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CLINICAL CARDIOLOGY ALERT

A monthly update of developments in cardiovascular disease

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INSIDE

Financial Disclosure:

Clinical Cardiology Alert's physician editor, Michael H. Crawford, MD, is on the speaker's bureau for Pfizer. The peer reviewer, Rakesh Mishra, MD, reports no consultant, stockholder, speaker's bureau, or other financial relationship with any company related to this field of study.

Should We RELOAD Patients on Long-term Clopidogrel?

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MBBS, PhD

Assistant Professor of Medicine, Interventional Cardiology, University of California, San Francisco

Dr. Boyle reports no financial relationships relevant to this field of study.

Source: Collet JP, et al. Dose effect of clopidogrel reloading in patients already on 75-mg maintenance dose: the Reload with Clopidogrel Before Coronary Angioplasty in Subjects Treated Long Term with Dual Antiplatelet Therapy (RELOAD) study. *Circulation*. 2008;118:1225-1233.

PLATELET INHIBITION WITH CLOPIDOGREL HAS BECOME AN IMPORTANT weapon against recurrent coronary events in patients with coronary artery disease. However, recent evidence shows that patient response to clopidogrel is variable, with some patients having suboptimal inhibition of platelet aggregation. Because platelet function testing is not widely available to tailor individual therapy for each patient, research has focused on a one-dose-fits-all approach to loading and maintenance doses of clopidogrel. While this approach has led to substantial reductions in clinical event rates, some patients still present with recurrent events on clopidogrel; whether a repeat loading dose will improve the platelet reactivity in these patients has not been studied. Accordingly, Collet et al designed this study to address the question of whether reloading with clopidogrel will improve platelet aggregation parameters.

They enrolled 166 patients who were stable on clopidogrel therapy and were scheduled for coronary angiography for either stable angina or unstable angina. Patients had to be stable on clopidogrel for at least one week, but over 90% were on clopidogrel for at least one month. In an interesting trial design, platelet function testing was performed at baseline, and the patients were then assigned to receive a 300 mg, 600 mg, or 900 mg initial loading dose; platelet function testing was performed four hours later. The three groups then received an additional 600 mg, 300 mg or 0 mg loading dose, respectively, so that all patients received a total of 900 mg after four hours, and platelet function testing was repeated at 24 hours. All patients were on low-dose aspirin and clopidogrel 75 mg/day thereafter for the 30-day follow-up. Collet et al used several methods to assess platelet function at each time-point.

VOLUME 27 • NUMBER 11 • NOVEMBER 2008 • PAGES 81-88

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They measured residual platelet aggregation (RPA) by light transmission aggregometry in response to ADP 20 micromol/L at baseline, four hours after the first loading dose and at 24 hours. From this data, they calculated the inhibition of RPA (IRPA) as a percentage change in RPA from baseline to 4 and 24 hours, to reflect the anti-platelet effect of the repeat loading doses of clopidogrel. The primary endpoint of the study was IRPA at four hours. As a comparison, the also used ADP doses of 5, 10, and 50 micromol/L. They also included suboptimal response to clopidogrel (defined as > 50% RPA at baseline and < 10% IRPA after loading dose) as a secondary endpoint. In addition, they also used the VerifyNow point-of-care P2Y12 assay to measure suboptimal inhibition (defined as < 15%) at baseline and after loading doses. Importantly, patients taking other anti-platelet medication, oral anticoagulants, or non-steroidal anti-inflammatory drugs were excluded from the study.

The baseline characteristics were not different between groups. Approximately half the patients in each group had stable angina and the other half had unstable angina. Approximately 50% in each group underwent percutaneous coronary intervention (PCI). The primary endpoint, IRPA at four hours, was significantly greater in the 900 mg loading group vs the 600 mg loading dose (64 ± 38% vs 40 ± 53%; $p = 0.017$) or the 300 mg loading dose (30 ± 57%; $p = 0.0008$). After 24 hours, when all three treatment strategies had received a total of 900 mg of clopidogrel, there was no difference in IRPA between groups. There was a strong correlation between the RPA measured by light transmission aggregometry and the P2Y12 reaction units measured by the VerifyNow point-of-care assay.

Suboptimal response to clopidogrel at baseline was seen in 15.3%, assessed by RPA in > 50% and in 11.1% assessed by P2Y12 assay. There was a poor concordance (Kappa statistic 0.2) between these two methods to identify poor responders. Measured by IRPA < 10%, fewer poor responders were found four hours after 900 mg loading dose, than with either the 600 mg or 300 mg loading doses ($p = 0.004$), but by 24 hours, when all groups had a total of 900 mg, there was no longer a difference between groups. As expected, there were no differences in bleeding between groups because they all eventually had the same total loading dose. Importantly, there were no TIMI major bleeds. TIMI minor bleeds were seen in 4, 3, and 3 patients in the 300 mg, 600 mg, and 900 mg initial loading dose groups, respectively. No strokes, one peri-procedural myocardial infarction (600 mg group), and two deaths (one aortic dissection — 300 mg group; one cancer-900 mg group) occurred during the 30-day follow-up. Collet et al conclude that the level of platelet inhibition can be improved in patients treated with a maintenance dose of 75 mg/day of clopidogrel undergoing PCI by using high reloading doses.

■ COMMENTARY

Collet et al demonstrate a dose-dependent improvement in platelet inhibition four hours after a repeat loading dose in patients who are chronically on clopidogrel 75 mg/day. The highest dose of 900 mg in this study reduced the RPA, improved the percent IRPA, and reduced the number of poor responders to clopidogrel. The data presented here are consistent with recent reports in the literature that higher loading doses can reduce platelet aggregation and reduce clinical events. This study was not designed or powered to address hard clinical event endpoints. However, it demonstrates that clopidogrel responsiveness can be modulated by higher doses. Previously, some had suggested that doses higher than 600 mg conferred no additional benefit on platelet reactivity. This study stands in direct contradiction to this theory. The initial 4-hour data after the first loading dose is strengthened by the 24-hour data that shows all group can improve their RPA with a total dose of 900 mg of clopidogrel.

The poor concordance between the P2Y12 assay and the light transmission aggregometry in identifying poor responders to clopidogrel is intriguing. Without demonstrating differences in clinical endpoints, it is not possible to say which is more accurate in identifying clopidogrel hyporesponsiveness, and this requires further study. The low rates of clinically significant bleeding are encouraging.

Clinical Cardiology Alert, ISSN 0741-4218, is published monthly by AHC Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

EDITORIAL GROUP HEAD: Russ Underwood.
MANAGING EDITOR: Leslie Hamlin.
MARKETING PRODUCT MANAGER: Schandale Kornegay.

GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Clinical Cardiology Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $42. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

Subscriber Information

Customer Service: 1-800-688-2421
Customer Service E-Mail: customerservice@ahcmedia.com
Editorial E-Mail: jennifer.corbett@ahcmedia.com

Subscription Prices

United States
1 year with Free AMA Category 1 credits: $319
Add $17.95 for shipping & handling.
(Student/Resident rate: $125).

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Questions & Comments

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These data support the use of high loading doses of 900 mg of clopidogrel in patients undergoing PCI regardless of the presence or absence of prior long-term therapy. ■

Management of Type B Aortic Dissection

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Chang CP, et al. The role of false lumen size in prediction of in-hospital complications after acute type B aortic dissection. *J Am Coll Cardiol*. 2008;52:1170-1176.

Uncomplicated type B aortic dissection (origin distal to left subclavian artery) is usually treated medically. However, early mortality is 10%-12%, and is due to complications. The ability to predict who will develop complications could help reduce mortality by permitting earlier interventions. Thus, Chang et al from Taiwan assessed CT scans in 55 consecutive type B dissections to see if there were anatomical clues to subsequent complications. Complications were defined as death due to dissection; progression of dissection; rupture of the aorta; and end-organ hypoperfusion. Of the 55 patients, 31 had a stable in-hospital course and 24 had complications. CT measurements included maximum aortic diameter, maximal false lumen area (MFLA), minimal true lumen, number of branch vessels involved (BVI), and total longitudinal length of the dissection. MFLA was significantly larger in the complications group (1,899 vs 558 mm^2, $p < .001$), and BVI was higher (3.3 vs 1.0, $p < .001$). Only MFLA and BVI were independent predictors of complications on multivariable analysis. An initial MFLA > 922 mm^2 or a BVI of two or more were associated with a higher incidence of in-hospital complications. Chang et al concluded that a large initial MFLA and higher BVI by CT are predictors of a complicated hospital course in type B aortic dissection.

■ **COMMENTARY**

The management of type B aortic dissection is problematic. Most patients do well with medical therapy, but some have complications which are often fatal. In this consecutive series, 44% had complications, of which 17% died in the hospital. If these patients could be intervened upon earlier, especially with stent-grafts, prognosis may be improved. In this series and others, clinical features did not predict outcomes, but aortic characteristics on CT scans do. Prior studies have shown some relation between aortic size and outcomes, but this study focused on the two lumens in a dissection and came up with more powerful predictors. All the CT aortic measures made were univariate predictors of complications, but two, MFLA and BVI, were independent predictors of any complication. MFLA was a robust predictor of all complications, but BVI predicted organ hypoperfusion and progressive dissection better than rupture. This makes sense because if the thin-walled false lumen continues to expand, it would be reasonable to predict rupture, progressive dissection, and eventual organ under perfusion. So the false lumen size seems to be the key variable. Chang et al suggest that if the MFLA is greater than around 900 mm^2, one should consider an intervention to prevent complications. This is a small trial, and this hypothesis will need to be tested prospectively, but until that is accomplished, this seems to represent good advice for the management of acute type B aortic dissection. ■

Appropriate Utilization of EMS Services

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD
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Dr. DiMarco is a consultant for Novartis, and does research for Medtronic and Guidant.

Source: Sasson C, et al. Prehospital termination of resuscitation in cases of refractory out-of-hospital cardiac arrest. *JAMA*. 2008;300:1432-1438.

The cardiac arrest registry to enhance survival (CARES) is a registry designed to help local emergency medical system officials monitor outcomes of out-of-hospital resuscitation. In this paper, data from eight cities in the United States are analyzed to determine if termination of resuscitation rules can be successfully applied in routine practice. The two proposed sets of guidelines were classified as the basic life support (BLS) and the advanced life support (ALS) rules. The BLS rule had three components. The event could not be witnessed by emergency medical services personnel; no automated external defibrillator was used or any manual shock applied in the out-of-hospital setting, and there was no return of spontaneous circulation. The ALS rule added two additional criteria. The arrest could not be witnessed by a bystander, and no bystander-administered car-

diopulmonary resuscitation had been attempted. This current paper tests the ability of these rules in classifying patients who are unlikely to survive to hospital discharge after an out-of-hospital cardiac arrest.

The CARES registry collects data from 911 call centers, EMS personnel, and the receiving hospitals. To protect privacy, individual identifiers are removed from the data. Characteristics of the arrest are then correlated with short- and long-term survival. In this paper, the data set was used to calculate the sensitivity, specificity, and positive and negative predictive values of the BLS and ALS rules for identifying patients likely to not survive to hospital discharge. The goal of the study was to develop accurate indicators for termination of resuscitation that would prevent unnecessary emergency transports to the hospital, yet now compromise potential for meaningful survival.

The CARES registry data covered in this report included 7,235 cases collected from 19 EMS agencies and 111 hospitals in eight United States cities. To this group, standard exclusion criteria were applied, so that 5,505 cardiac arrest cases comprised the final study group. The overall group was 60% male with a mean age of 64.4 years. Sixty-five percent of the arrests occurred at home, 14.5% in nursing homes or assisted-living facilities, and 21% in public settings. The initial rhythm recorded was ventricular fibrillation or ventricular tachycardia in 18.3%, and unknown shockable rhythm in 5.3%, and either an unknown shockable rhythm, asystole, or pulseless electrical activity in the remainder. The arrest was witnessed by a bystander in 37% of the patients and by EMS personnel in 12%. Using local protocols, 947 patients were pronounced dead in the out-of-hospital setting and were not transported emergently with on-going resuscitation attempts to the hospital. Return of spontaneous circulation in the out-of-hospital setting was achieved in 30.7% of the patients. Survival to hospital admission was noted in 21.9% of the patients, with 7.1% surviving to hospital discharge. Overall, 3.5% of the cases survived to discharge and had a normal, or nearly normal, functional status. If the BLS termination rule had been applied, 2,592 patients would have had resuscitation attempts terminated in the out-of-hospital setting. Of these patients who met BLS criteria for termination, only 70 could be resuscitated in the emergency department and admitted to the hospital but, of these, only five (0.2% of the entire group) survived to hospital discharge. Use of the BLS rule would have resulted in an out-of-hospital pronouncement of death of 47%. If the more conservative ALS rule had been applied, then 1,192 patients would have had termination of resuscitation out-of-hospital. Of these, 24 patients were resuscitated in the emergency department but none survived to hospital discharge.

Sasson et al conclude that the BLS rule for termination of resuscitation identifies with a high specificity and a high positive predictive value, patients with out-of-hospital cardiac arrest who have a very low likelihood of survival to hospital discharge. Implementation of this rule could substantially reduce the risks and costs associated with high-speed transports of patients in the setting of ongoing resuscitation attempts. This, in turn, would decrease pressure on overburdened EMS systems and allow emergency department staff to focus on patients with a greater probability of survival.

■ **COMMENTARY**

Each year, there are approximately 175,000 out-of-hospital sudden cardiac arrests in the United States. In patients with ventricular fibrillation and ventricular tachycardia, early defibrillation (or cardioversion) is the key to survival. Bystander CPR can widen the window of opportunity for successful defibrillation in some cases. Despite widespread efforts over many years to decrease EMS response times and put defibrillators in the hands of first responders and lay rescuers, overall survival after an out-of-hospital cardiac arrest remains low. Many cardiac arrest victims with virtually no hope for survival are transported as emergencies to the nearest hospital. This places rescuers and others at risk of injury during the transport and increase costs within the EMS system with little or no return. In this paper, simple rules are evaluated that would permit EMS responders to discontinue resuscitation effects in the field. The BLS guideline used here is simple and, if adopted, would eliminate a large number of futile transports and emergency room resuscitation attempts. If we can make our EMS systems more efficient, they will be able to focus their limited resources on patients with a realistic chance for survival. ■

Discordant Results of Exercise Echo and ECG

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Al-Mallah M, et al. Long term favorable prognostic value of negative treadmill echocardiogram in the setting of abnormal treadmill electrocardiogram: a 95 month median duration follow-up study. *J Am Soc Echocardiogr*. 2008;21: 1018-1022.

SINCE BOTH TREADMILL EXERCISE ECG AND ECHO HAVE independent prognostic value when studied alone, what does the ECG response add to a negative exercise

echo? To answer this question Al-Mallah et al from Henry Ford Hospital in Detroit evaluated consecutive Bruce protocol exercise echo studies and separated out 677 patients who had a negative echo study. They excluded those with uninterruptable ECGs. A positive or negative ECG response indicative of ischemia further separated the patients (598 negative, 79 positive). Patients were followed for a median of 95 months to identify major adverse cardiac events (MACE): death, myocardial infarction, or revascularization.

Results: MACE occurred in 8.6% of the patients with negative exercise echoes, with an annual event rate of 1%. Although the raw data exhibited more events in the ischemic ECG group (15 vs 8%, $p = 0.025$), when the data were adjusted for clinical and stress test variables, an ischemic ECG response was not independently predictive of MACE ($p = 0.2$). Also, for the first five years of follow-up, there was no difference between the ECG groups in the raw MACE. Independent predictors of MACE were female sex, prior coronary heart disease, exercise duration, and chest pain at peak exercise. Al Mallah et al concluded that patients with negative exercise echo studies have an excellent long-term prognosis that is not influenced by the exercise ECG results.

■ **COMMENTARY**

Not infrequently I will be called to assess an exercise echo on a patient of mine who had a positive ECG response. Often the echo is negative, and I reassure the patient, but there is always a lingering doubt concerning whether the ECG response is correct. This study relieves some of that anxiety, since patients with a negative exercise echo had an excellent prognosis, especially for the first five years. This suggests that the warranty on a negative exercise echo is about five years. This study is consistent with the results of previous studies with shorter follow-up periods. However, the study does show that you cannot look at the echo results in isolation. The raw data showed that a positive ECG response was predictive of MACE, but that it was explained by other clinical features such as female sex, low exercise duration, angina at peak exercise, and patient factors such as known coronary heart disease. Thus, the whole patient and all the features of the exercise response need to be factored into your clinical assessment.

There are several limitations to this study which may have biased the results. They included patients with known disease which probably increased the event rate. It was a retrospective single-center study, and charts were used for follow-up. The exercise studies were done before the use of contrast and harmonic imaging at their center; today's echo sensitivity for wall motion may be better. They do not discriminate between ECG leads. It is know that the specificity of the inferior leads is poor. About 80% of the patients achieved 85% maximal predicted heart rate, so 20% had inadequate stress tests. However, this is a consecutive series of real-world patients referred for stress testing and as such represents a valuable observation. ■

Esophageal Injury during RF Ablation Procedures

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Source: Singh SM, et al. Esophageal injury and temperature monitoring during atrial fibrillation ablation. *Circulation: Arrhythmia Electrophysiology*. 2008;1:162-168.

In this report, Singh et al report a two hospital study on the use of esophageal temperature monitoring during atrial fibrillation ablation procedures. This was a nonrandomized study that included 81 patients who underwent AF ablation followed by a post procedural, not symptom-driven esophageal endoscopy within three days of the ablation procedure. Sixty-seven patients underwent luminal esophageal temperature (LET) monitoring during their ablation procedure, whereas 14 did not. LET monitoring was performed using a 9Ff single thermocouple esophageal temperature probe that was inserted and advanced into the esophagus using fluoroscopic guidance. The position of the tip of the temperature probe was monitored fluoroscopically throughout the procedure and was adjusted to the level of the ablation catheter before application of each ablation lesion. Procedures could be performed either under conscious sedation or general anesthesia. Ablation lesions were placed with either internally or externally irrigated catheters. RF energy delivery was set to a maximum of 35 W and 400 C. RF applications were terminated if the LET exceeded 38.50 C in patients. Esophageal ulceration was attributed to the AF ablation if it was located on the anterior wall of the mid esophagus adjacent to the pulsating heart. Patients with ulcerations were treated with high-dose proton pump inhibitor therapy for one week with repeat endoscopy to ensure ulcer healing.

The study population was an average group undergoing an ablation for atrial fibrillation. There were 81 patients with a mean age of 58 years. Paroxysmal atrial fibrillation was present in 44%, with a mean duration of atrial fibrillation of over four years. Sixty-five percent had a structurally normal heart. The mean left atrial size was 43 mm. Procedures were performed under general anesthesia in 13% of the patients with LET monitoring vs 43% of those

without LET monitoring. Although radio frequency energy application was stopped, if the LET reached 38.50 centigrade, higher temperatures were noted in half of the patients. There was not a clear relationship between the maximum LET recorded and the presence of ulcerations. However, a trend toward more ulceration was noted in patients with maximum LET ≥ 39°. In the LET monitoring group, four of 67 patients (6%) had esophageal ulcers visualized during the follow-up endoscopy. In contrast, five of 14 patients without LET monitoring were found to have post-procedure esophageal ulcers. An interesting but unexplained finding was the presence of pericarditis or pericardial effusion in six of 67 patients with LET monitoring vs none of the patients without LET monitoring. The AF recurrence rate was 31% among the patients who underwent LET monitoring and 43% in those without LET monitoring.

Ulcerations in patients without LET monitoring appeared longer and more linear compared with ulcerations observed in patients who had LET monitoring. All ulcerations had healed by the follow-up EGD at one week. Left atrial esophageal fistulae did not develop in any patient.

Singh et al conclude that LET monitoring is straightforward, inexpensive, well tolerated, and may decrease the risk of esophageal thermal injury during catheter ablations for atrial fibrillation.

■ **COMMENTARY**

Atrio-esophageal fistula formation is a rare but life-threatening complication of ablation procedures for atrial fibrillation. Patients who develop fistulae present with sepsis and air embolism usually one to two weeks after the procedure; the mortality rate is very high. The mechanism for the fistula formation is thought to be thermal injury to the esophageal muscular wall during the procedure. It can be seen with all types of ablative energy, including radio frequency, high-intensity-focused ultrasound, and cryothermy. The esophageal wall lies in close proximity to the posterior wall of the left atrium. Since the left atrial wall is quite thin, thermal injury to the muscular wall of the esophagus may be difficult to avoid when posterior left atrial structures need to be ablated.

There are a number of different approaches that may be used to prevent esophageal injury. Various imaging techniques, including fluoroscopic visualization of barium in the esophagus, intracardiac ultrasound image monitoring, and correlation with pre-procedure CMR and CT scans may be used. The operator can reduce the energy when the esophagus is in close proximity to the ablation catheter. Increased mobility of the esophagus, seen in patients who undergo ablation using conscious sedation, compared to when general anesthesia is used, may also be protective. The technique described here of luminal esophageal temperature monitoring may have some value but also some significant practical limitations. It may be difficult to position the single thermistor precisely at the point of maximum temperature during lesion placement, and one could be fooled if folds of the esophagus or differences in projection caused one to miss the area of peak injury. The major observation from this paper is the relatively high rate of esophageal ulceration noted. Overall, in the entire series, 11% of the patients developed esophageal ulcerations. Fortunately, these were all asymptomatic and resolved quickly with proton pump inhibitor therapy. This high frequency of injury, however, should make electrophysiologists performing catheter ablations even more carefully to guard against the possibility of esophageal damage. ■

Best Medical Therapy vs Revascularization for Stable Angina: The Beat Goes on!

ABSTRACT & COMMENTARY

By Jonathan Abrams, MD

Professor of Medicine, Division of Cardiology, University of New Mexico, Albuquerque

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

Source: Schomig A, et al. Meta-analysis of 17 randomized trials of a percutaneous coronary intervention-based strategy in patients with stable coronary artery disease. *J Am Coll Cardiol*. 2008;52:894-904.

A long-standing controversy exists regarding use of angioplasty (PCI) vs best or optimal medical therapy in subjects with stable coronary disease (CAD). The recent COURAGE trial has spurred an increased interest in this issue, as comparable survival and MI outcomes with PCI or bypass surgery were found with optimal medical therapy (OMT) alone vs PCI and OMT. The TIME trial comparing medical vs PCI in the elderly (> 75) reported similar outcomes at one year, but more adverse outcomes at six months (Pfisterer M, et al. *JAMA*. 2003 289:1117-1123). This report from Munich, Germany, is a meta-analysis of 17 trials of PCI with OMT compared to OMT alone. The purpose of the meta-analysis is "to evaluate whether PCI affects long-term prognosis in patients with stable CAD." Eligible subjects had stable CAD; patients with ACS were excluded. All trials reviewed were prospective and randomized. Trial dates ranged from 1993 to 2007, including COURAGE. Baseline characteristics between the two cohorts were equivalent. Extensive

statistical tests were used in this analysis. The primary end point was all-cause death, death due to cardiac causes, or myocardial infarction. A total of 17 randomized trials consisting of 7,513 subjects, average age 60; 82% were male; half had a prior MI. Ninety-two percent of the invasive group underwent revascularization (drug eluting stents rarely). Twenty-eight percent of subjects assigned to medical treatment crossed over to revascularization over the average 51 months of the study.

Results: Subjects in the PCI group enjoyed a 20% reduction in the odds ratio of all-cause death. Superiority of PCI over medical therapy was found in 14 trials. PCI was associated with a 26% reduction in the odds ratio for all-cardiac death. Overall, during an average 51-month follow-up, PCI patients had a benefit, with a 20% decrease in the odds ratio of events compared to the medical treatment only strategy. Stents were used in < 50% of subjects, almost all non-drug eluting. Schomig et al emphasize that this study "constitutes a consistent and comprehensive investigation of available evidence by meta-analytical methodology. They emphasize that the meta-analytic approach worked well "with a substantial reduction of long-term mortality by this strategy."

PCI was considerably more advantageous in patients with a recent prior MI. A 20% reduction in odds ratio of death was noted in multiple analyses of the database. Twenty-eight percent of the OMT-alone patients received a non-protocol revascularization over long-term follow-up.

Schomig et al conclude, "There is little doubt that PCI relieves ischemia and improves exercise capacity of patients with angina pectoris." They underscore the fact that a substantial reduction of events was seen over an average of 51 months in the PCI cohort; they suggest that PCI resulted in a greater decrease of risk of non-fatal MI "because of improvement in technique." Schomig et al posit that in prior large MI patients, PCI is particularly beneficial. They "suggest that a PCI-based invasive strategy may improve long-term survival compared with a medical treatment-only strategy in patients with stable CAD; they call for a new large clinical trial powered for evaluating the impact of PCI on long-term mortality.

■ COMMENTARY

This extensive meta-analysis addresses almost 15 years of reports in the literature assessing the controversial subject of routine PCI or bypass surgery in patients with stable angina and CAD, as opposed to a strategy of medical therapy alone. The somewhat surprising finding of the meta-analysis is that there was a 20% reduction in fatal events in revascularized patients compared to OMT. Furthermore, 28% of OMT subjects ultimately had a non-protocol revascularization in the follow-up period of 51 months.

The lack of increased risk of adverse outcomes in the PCI patients may be considered a positive finding along with reduced overall mortality with this strategy. The PCI-based strategy was associated with a reduced risk of large prior MI leading cardiac death and "at least, no increase in the long-term risk following smaller non-fatal MI." It is of interest that a considerable number of the trials comparing a PCI strategy with a medical treatment strategy do not come to the same conclusion, although the overall pooled analysis in this report does represent a large data base, with an average follow-up period of 51 months. The consistency of a 20% reduction in the odds ratio of death with PCI vs continued medical treatment has been suggested in the past, but has not been believed to be a substantial finding. This meta-analysis answer is consistent with previous reports comparing the two strategies. Several large trials that may be familiar to readers include ACME-1 and ACME-2, reported in 1997, RITA-2 in 2003, and in the recently published COURAGE trial in 2007. Of note, DANAMI, SWISS-II, and INSPIRE did find an improvement in non-fatal MI with OMT only.

In PCI subjects, the data analysis in the current report focuses on fatal events and MI. Early relief of angina with revascularization has clearly been shown to be robust in many early trials, but with perhaps regression to the mean, resulting in equal event rates by two years. One major issue relates to the availability of new therapies over time, with the probability that either PCI and/or optimal medical therapy have become more effective during the meta-analysis period of 17 years. The answer is clearly a "yes," and this underscores the conclusion of the meta-analysis that it may favor one strategy over the other because of the greater improvement in effectiveness in one therapy vs another. Of probable great importance, standard medical therapy today is very different from five, 10, or 15 years ago, and includes the currently recommended cocktail of aspirin, a statin, a beta blocker, clopidogrel, and in many cases, an ACE inhibitor. Cath lab techniques have also improved over the time period of the report, particularly the use of stenting in many of the recent reports. It is arguable whether there has been a greater improvement in PCI technique vs the widespread use of protective medical therapy over the past 15-year period. In any case, these data are reassuring, indicating that an early invasive approach in stable patients with CAD appears to do no harm and may be better for some stable angina subjects who continue to have angina. Certainly, most previous studies have favored an early revascularization strategy, particularly with ACS patients. The impressive benefits of medical therapy in COURAGE and other trials suggests the conclusion that we are probably doing no harm with cath and angioplasty in stable patients.

Note: In an accompanying commentary, Dr. Robert

O'Rourke comments about the meta-analysis and concludes that aggressive medical therapy should be the approach to stable symptomatic angina, with PCI or CABG only for "moderate to severe angina whose symptoms persist." (O'Rourke RA. *J Am Coll Cardiol*. 2008: 52:905-907) ■

CME Questions

42. With a negative echo study, which exercise parameters are of prognostic value?
a. Exercise angina
b. A positive ECG response
c. Reduced exercise capacity
d. A & C

43. Complications of acute type B aortic dissection can be predicted independently by:
a. large false lumen area.
b. large mean aortic diameter.
c. more branch vessel involvement.
d. A & C

44. Revascularization for chronic stable CAD patients results in:
a. a reduction in symptoms.
b. a reduction in mortality.
c. improved exercise capacity.
d. All of the above

45. RF ablation of atrial fibrillation can lead to:
a. persistent atrial flutter.
b. esophageal ulcers.
c. atrio-esophageal fistulae.
d. B & C

46. A recent trial supports which loading dose of clopridogrel pre-PCI?
a. 300 mg
b. 600 mg
c. 900 mg
d. 1200 mg

Answers: 42. (d); 43. (d); 44. (d); 45. (d); 46. (c)

CME Objectives

The objectives of *Clinical Cardiology Alert* are to:

• present the latest information regarding illness and treatment of cardiac disease;

• discuss the pros and cons of these interventions, as well as possible complications;

• discuss the pros, cons, and cost-effectiveness of new and traditional diagnostic tests; and

• present the current data regarding outpatient care of cardiac patients. ■

United States Postal Service
Statement of Ownership, Management, and Circulation

1. Publication Title	2. Publication No.	3. Filing Date
Clinical Cardiology Alert	0 7 4 1 - 4 2 1 8	10/1/08
4. Issue Frequency	**5. Number of Issues Published Annually**	**6. Annual Subscription Price**
Monthly	12	$319.00

7. Complete Mailing Address of Known Office of Publication *(Not Printer) (Street, city, county, state, and ZIP+4)*
3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, Fulton County, GA 30305
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8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not Printer)*
3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do Not Leave Blank)*
Publisher *(Name and Complete Mailing Address)*
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AHC Media LLC, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305
Editor *(Name and Complete Mailing Address)*
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Full Name	Complete Mailing Address
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13. Publication Name: Clinical Cardiology Alert
14. Issue Date for Circulation Data Below: September 2008

15. Extent and Nature of Circulation			Average No. of Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
a. Total No. Copies *(Net Press Run)*			1140	1081
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	730	706
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c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2)*			784	757
d. Free Distribution by Mail *(Samples, Complimentary and Other Free)*	(1)	Outside-County as Stated on Form 3541	10	12
	(2)	In-County as Stated on Form 3541	3	3
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e. Free Distribution Outside the Mail *(Carriers or Other Means)*			20	20
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g. Total Distribution *(Sum of 15c and 15f)*			817	792
h. Copies Not Distributed			323	289
i. Total *(Sum of 15g. and h.*			1140	1081
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			96%	96%

16. Publication of Statement of Ownership
Publication required. Will be printed in the November 2008 issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: President and CEO — Date: 9/28/08

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PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert*, *Clinical Oncology Alert*, *Critical Care Alert*, *Infectious Disease Alert*, *Internal Medicine Alert*, *Neurology Alert*, *OB/GYN Clinical Alert*, *Primary Care Reports*, *Travel Medicine Advisor*.

Safety of Inhaled Anticholinergics for COPD Scrutinized

In the Issue: Ongoing safety review of tiotropium; raloxifene reduces the risk of endometrial cancer; one-day treatment with famciclovir may be as effective as 3-day treatment with valacyclovir; new Clinical Practice Guideline from the American College of Physicians regarding pharmacologic treatment for low bone density and osteoporosis; FDA Actions.

THE SAFETY OF INHALED ANTICHOLINERGICS FOR the treatment of chronic obstructive pulmonary disease (COPD) has come under scrutiny in recent months. In July, the FDA issued an "Early Communication" about an ongoing safety review of tiotropium (Spiriva®) the most widely used agent for the treatment of COPD. The review is focused on a possible increased risk of stroke and is based on a pooled analysis of 29 trials which showed the risk of stroke at 8 patients per 1000 treated with tiotropium versus 6 patients per 1000 treated with placebo.

Now two new studies suggest that inhaled anticholinergics (ipratropium [Atrovent®] and tiotropium) increase the risk for all-cause mortality and cardiovascular disease in patients with COPD. In a large meta-analysis (*JAMA* 2008;300: 1439-1450), researchers reviewed 17 trials involving nearly 15,000 patients with COPD who were randomized to an inhaled anticholinergic or control. The primary outcome was a composite of cardiovascular death, MI, or stroke. The secondary outcome was all-cause mortality. The primary outcome occurred in 1.8% of patients receiving inhaled anticholinergics and 1.2% of patients receiving control therapy (RR 1.58, 95% CI, 1.21-2.06; $P < 0.001$). Inhaled anticholinergics significantly increased risk of MI, cardiovascular death, and all-cause mortality (RR 1.26). When the analysis was restricted to long-term trials, the risk was even greater for cardiovascular death, MI, or stroke (RR 1.73). The number needed to harm for MI was 174 per year, while the number needed to harm for cardiovascular death was 40 per year. The authors concluded that inhaled anticholinergics are associated with a significantly increased risk of cardiovascular death, MI, or stroke among patients with COPD.

In a second nested, case-control study (*Ann Intern Med* 2008;149:380-390), the National Veterans Affairs databases were used to review all-cause mortality, respiratory and cardiovascular deaths, and exposure to COPD medications including inhaled corticosteroids, ipratropium, long-acting beta agonists, and theophylline in the 6 months preceding death. The adjusted odds ratios for all-cause mortality were 0.80 for inhaled chronic steroids, 1.11 for ipratropium, 0.92 for long-acting beta agonists, and 1.05 for theophylline. Ipratropium was associated with increased cardiovascular deaths (OR 1.34), whereas inhaled corticosteroids were associated

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

with reduced risk for cardiovascular death (OR 0.80). The authors conclude that there is a possible association between ipratropium and elevated risk for all-cause and cardiovascular death and that further studies are needed. They also suggest that the risk of ipratropium may be somewhat mitigated by concomitant use of inhaled corticosteroids, but caution should be exercised if ipratropium is used alone in patients with recently diagnosed COPD.

Raloxifene reduces endometrial cancer risk

It is well known that raloxifene reduces the risk of breast cancer; now there is evidence that the drug reduces the risk of endometrial cancer as well. Raloxifene (Evista®) is a selective estrogen receptor modulator (SERM) that is indicated for treatment and prevention of osteoporosis and for breast cancer prevention. Researchers from the University of Pennsylvania compared endometrial cancer rates in women on raloxifene, tamoxifen, and non-users of SERMs in a case-control study of 547 women with endometrial cancer and 1410 controls. After adjustment for other risk factors the odds of endometrial cancer among raloxifene users was 50% that of non-users (OR = 0.50; 95% CI, 0.29-0.85), whereas tamoxifen users had 3 times the odds of developing endometrial cancer compared to raloxifene users (OR = 3.0; 95% CI, 1.3-6.9). Among raloxifene users who developed endometrial cancer, the tumors had a more favorable histologic profile and were predominantly stage I and low grade. The authors conclude that raloxifene users have significantly lower risk of developing endometrial cancer compared with tamoxifen users and SERM non-users, perhaps even suggesting a role for raloxifene and prevention of endometrial cancer (*J Clin Oncol* 2008; 26:4151-4159).

One-day famciclovir = three-day valacyclovir

For patients with recurrent genital herpes outbreaks, one-day treatment with famciclovir may be as effective as 3-day treatment with valacyclovir, according to a new study. In a double-blind parallel group study, 1179 adults with a history of recurrent genital herpes were randomized to receive either famciclovir 1000 mg twice daily for one day vs valacyclovir 500 mg twice daily for 3 days. Patients initiated treatment within 6 hours after a recurrence. Approximately one-third of patients in each group aborted genital herpes outbreaks altogether, but for those who went on to develop lesions, median time to healing was 4.25 days for famciclovir vs 4.08 days for valacyclovir. Time to healing was the same in both groups and the incidence of adverse affects was 23.2% for famciclovir vs 22.3% for valacyclovir. The study demonstrates that a single day of famciclovir (1000 mg twice daily) is equivalent to 3 days of valacyclovir (*Clin Infect Dis* 2008;47:651-658). Other regimens for treatment of recurrent HSV episodes include acyclovir 800 mg 3 times daily for two days or 400 mg three times daily for 3-5 days, famciclovir 125 mg twice a day for 3-5 days, or valacyclovir 500 mg twice daily for 3 days. Both acyclovir and famciclovir are available generically, but acyclovir is considerably less expensive; however, the convenience of a one-day treatment with famciclovir may be worth the extra cost for many patients.

New practice guideline for osteoporosis

The American College of Physicians has issued a Clinical Practice Guideline regarding the pharmacologic treatment of patients with low bone density or osteoporosis (*Ann Intern Med* 2008; 149:404-415). The expert committee recommends that clinicians offer pharmacologic treatment to men and women who have known osteoporosis and to those who have experienced fragility fractures. They also recommend that pharmacologic treatment should be considered for men and women who are at risk of developing osteoporosis and that the choice of pharmacologic treatment should be based on assessment of risk and benefits in individual patients. The guideline reviews different treatment modalities including bisphosphonates, calcitonin, estrogen, teriparatide, SERMs, testosterone, and calcium plus vitamin D. Left unanswered are the questions of duration of treatment with bisphosphonates and the optimal dose of calcium and vitamin D.

FDA actions

The FDA has issued warning letters to Ranbaxy Laboratories Ltd. of India in an Import Alert for the company's generic drugs produced in two Indian plants. The warning letters identify concerns about deviations from U.S. current Good Manufacturing Practice requirements at Ranbaxy's manufacturing facilities and the Import Alert allows officials to detain at the rest border any active pharmaceutical ingredients manufactured at Ranbaxy facilities. Ranbaxy manufacturers more than 30 generic drugs including commonly used antibiotics, antihypertensives, and antivirals. ■

Clinical Briefs in
Primary Care
The essential monthly primary care update
By Louis Kuritzky, MD
Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*
VOLUME 13, NUMBER 11 PAGES 21-22 NOVEMBER 2008

Cognitive Impairment Progression Blunted by Exercise

Source: Lautenschlager NT, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: A randomized trial. *JAMA* 2008; 300:1027-1037.

CLINICAL TRIALS OF PHARMACOTHERAPY to prevent progression of cognitive decline in those with mild cognitive impairment (MCI) have been disappointing; neither cholinesterase inhibitors (donepezil, rivastigmine, galantamine), vitamin E, nor COX-2 inhibitors has demonstrated any clinically meaningful benefit in placebo-controlled MCI trials.

Observational data are consistent that regular physical activity, even if started late in life, is associated with reduced risk of dementia. Whether exercise might prevent progression in persons with MCI was the subject of this first randomized trial to address the issue.

Subjects (n = 170) with MCI between the ages of 50-77 (mean age, 68.6 years) were randomized to receive either 50-min sessions of moderate-intensity exercise (e.g., brisk walking, ballroom dancing, and swimming) three times weekly vs control (general education about health, including physical activity, diet, alcohol, and stress management). All educational materials were also provided to the intervention group. All participants (control and intervention) wore a pedometer and provided diaries of daily total number of steps. Physical activity and cognitive function were assessed at 6, 12, and 18 months after randomization.

At each assessment point, cognitive scores for the intervention group were better than the control group. The intervention group averaged approximately 6000 more steps/week than the control group. Exercise, averaging as little as 21 min/day, reduces cognitive decline in persons with MCI. ■

Incidentalomas in the Knee

Source: Englund M, et al. Incidental meniscal findings on knee MRI in middle-aged and elderly persons. *N Engl J Med* 2008;359:1108-1115.

ONE OF THE PRIMARY THINGS THAT has stood in the way of definitive diagnosis of acute low back pain is the extraordinarily high rate of false-positive findings seen on plain films, CT, or MRI. Indeed some studies suggest that as many as half of healthy, asymptomatic individuals studied by MRI of the lumbar spine have findings consistent with disk pathology.

Little is known about the frequency of incidental findings seen upon MRI of the knee, since studies generally investigate symptomatic individuals; subsequent radiographic findings, if they correlate with symptomatology, have been taken to support a causal relationship.

Englund et al performed an MRI of the right knee in 991 randomly selected adult subjects ages 50-90 in Massachusetts. Excluded subjects included those with rheumatoid arthritis, knee replacement, terminal illness, or non-ambulatory status.

The incidence of meniscal tears seen ranged from 19% in the youngest women (ages 50-59) to 56% in senior men (ages 70-90). Among the group with radiographic changes of osteoarthritis, the frequency of meniscal tears in symptomatic and asymptomatic individuals was similar (63% vs 60%, respectively). Overall, the majority of persons (60%) with meniscus tears confirmed by MRI had no symptoms referable to the knee.

It appears that as with back MRI, incidental findings of pathology are frequent, and call into question an ironclad attribution of knee symptoms to positive findings on MRI. ■

Hormone Replacement and Skin Health in Menopausal Women

Source: Phillips TJ, et al. Does hormone therapy improve age-related skin changes in postmenopausal women? *J Am Acad Dermatol* 2008;59:397-404.

AS LITTLE AS A DECADE AGO, MENOpausal status alone was the ticket of admission to advocate hormone replacement therapy (HRT). The "story line" went that HRT prevented cognitive decline, improved symptoms, enhanced cardiovascular health, and preserved cutaneous health, i.e., reduced age-related wrinkles, dryness, and laxity. Unfortunately, HRT has failed to live up to numerous of its hopeful claims.

To study the effects of HRT on menopausal women's skin, 485 subjects were randomly assigned to placebo or two different HRT doses in double-blind fashion. Dermatologists evaluated skin wrinkling, laxity, and texture (as did the patients) over a 48-week interval. The mean age of the women was 54 years.

At study end, there were no statistically significant differences in any primary endpoint of the trial. When the data were analyzed for impact of baseline levels of estradiol, race, or age, no meaningful differences were found. During the trial, all study groups enjoyed some skin improvements attributable to daily application of moisturizing cream and sunscreen, but HRT added nothing to this. Claims that HRT provides reduced risk of age-related skin changes are not supported by this trial. ■

Reconfirmation of the Death of Homocysteine

Source: Ebbing M, et al. Mortality and cardiovascular events in patients treated with homocysteine-lowering B vitamins after coronary angiography: A randomized controlled trial. *JAMA* 2008;300:795-804.

HOMOCYSTEINE (HCYS) HAS ALL THE trappings of a first-rate cardiovascular risk factor: as strong an association with CVD endpoints as cholesterol, ease of identification, and simplicity of modulation. Trouble is, trials to date have been unable to show that reductions of homocysteine provide meaningful benefits to patients. Indeed, one recent commentary following a large double-blind intervention-

Clinical Briefs in Primary Care is published monthly by AHC Media LLC.

Associate Publisher: Coles McKagen. **Editor:** Stephen Brunton, MD. **Senior Managing Editor:** Paula Cousins. This is an educational publication designed to present scientific information and opinion to health professionals, stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for the layman.

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al trial of HCYS for cardiovascular endpoints began with "The homocysteine hypothesis is dead … ."

Apparently as undaunted as Mark Twain ("The reports of my death are greatly exaggerated …"), Ebbing et al tested HCYS reduction through B vitamins after coronary angiography. The primary endpoint of the study was all-cause mortality, non-fatal stroke and MI, and hospitalization for unstable angina (composite).

The trial (n = 3096) was designed to follow patients for 4 years, but was stopped at 38 months due to information from another trial that had reported a possible negative effect of B vitamin intervention. B vitamins did reduce HCYS by approximately 30%, but failed to have any impact (positive or negative) upon endpoints. The HCYS hypothesis is still dead. ■

Pramlintide as a Weight-Loss Adjunct

Source: Smith SR, et al. Sustained weight loss following 12-month pramlintide treatment as an adjunct to lifestyle intervention in obesity. *Diabetes Care* 2008;3:1816-1823.

SOMETHING THAT NEITHER MOTHER NOR medical school taught us was that more than one hormone is secreted from the beta cells of the pancreas in response to rising glucose. In conjunction with insulin, the hormone amylin is released. Pramlintide is a synthetic form of amylin. The physiologic effects of amylin include slowed gastric emptying (thereby slowing the rate of glucose delivery to the intestine), suppression of glucagon, and centrally mediated satiety. For addressing obesity, there is great conceptual appeal to an agent that improves satiety.

Smith et al performed a double-blind, placebo-controlled trial of various doses of subcutaneous pramlintide (bid to tid) in obese, nondiabetic subjects, who were also receiving intensive lifestyle (diet/exercise) intervention. The initial 4-month double-blind phase was followed by a 4-month single-blind extension (for those who completed the initial phase without protocol violation).

Weight loss was dose-proportional: At 360 µg twice daily the placebo-corrected weight loss was 3.3 kg at month 4 and 7.2 kg at month 12. No safety concerns were seen. Nausea, which is also the most common adverse event seen in diabetic subjects, was mostly mild to moderate, and improved over time. Nausea is not the mechanism of action, since weight reduction was similar in those who did and did not experience nausea. These initial data are encouraging that pramlintide may find a role in enhancing weight loss when used in conjunction with lifestyle intervention. ■

Undiagnosed Diabetes in Obese Americans

Source: Wee CC, et al. Obesity and undiagnosed diabetes in the U.S. *Diabetes Care* 2008;31:1813-1815.

NO CLINICIAN IS SURPRISED TO SEE that diabetes often goes undiagnosed. Patients can persist with modest symptoms, or even asymptomatically, for protracted periods during the early stages of type 2 diabetes. The fact that literally half of type 2 diabetics have one or more of the traditional complications of diabetes (neuropathy, nephropathy, retinopathy, dermopathy) at the time of clinical diagnosis attests to the fact that diagnosis lags substantially behind disease onset.

Most type 2 diabetics are obese, and obesity provides an environment that promotes insulin resistance, a cardinal dysfunction in early diabetes and pre-diabetes. Hence, scrutiny of obese subjects provides a window of observation into a population felt to be at greater risk for developing diabetes. On the one hand, the clinician might think that the presence of obesity would prompt greater vigilance for diabetes; on the other hand, there is evidence that compared to the non-obese, obese individuals experience delays in receiving preventive care.

From the 1999-2004 NHANES data, it was determined that 9.8% of the population had diabetes (defined as FBG > 126 mg/dL). Slightly more than one-fourth (28.1%) of persons with FBG > 126 mg/dL had not been diagnosed with diabetes. When parsed into BMI categories, normal weight individuals were actually less likely to have undiagnosed diabetes than overweight or obese persons (22.2% vs 32.5% vs 27.4%, respectively). Because more than one-half of undiagnosed diabetes is seen in overweight and obese individuals, enhanced vigilance is appropriate. ■