control if they believe that the medicine will hasten death. However, the American Medical Association's Code of Ethics endorses doing exactly that, if the primary purpose is to relieve pain or suffering. In "official" parlance, "Physicians have an obligation to relieve pain and suffering and to promote the dignity and autonomy of dying patients in their care." This includes providing effective palliative treatment even though it may foreseeably hasten death.[6]

Depression is also a significant and frequent finding in the terminally ill,[7-9] and there is some evidence that depression is undertreated in terminal patients.[8] In the current study, the eight patients who would have requested PAS/euthanasia at the time of study were significantly more depressed than the other study patients, but there was no difference in their report of pain as a symptom. The article does not include information on antidepressant treatment of this group, though 24% of the 70 patients were on antidepressants.

Fear of being a financial burden is listed as a reason for PAS/euthanasia in some studies of terminal patients.[10] However, in the current study, the Canadian patients had access to state-funded palliative care services, at no personal financial cost.

This study and others spotlight the fact that we do not do a very good job with end-of-life care. My reading to prepare this commentary turned up documentation that

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we are perceived as inaccessible to terminal patients and their families, that we undertreat pain and depression, and that we sometimes expend vast resources for little benefit. As a result, patients and their families feel that they have lost control at the most vulnerable time in their lives. No wonder they request that it be ended!

The American Medical Association is attempting to address this problem with a program called Education for Physicians on End-of-Life Care (EPEC). You can learn more about this program by visiting the AMA web site at www.ama-assn.org and clicking on or searching for EPEC. This educational program is divided into 12 Modules and four Plenary Sessions, and includes modules on Pain Management, Physician-Assisted Suicide, and Withholding/Withdrawing Treatment. ❖

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Helicobacter pylori and Functional Dyspepsia: A New Twist to the Tale!

ABSTRACTS & COMMENTARY

Synopsis: *The small but significant advantage for omeprazole 20 mg in the H. pylori-positive patients was, perhaps, related to enhanced acid secretion in the presence of H. pylori.*

Sources: Blum AL, et al. *Gut* 2000;47:473-480; McColl KE. *Gut* 2000;47:461-462.

After a complete diagnostic workup, 792 patients with functional dyspepsia were randomized to two weeks of treatment with either placebo, ranitidine 150 mg, omeprazole 10 mg, or omeprazole 20 mg daily. Therapeutic response was evaluated according to *Helicobacter pylori* status. Remission rates (%) at the end of therapy were as shown in the Table.

Table

Remission Rates at the End of Therapy

H. pylori status	Placebo	Ran 150 mg	Omep 10 mg	Omep 20 mg
+	42	50	48	59
-	66	73	64	71

The therapeutic gain for treatment over placebo was significant only for omeprazole 20 mg in *H. pylori*-positive patients (17.6%). However, omeprazole 20 mg led to a significant rate of complete disappearance of symptoms in all patients. Interestingly, relapse rates among responders were low (< 20%) at follow-up at six months. Blum and associates concluded that the small but significant advantage for omeprazole 20 mg in the *H. pylori*-positive patients was, perhaps, related to enhanced acid secretion in the presence of *H. pylori*.

COMMENT BY EAMONN M. M. QUIGLEY, MD

The role of *H. pylori* in functional (or nonulcer) dyspepsia remains highly controversial. While no one would dispute the potential benefits of a test-and-treat policy in dyspepsia, in general (also referred to as un-investigated dyspepsia), due to the defined role of this organism in peptic ulcer disease,[1] results of *H. pylori* eradication in functional dyspepsia have been divergent.[2] This study addressed another important clinical issue; namely, will *H. pylori* status influence the response to empiric acid-suppressive therapy in functional dyspepsia? The answer is yes; at least in the short term. While Blum et al did not detect any significant difference in remission rates between placebo and the various acid-suppressive regimes tested in *H. pylori*-negative patients, a small but significant therapeutic advantage was found for omeprazole 20 mg in *H. pylori*-positive patients. However, placebo response rates were high (66% in the *H. pylori*-negative group!) and response rates were lower for all groups in *H. pylori*-positive patients. Blum et al suggested that *H. pylori* eradication may render these dyspeptic patients more resistant to acid suppression and concluded that this was yet another argument against *H. pylori* eradication! However, an accompanying editorial argues, with equal vigor, that the difference in response rate

could have resulted from a preponderance of pre-ulcer disease in the *H. pylori*-positive group; a condition that could have been more effectively and permanently treated by *H. pylori* eradication. The debate continues. ❖

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Long-term Outcome in Asymptomatic Men with Exercise-Induced Premature Ventricular Depolarizations

ABSTRACTS & COMMENTARY

Synopsis: *Apparently well males who exhibit frequent PVCs during exercise have a higher rate of both cardiovascular as well as all-cause mortality.*

Sources: Jouven X, et al. *N Engl J Med* 2000;343:826-833; Calkins H. *N Engl J Med* 2000;343:879-880.

During the period of 1967 to 1972, jouven and colleagues subjected 93.4% of all apparently well male Paris Civil Service employees to a standard bicycle exercise stress test with the objective of determining the short- and long-term prognosis associated with premature ventricular contractions (PVCs) occurring at rest, during exercise, and during the immediate post-exercise period. At entry, subjects ranged from 42 to 53 years of age. Apparently well was defined as lacking a systolic BP more than 180 mm Hg, having no history of diabetes mellitus, and having no abnormality on a standard resting 12-lead ECG. Subjects were followed until January 1, 1991—a total of 23 years. Vital statistics were available for all but 355 (5.5%) of the 6456 subjects.

Exercise testing was positive for ischemia in 4.4% of subjects. Frequent PVCs occurred before exercise in 0.8%; during exercise in 2.3%; and in 2.9% during recovery from exercise. Infrequent premature contractions occurred before exercise in 2%; during exercise in 8.5%; and, in 7.3% during recovery from exercise. During the 23 years of follow-up, no difference was found in either overall or cardiovascular mortality rate between those who had none, infrequent, or frequent PVCs before exercise. In striking contrast, subjects who had frequent PVCs during exercise had a significantly higher all-cause (41.3%) and cardiovascular mortality (16.7%) compared to those who had either no (27.9% all-cause and 16.7% CV) or infrequent VPBs (26.3% all-cause and 6.8% CV) during exercise. Those who had frequent PVCs during the recovery phase had a higher all-cause mortality rate but did not have a higher CV mortality rate than those with no or infrequent PVCs.

Significantly, subjects who demonstrated ischemic ECG changes during exercise rarely exhibited frequent PVCs; conversely, those who demonstrated frequent PVCs during exercise rarely demonstrated ischemic ECG changes. Jouven et al make the following conclusions: 1) apparently well males who exhibit frequent PVCs during exercise have a higher rate of both cardiovascular as well as all-cause mortality; 2) the reason for this PVC-related increase is something other than ischemic heart disease; and 3) the long-term increase in cardiovascular mortality associated with exercise-induced PVCs is of the same magnitude as that associated with ischemia. Jouven et al suggest that exercise-induced PVCs may reflect the effects of catecholamines and/or may reflect that these subjects had some form of cardiomyopathy (for example, right ventricular dysplasia).

COMMENT BY MICHAEL K. REES, MD, MPH

In an accompanying editorial, Calkins remarks that, "remarkably little is known about the long-term prognostic implications of exercise-induced ventricular arrhythmias." He notes that the study by Jouven et al is the first to evaluate their prognostic implications. Clinicians now know that exercise-induced PVCs are not benign and that individuals who exhibit some require further careful investigation and regular long-term follow-up. ❖

Effect of Patient Reminder/ Recall Interventions on Immunization Rates

ABSTRACT & COMMENTARY

Synopsis: *A variety of patient reminder systems were effective in improving rates in 80% of the studies, raising rates from 5-20 percentage points for both childhood and adult vaccinations in a variety of different settings. Telephone reminders were the most effective but also the most expensive.*

Source: Szilagyi PG, et al. *JAMA* 2000;284:1820-1827.

Two independent reviewers evaluated all English-language studies published over 30 years

through 1998 using patient reminder or recall systems for the commonly recommended adult and childhood vaccines. Five bibliographic search engines including MEDLINE were used, and reference lists from all relevant articles were also reviewed to identify suitable research. Studies had to include outcome measures of immunization rates, and study designs had to be either randomized controlled trials, controlled before-and-after studies, or interrupted time series studies.

A total of 109 studies were identified from which 41 met eligibility criteria and were further analyzed. The main reasons for exclusion were lack of a control group or using different outcome measures. Effectiveness was shown in 33 of the 41 studies (80%), as measured by increases in immunization rates from 8% to 18% over baseline. Increases were found for both children and adults, and also for different settings although private practice was somewhat lower than academic settings (8% increase vs 21%). All types of reminders showed increases, with the largest coming from telephone reminders (25%) and least from single letters (7%). Several studies combined reminders such as postcards and telephone calls, or combined patient reminders with physician reminders, and no clear advantages of one approach over another were seen, although more improvements were generally seen with more intensive and combined reminder systems.

Analysis of those studies that did not show improvements in immunization rates revealed multiple confounding variables, such as small sample sizes, high baseline rates to begin with, or less targeted reminders. There were no clear trends in these failures for type of practice setting, patient population, or type of reminder/recall system used.

Fifteen of the studies included cost information, which varied widely both due to different types of reminder systems used, and because different methods were used to calculate costs. Short-term and single reminders were the least expensive, with ranges of $7-10 per patient vaccinated. Some studies noted that patient reminders had the added benefit of increasing preventive visits for other services in addition to immunizations, so enhanced benefits were seen.

Based on the results of this extensive review, Szilagyi and colleagues recommend that all primary care physicians seriously consider incorporating reminder/recall systems into their practices.

COMMENT BY MARY ELINA FERRIS, MD

Despite sustained efforts to increase immunization rates for both children and adults, there remains room for overall improvement in some childhood vaccination rates and in influenza and pneumococcal vaccinations for adults. Recent data for children in 1998 show 79% achieved the required shots by age 4, although only 43% had the recommended varicella shot. Adults reported by phone survey in 1997 that 65% had their annual flu shot, but only 45% recalled receiving pneumococcal vaccine.[1,2] Certain populations such as African-Americans consistently have lower rates that also need public attention.

The question of "what works" to improve these rates is answered in this article and should provide support for the financing of patient reminder systems. All types of reminders were effective, and they worked in a variety of different settings. The only glaring deficiency in this information is whether the reminder/recall systems also worked for specific ethnic and cultural populations, who may have different barriers to immunization that would not be overcome with a simple reminder. Interviews with older adults who did not receive influenza and pneumococcal shots state most commonly that they didn't know the shots were needed, although 40% of them also expressed concerns about vaccine safety and side effects.

Technology should be incorporated into our practices to assist us with routine reminders, not only for immunizations but for other preventive services as well. Szilagyi et al suggest that future research should focus on implementation strategies, and that primary care practices should begin now to use reminder systems as a proven population-based approach to affect the larger community beyond our individual encounters. ❖

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Pharmacology Update

Glyburide and Metformin Tablets (Glucovance—Bristol-Myers Squibb)

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

The fda recently approved a fixed combination of glyburide and metformin for the treatment of

type 2 diabetes mellitus. The product, marketed under the trade name Glucovance, combines two of the most popular antidiabetic medications in one tablet. With metformin losing its patent next year, Bristol-Myers Squibb is hoping for success with this product and its recently approved long-acting form of metformin (Glucophage XL).

Indications

Glyburide/metformin is indicated as initial therapy as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are inadequately managed by diet and exercise.[1]

It is also indicated for second-line therapy when diet, exercise, and initial therapy with a sulfonylurea or metformin do not achieve adequate glycemic control.[1]

Dosage

Glucovance is available in three strengths: 1.25 mg/250 mg, 2.5 mg/500 mg, and 5 mg/500 mg of glyburide and metformin, respectively. As initial therapy, the recommended starting dose is 1.25 mg glyburide and 250 mg metformin once or twice daily with meals. Dosage may be increased in 1.25 mg/250 mg increments per day every two weeks up to a maximum of 10 mg/2000 mg per day. For second-line therapy, the recommended starting dose is 2.5 mg/250 mg or 5 mg/500 mg twice daily with meals.[2]

Potential Advantages

A fixed combination may improve medication adherence in those currently taking the drugs separately.

Potential Disadvantages

A fixed combination is less flexible than titration of the separate agents.

Comments

The combination of a sulfonylurea and metformin has been widely used and studied. These drugs have different mechanisms of action—one addresses insufficient insulin release while the other modulates insulin resistance.

A lower-dose combination may achieve comparable or better glycemic control than higher-dose monotherapy with potentially fewer side effects.[1,2,4,5] Fewer episodes of hypoglycemia and weight gain than glyburide alone and a lower incidence of gastrointestinal side effects compared to metformin alone have been reported.[2,5] In a large 20-week, double-blind placebo, U.S. multicenter trial (n = 806) reported by the manufacturer, the fixed-dose combination resulted in a reduction in HbA1c of 1.48-1.53% compared to 1.03% for metformin alone ($P < 0.05$) or 1.24% for glyburide alone ($P < 0.05$).[1]

Fasting blood sugar (FBS) was reduced 40.1-41.5 mg/dL compared to 35.7 mg/dL for glyburide and 21.2 mg/dL for metformin but was not statistically significantly different. These subjects were treatment naive with a mean baseline HbA1c of 8.14-8.23% and mean fasting plasma glucose of 175-179 mg/dL. Subjects were initiated on 2.5 mg of glyburide, 500 mg of metformin, and 1.25 mg/250 mg or 2.50 mg/500 mg of glyburide/metformin, and were titrated as needed to a maximum of four tablets daily. The mean final doses were 5.3 mg for glyburide, 1317 mg for metformin, 2.78 mg/557 mg and 4.1 mg/824 mg for the glyburide/metformin.

In a 16-week, double-blind, active-controlled, U.S. trial (n = 639), the combination of glyburide/metformin resulted in a reduction of HbA1c of 1.69-1.70% compared to glyburide ($P < 0.001$) and 1.90-1.91% compared to metformin ($P < 0.001$).

Fasting blood sugar was reduced 51.3 to 59.9 mg/dL compared to glyburide ($P < 0.001$) and 64.2-72.7 mg/dL compared to metformin ($P < 0.001$).[1] These were subjects who were previously not adequately controlled on 10 mg of glyburide or 20 mg of glipizide. Mean baseline HbA1c ranged from 9.43-9.63% and fasting plasma glucose of 210-218 mg/dL. Subjects were initiated on 20 mg (fixed-dose) of glyburide, 500 mg of metformin, and 2.5 mg/500 mg or 5 mg/500 mg of glyburide/metformin.

Dose titration was allowed up to a maximum of four tablets daily for metformin and glyburide/metformin. The mean final doses were 20 mg (fixed dose) for glyburide, 1840 mg for metformin, 8.8 mg/1760 mg and 17 mg/1740 mg for glyburide/metformin. Glucovance is priced at $0.65/tablet for the 1.25 mg/250 mg strength tablet and $0.78 for the 2.5 mg/500 mg and 5 mg/500 mg strength tablets. These prices compare favorably to metformin and glyburide prescribed separately and are not much different than metformin 500 mg alone—$0.69.

Clinical Implications

Most patients with type 2 diabetes have defects in insulin production as well as insulin resistance.[2] Thus, combination therapy that addresses both of these problems seems logical. In addition, combination therapy gain additive benefits and may reduce side effects associated with higher doses of monotherapy. Proponents of early combination therapy at low dosages question the wisdom of titrating initial monotherapy to maximum dose before adding a second drug.[2] Glucovance offers a fixed-dose combination alternative to initial monotherapy as well as second-line therapy if monotherapy has failed. ❖

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CME Questions

39. Frequent PVCs may occur before, during, or in the resting phase of an exercise tolerance test. Which one of the following statements is correct?

a. Frequent PVCs occurring before an exercise tolerance test are associated with an increase in cardiovascular mortality.
b. Frequent PVCs occurring during an exercise tolerance test are associated with an increase in cardiovascular mortality.
c. Frequent PVCs occurring during the resting phase of an exercise tolerance test are associated with an increase in cardiovascular mortality.

40. In terminal patients, pain control is:

a. rarely a problem.
b. enhanced by a nurse educator intervention.
c. improved by patient empowerment and feedback.
d. cited as a reason to consider physician-assisted suicide.
e. supposed to be limited if adequate pain control would hasten death.

41. Which one of the following have been proven to increase immunization rates in children and adults?

a. Postcard reminders
b. Telephone call reminders
c. Single letter reminders
d. All of the above

42. Which is *not* true about glyburide/metformin (Glucovance)?

a. It comes in three different dose combinations
b. The mechanism of action of each drug is different
c. The maximal dose is once a day
d. It is approved as initial therapy of type 2 diabetes

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PS Form **3526**, September 1999 *(Reverse)*

By Louis Kuritzky, MD

Incidence Trends for Colorectal Cancer

Clinicians use a variety of tools to screen for colorectal cancer, including rigid sigmoidoscopy, flexible sigmoidoscopy, and colono-scopy. Success of such methods is predicated upon tumors being resectable and within the reach of the tool used. There has been literature support for the observation that tumor geography is shifting such that "left-sided" tumors (i.e., located in the sigmoid colon and more distal, excluding the anus) are becoming less frequent, and "right-sided" tumors (i.e., proximal to the sigmoid colon) more common. Flexible sigmoidoscopy, which detects left-sided tumors, maintains its viability only so long as a sufficient proportion of disease burden remains within the 65 cm range. If tumor burden geographically shifts sufficiently, choice of screening tool will be directly affected.

The purpose of the current study was to examine, by means of analysis of the California State Cancer Registry, the incidence of left-sided and right-sided colon cancers. It would be anticipated that sigmoidoscopy would favor reduction in incidence of left-sided cancers.

Overall, colorectal cancer incidence decreased steadily by 19% over 10 years, but left-sided cancers decreased more than twice as much as right-sided tumors. A good deal of this left-sided cancer reduction is attributed to sigmoidoscopic screening and subsequent tumor resection. Inciardi et al posit that the increased frequency of right-sided colorectal cancers should stimulate consideration of modification of screening processes, in essence to more frequently use colonoscopy as the routine screening tool. ❖

Inciardi JF, et al. Am J Med 2000; 109:277-281.

Osteoporotic Fractures Study

The public health as well as personal effect of osteoporosis (OSPS) and its sequelae remains abundant. The last five years have seen a proliferation of available tools to combat and prevent this disorder, including agents shown to effectively reduce fractures in subjects at risk for glucocorticoid-induced OSPS in both genders. Calcitonin (CTN) has demonstrated an ability to decrease bone resorption and improve or stabilize bone mineral density (BMD) in osteoporotic patients. Since BMD is a surrogate end point, and the patient and clinician alike are ultimately concerned with fracture reduction efficacy, the issue that no large, randomized, prospective trial of CTN for fracture reduction has been performed may have been a limiting factor in therapeutic selection of this agent for treatment of OSPS. To that end, the Prevent Recurrence of Osteoporotic Fractures (PROOF) study (n = 1255) was undertaken.

Subjects were randomized to receive either calcitonin nasal spray at doses of 100-400 IU daily, or placebo, in addition to 1000 mg/d calcium supplements and 400 IU vitamin D daily. Inclusion criteria were postmenopausal status, and presence of either vertebral fractures or BMD greater than 2 standard deviations below normal. Patients were followed for five years.

Use of CTN (200 IU/d) resulted in a 33% reduction in new vertebral fractures, even in persons without a major effect on BMD. Whether CTN reduces fracture through decreased bone turnover, improved bone quality, improved bone strength, improved bone mineralization, or some combination of such factors remains to be determined. ❖

Chesnut CH, et al. Am J Med 2000; 109:267-276.

Periodontal Disease and CHD Risk

Atherosclerosis, at its most fundamental level, is felt to be an inflammatory disease. Much attention has recently been focused upon the associations observed between disorders like periodontitis and gingivitis with cardiovascular end points such as myocardial infarction (MI). Since MI, gingivitis, and periodontal disease all occur with increasing age, increased duration of smoking, and increased body fat, it has been unclear whether the association of oral disorders and coronary disease is causal, or merely concomitant.

In order to better define this relationship, Hujoel et al studied data from the 1971-1975 NHANES 1 study (n = 8032). Addressing status of participants for the presence or absence of periodontitis or gingivitis at baseline, the population of adults age 26-74 who were followed through 1992 in whom a first MI occurred. Each of the participants underwent a general history and physical examination, laboratory tests, and a dental examination.

Gingivitis at baseline was not associated with cardiovascular risk; the presence of periodontitis was associated with a trend toward greater coronary heart disease, but this association did not achieve statistical significance. Since this study is the largest to date to address this issue, it is felt that the association of poor oral health with cardiovascular end points, if any, must be small. On the other hand, even if the absolute contribution to cardiovascular risk is small since periodontitis is a common disorder, future studies addressing larger populations might better delineate the potential for effect on end points like MI. ❖

Hujoel PP, et al. JAMA 2000;284: 1406-1410.

In Future Issues: Is Snoring a Risk Factor for Death?