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New Hope for COPD?

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

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

Synopsis: *Inhaled salmeterol and fluticasone, singly or in combination, reduce the rate of decline of the FEV1 in patients with moderate-to-severe COPD.*

Source: Celli BR, et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: Results from the TORCH Study. *Am J Respir Crit Care Med* 2008;178:332-338.

THIS PAPER IS A REPORT FROM THE TOWARD A REVOLUTION IN COPD Health (TORCH) study, which was funded by GlaxoSmithKline but implemented by six academics.[1] The TORCH study was a 3-year, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Eligible patients were stratified by smoking status and randomized to receive by inhalation one of the following 4 regimens twice daily: 50 µg salmeterol + 500 µg fluticasone, 50 µg salmeterol, 500 µg fluticasone propionate, or placebo. All other corticosteroids and inhaled long-acting bronchodilators were stopped for the study, but other COPD medications were allowed.

The primary efficacy endpoint of TORCH was all-cause mortality at 3 years. Other endpoints included exacerbation rate, measures of health status, and post-bronchodilator spirometry. Careful attention was paid to reliability and consistency of spirometric measures.

The study population for TORCH was 6112 patients, but only 5343 (87%) had at least one on-treatment FEV1 and could be included in the analysis. The included patients had a mean age of about 65 years, a mean body mass index (BMI) of about 25 kg/m^2, and a baseline FEV1 of about 1235 mL (about 44% predicted); about three-fourths were men. The number of patients was smaller in the placebo group because more patients from the placebo group withdrew within the first 24 weeks. During the study, 187 (3%) patients took tiotropium in addition to the study medication.

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The rate of decline of FEV1 was slowest in patients on combined fluticasone + salmeterol, and fastest in those who were randomized to the placebo arm. From week 24 onward, the adjusted rate of decline in FEV1 was 39 mL/yr for fluticasone + salmeterol, 42 mL/yr for single treatment with fluticasone or salmeterol, and 55 mL/yr for placebo. There were statistically significant differences in the rate of decline for any of the three active pharmacologic treatments compared to placebo. Analysis of individual regression slopes or of percent-predicted FEV1 produced similar findings. The effect of treatment on FEV1 occurred regardless of smoking status, sex, age, baseline FEV1, region of origin, ethnicity, BMI, previous exacerbations, and medication treatment prior to being in the study.

Besides inhaled medication use, other factors were significantly associated with rate of decline of pulmonary function. Those who had quit smoking, women, patients age 65 or older, and those whose FEV1 was < 30% of predicted at baseline also experienced a slower rate of decline of FEV1 in absolute mL/yr. In addition, patients whose BMI was ≥ 25 kg/m^2 showed a slower decline in lung function, as did patients who were from the Asia Pacific and Eastern Europe regions. There was also an association between number of exacerbations documented during the study period and the rate of decline of FEV1, with higher rates of decline being evident in patients experiencing more exacerbations.

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■ COMMENTARY

This study shows, for the first time, that pharmacologic treatment slows the decline in lung function in patients with fairly significant COPD. FEV1 is an important metric, as it predicts many important outcomes, including everything from sleep complaints to mortality. The results of this study are in contrast to several previous studies that failed to demonstrate that pharmacologic treatment affects the decline in pulmonary function in a statistically significant way. The Lung Health Studies 1 and 2,[2,3] ISOLDE,[4] BRONCHUS,[5] and EUROSCOP[6] failed to consistently demonstrate important differences in the rate of decline of pulmonary function for those with COPD who received pharmacologic treatment, although they did establish that the rate of decline of FEV1 in older COPD patients is about 60 mL/yr. The TORCH study found a similar rate of decline of FEV1 in the placebo group (about 55 mL/yr), but any of the three active drug treatments essentially cut this rate in half.

In the current study, the authors noted that their findings that higher BMI and region of origin (Asian Pacific and Eastern European) predicted slower deterioration in pulmonary function are novel, and they point out that this may help to explain within-subject variations in FEV1 decline. Their finding that women with COPD lost FEV1 at a slower rate is not new; it confirms work from the Lung Health Study. And, of course, they showed that those who had quit smoking fared better than those who continued to smoke, which has been consistently found in previous work. Prior to this report from the TORCH study, in fact, smoking status was the only modifiable risk factor clearly demonstrated to affect rate of decline of FEV1.

The main result of this trial, i.e., the effect of pharmacologic treatment on mortality, was published last year.[1] In that study of 6112 patients, all-cause mortality rates were 12.6% in the combination-therapy group, 15.2% in the placebo group, 13.5% in the salmeterol group, and 16.0% in the fluticasone group. The hazard ratio for death in the combination-therapy group barely missed statistical significance, but the mortality rates for salmeterol or fluticasone alone did not differ significantly from that for placebo. Further, the combination regimen reduced the annual rate of exacerbations from 1.13 to 0.85 and improved health status and spirometric values ($P < 0.001$ for all comparisons with placebo). There was no difference in the incidence of ocular or bone side effects among groups, but the probability of pneumonia was higher among patients receiving fluticasone.

In the accompanying editorial, Suissa points out that many FEV1 measurements were missing in this analysis

of pulmonary function decline, particularly for the placebo group patients, who dropped out at greater rates than the active treatment patients.[8] The editorial also addresses the practical application of this new knowledge. Since fluticasone, salmeterol, or the combination appear to have very similar beneficial effects on the rate of pulmonary function deterioration and exacerbations, which treatment is best to use? Suissa notes that a secondary analysis of the TORCH data on the independent contribution of each component of the treatment showed that any reduction in mortality was due to the bronchodilator (salmeterol) component and not the corticosteroid (fluticasone) component,[9] and that inhaled corticosteroids have been associated with increased risk of glaucoma, osteoporosis, cataracts, and pneumonia.

COPD is a miserable and prevalent disease. This new information may help us to do a better job in caring for these patients. ■

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CT Colonographic Screening: Does the Technique Merit Widespread Adoption?

ABSTRACT & COMMENTARY

By Malcolm Robinson, MD, FACP, FACG

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

Synopsis: *CT colonographic screening of asymptomatic adults identified 90% of polyps or cancers measuring 10 mm or more.*

Source: Johnson CD, et al. Accuracy of CT colonography for detection of large adenomas and cancers. *N Engl J Med* 2008;359:1207-1217.

COLORECTAL CANCER IS THE THIRD MOST COMMON malignancy in the United States, and it's the second leading cause of cancer deaths. Screening is believed to be very important for interrupting the natural history of colon cancer. Anything that improves early detection of adenomas and early carcinomas would be most welcome, and many radiologists have been very enthusiastic about the promises of CT colonography. This technique rapidly examines the entire colon in a minimally invasive way without any need for sedation.

In the present study, 2600 asymptomatic volunteers ≥ 50 years of age in need of screening colon examinations were recruited at 15 U.S. centers. Some radiologists used 2-dimensional software, others a 3-dimensional version. All selected radiologists were considered to be highly qualified in the interpretation of CT colonographic examinations and had been tested for such competence. A total of 2531 patients successfully completed CT colonography followed by colonoscopy (99% on the same day as the CT exam). The primary study endpoint was the detection by CT colonography of histologically determined adenomas and adenocarcinomas ≥ 10 mm in size. Results among radiologists were averaged. Calculations were made for sensitivity, specificity, false-positive rate, and positive predictive value. However, the bottom line result of the study was that CT colonography correctly identified 90% of polyps and cancers measuring 10 mm or more. Using this technology, 65% of 5 mm lesions were identified, and 78% of 6 mm lesions

were correctly diagnosed with increasing accuracy as size approached 10 mm. Radiologists varied in their detection rates from 67% to 100%, with 47% of radiologists identifying all of the large (≥ 10 mm) lesions. By contrast, 128 large (≥ 10 mm) adenomas or carcinomas were found on colonoscopy in 109 of the 2531 patients (4%). A total of 547 lesions 5 mm or larger were found including 136 hyperplastic polyps (25%), 7 lipomas (1%), and 30 miscellaneous non-neoplastic lesions. One 10 mm rectal cancer was missed on CT colonography. A total of 30 lesions ≥ 10 mm were reported on CT colonography and not found on the initial colonoscopy. Only 15 of these 27 participants returned for a second colonoscopy. Five of 18 lesions seen on the CT exam could be confirmed (one turning out to be a 35 mm tubulovillous adenoma with dysplasia). For various reasons, colonoscopy was not repeated in the other 12 patients. Polyethylene glycol preparation was utilized in 40% of patients, sodium phosphate in 55%, and magnesium citrate in 4%. Barium sulfate was employed for fecal tagging for the CT, and iodinated contrast material was used for fluid tagging. Glucagon was administered pre-CT in 92% of participants. Adverse events included nausea and vomiting for less than 24 hours in one patient after CT colonography and *E. coli* bacteremia 24 hours after both procedures had been done. One patient was hospitalized for post-polypectomy bleeding. As in other studies of CT colonography, various extracolonic findings were identified at CT. The follow-up and relevance of these were not described.

This study indicated that 17% of this patient population would have been referred for colonoscopy for lesions of 5 mm or more had this not been an investigation already requiring colonoscopy. No differences were found in the software types utilized (i.e., 2-dimensional vs 3-dimensional). The authors propose that CT colonography might lead to an increased acceptance of colorectal screening by relevant populations.

■ COMMENTARY

This study has results similar to previous reports. Although the concept of a rapid radiographic evaluation of the colon seems attractive, the actualities are not encouraging. In the first place, this procedure is quite expensive. Second, the major obstacle to colonoscopy is the pre-procedure preparation, which is the same for CT colonography as for colonoscopy. Third, and most important, colonoscopy not only finds colon lesions, it also allows their removal. As a result, colonoscopy is both diagnostic and potentially curative. To me, the most valuable role of CT colonography would be the evaluation of patients in whom colonoscopy proves incomplete or otherwise unsuccessful. However, if this were the only indication, no radiologist would ever have enough cases to warrant full training to competence in this tech nology. Many patients do not like CT colonography, which involves insufflations of gas or air into the rectum during the procedure. In previous studies, patients have preferred colonoscopy to CT colonography. Colonoscopy is presumably better accepted because of the utilization of sedation for almost all of these procedures. Considerable scatter was observed in individual sensitivities of these trained radiologists in successful polyp identification. This suggests that wide adoption of this technique in communities would be unwise. I predict that there is a very limited future for CT colonography in its present configuration. Others strongly disagree. Time will tell. ■

Intensive Glucose Lowering: Too Much of a Good Thing?

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

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

Synopsis: *Intensive hemoglobin A1c lowering does not reduce the rate of cardiovascular death, and results in an increase in hypoglycemic events.*

Source: Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545-2559.

Source: ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560-2572.

JUNE WITNESSED THE PUBLICATION IN THE *NEW ENGLAND Journal of Medicine* of two articles that challenge our understanding of the treatment of diabetes mellitus. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) and the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trials were

designed to test the hypothesis that tight control of type 2 diabetes mellitus (T2DM) would result in a decrease in cardiovascular disease. (Preterax® is a perindopril-indapamide combo and Diamicron® is the sulfonylurea, gliclazide. Neither product is available in the United States, but the ACE-inhibitor perindopril, Aceon®, is. Indapamide, previously marketed as Lozol®, is available generically.) Ten years ago the results of the U.K. Prospective Diabetes Study (UKPDS) were published.[1] Its conclusion was that intensive treatment of T2DM with insulin or a sulfonylurea (chlorpropamide, glibenclamide [aka, glyburide], or glipizide) with the goal of achieving a fasting plasma glucose < 6 mmol/L (108 mg/dL) resulted in a decreased risk of microvascular complications (nephropathy, retinopathy, etc.), but not macrovascular disease (myocardial infarction, heart failure, stroke, peripheral vascular disease, etc.). The average hemoglobin A1c (HbA1c) achieved in the intensive treatment group was 7.0 and in the usual care group 7.9. The authors of the current studies presumed that the UKPDS investigators didn't try hard enough and set the HbA1c bar lower. We'll review each study separately and then compare the two.

ADVANCE is a randomized controlled study conducted in Asia, Australasia, Europe, and North America. It enrolled 12,877 patients, and after reasonable exclusion, randomized 11,140 to either intensive glucose control (target HbA1c ≤ 6.5%) with gliclazide or standard care and followed them for 5 years. All patients received perindopril-indapamide. Patients in the intensive care group (ICG) who did not achieve the target HbA1c with increasing doses of gliclazide, saw the addition of metformin, thiazolidinediones, acarbose, or insulin (basal initially, then short-acting insulin at meals). The intervention and control groups were remarkably similar: average age 66 years, 42% female, duration of diabetes 8 years. Mean body mass index (BMI) was 28 kg/m^2 and waist circumference (WC) was 99 cm. In both groups, 32% had a history of major macrovascular disease. The mean HbA1c was 7.5% and mean fasting blood glucose (FBG) was 8.5 mmol/L (153 mg/dL).

BMI and WC did not change over the course of the study. However, the difference in body weight at the end of the study favored the standard care group (SCG) by 0.7 kg. The ICG pushed their mean HbA1c to 6.5% and their FBG to 6.6 mmol/L (119 mg/dL), while the SCG values fell to 7.2% and 7.8 mmol/L (140 mg/dL), respectively, significant differences. The mean systolic blood pressure (SBP) fell from about 145 mm Hg to 135.5 mm Hg in the ICG and 137.9 mm Hg in the SCG; this was statistically significant. The rate of smoking fell from 14% to 8% with no significant difference between the groups. At study's end, a larger percentage of patients in the ICG were using insulin and a thiazolidinedione than the SCG (40.5% vs 24.1% and 16.8% vs 10.9%). The combination of major macrovascular or microvascular events occurred in 18.1% of patients in the ICG vs 20.0% of patients in the SCG (hazard ratio [HR], 0.90; 95% confidence interval [CI], 0.82-0.98), which is significant. However, the reduction in microvascular events (HR, 0.86; 95% CI, 0.77-0.97) accounted for all of this. There was a reduction in new or worsening nephropathy in the ICG (HR, 0.79; 95% CI, 0.66-0.93), but no difference in new or worsening retinopathy. There was no significant reduction in macrovascular events (HR, 0.94; 95% CI, 0.84-1.06). There was a nonsignificant drop in mortality favoring the ICG (HR, 0.93; 95% CI, 0.83-1.06). Patients in the ICG were hospitalized more frequently than patients in the SCG (44.9% vs 42.8%; HR, 1.07; 95% CI, 1.01-1.13) and had more severe hypoglycemia (2.7% vs 1.5%; HR, 1.86; 95% CI, 1.42-2.40).

ACCORD is similar to ADVANCE, but different in several important respects. It is a 2 × 2 factorial trial that randomized 10,251 patients to intensive glycemic control (HbA1c < 6.0%) or standard care (HbA1c 7.0-7.9%) and intensive blood pressure control (SBP < 120 mm Hg) or standard care (SBP < 140 mm Hg) in middle-aged or older patients with established or at risk for cardiovascular disease. A subset was also randomized to fenofibrate or placebo in addition to simvastatin to control low-density lipoprotein (LDL) cholesterol. The BP and LDL studies are ongoing. The patients averaged 62.2 years, were 38.5% female, and had an average duration of T2DM of 10 years. Average weight was 93.5 kg with a mean BMI of 32.2 kg/m^2 and a mean WC of 106.8 cm. Mean SBP was 136 mm Hg. The initial median HbA1c was 8.1% and mean fasting serum glucose was 175 mg/dL. Thirty-five percent had a history of a previous cardiovascular event. Fourteen percent smoked cigarettes at the start of the study, 10% at the end.

By the fourth month of the trial, median HbA1c levels in the ICG had fallen to 6.7%, and by 1 year had stabilized at 6.4%. At 1 year, the median HbA1c level was 7.5% in the SCG. The ICG was highly medicated compared to the SCG. The most commonly used medications and medication classes were metformin (95% vs 87%), secretagogues (87% vs 74%), thiazolidinediones (92% vs 58%), and insulin (77% vs 55%). Somewhat counterintuitively, the ICG received ACE-inhibitors less frequently than SCG (70% vs 72%); however, mean SBP was lower in ICG (126.4 mm Hg vs 127.4 mm Hg). Both groups gained weight, but the ICG gained 3.1 kg more than the SCG. Hypoglycemia requiring medical

assistance occurred in 10.5% of the ICG compared to 3.5% of the SCG. The ICG saw a reduction in major microvascular events (HR, 0.86; 95% CI, 0.77-0.97), but not major macrovascular events (HR, 0.94; 95% CI, 0.84-1.06). Although nonfatal myocardial infarction occurred less frequently in the ICG (3.6% vs 4.6%), all-cause and cardiovascular death were more frequent (5.0% vs 4.0% and 2.6% vs 1.9%). The Data and Safety Monitoring Committee of ACCORD halted the glycemic control portion of the study earlier this year when the preplanned safety analysis indicated an increased all-cause mortality rate in the ICG. Follow-up at the time the study closed was 3.5 years.

■ **COMMENTARY**

Mae West famously quipped, "Too much of a good thing is wonderful." We can only imagine what she had on her mind, but it certainly wasn't glycemic control.

It's not clear what was at the root of the increase in mortality in ACCORD or the lack of improvement in ADVANCE despite near-normal HgbA1c levels. Is it the journey or the destination? In other words, did the medications used in these studies have adverse side effects or is euglycemia a deleterious condition in a diabetic? Was it the speed or the HbA1c depth to which ACCORD dived? Before you start snickering about those hypotheses, think about what happens when a hypernatremic patient is brought to normal electrolyte balance too quickly or when a starvation survivor is given something to eat. It could be the medications. There is good evidence that rosiglitazone increases the risk for heart attacks,[2] and both thiazolidinediones are associated with an increase in heart failure.[3]

Or could it be the passengers? It can be argued that comparing ACCORD and ADVANCE is comparing apples and oranges. The patients in ACCORD were younger, sicker, heavier, and wider at the waist; smoked

CME Questions

39. Which of the following was associated with reduced decline in lung function in patients with COPD in the TORCH study?
a. Male gender
b. BMI < 22 kg/m^2
c. Inhaled fluticasone and/or salmeterol
d. Being from the United States or Western Europe instead of the Asia Pacific Region

40. CT colonography successfully achieved which of the following?
a. Identification of 90% of colonoscopically identified polyps > 10 mm in size
b. Identification of 65% of ≥ 5 mm lesions found at colonoscopy
c. Consistent performance by all of the participating expert radiologists
d. All of the above
e. Only a and b

41. Choose the *incorrect* answer. Intensive glucose lowering results in:
a. worsening nephropathy.
b. no significant improvement in mortality.
c. more severe hypoglycemia.
d. no improvement in retinopathy.

Answers: 39. (c), 40. (e), 41. (a).

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.

more frequently, had more CVD at onset, and had worse glycemic control and longer duration of DM than the ADVANCE patients. Their SBP was lower at baseline and at the close of the study. Any or all of these in combination could reasonably predict more frequent deaths in ACCORD than ADVANCE, but this doesn't explain the increased deaths within ACCORD.

ADVANCE confirmed the reduction in new or worsening nephropathy seen in UKPDS, and we should be encouraged by this result. However, there does not at present appear to be a mortality or CVD advantage to aggressive lowering of HbA1c below 7.0%, which is just as well since we haven't done a good job of getting our patients to that level, let alone the lower[4] levels that ACCORD and ADVANCED achieved. ■

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Clinical Briefs

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville
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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 interventional 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. ■

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 in 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 iron-clad attribution of knee symptoms to positive findings on MRI. ■

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 prediabetes. 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, clinicians 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 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. ■

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Semi-Monthly	24	$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
Contact Person: Robin Salet
Telephone: 404/262-5489

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)*
Robert Mate, President and CEO
AHC Media LLC, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305
Editor *(Name and Complete Mailing Address)*
Paula Cousins, same as above
Managing Editor *(Name and Complete Mailing Address)*
Coles McKagen, same as above

10. Owner *(Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual. If the publication is published by a nonprofit organization, give its name and address.)*

Full Name	Complete Mailing Address
AHC Media LLC	3525 Piedmont Road, Bldg. 6, Ste 400
	Atlanta, GA 30305

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box → ☐ None

Full Name	Complete Mailing Address
Thompson Publishing Group Inc.	805 15th Street, NW, 3rd Floor
	Washington, D.C. 20005

12. Tax Status *(For completion by nonprofit organizations authorized to mail at nonprofit rates.) (Check one)*
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
☐ Has Not Changed During Preceding 12 Months
☐ Has Changed During Preceding 12 Months *(Publisher must submit explanation of change with this statement)*

PS Form **3526**, September 1998 *See instructions on Reverse)*

13. Publication Name: Internal Medicine Alert
14. Issue Date for Circulation Data Below: August 30, 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)*			2499	2134
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	2040	1723
	(2)	Paid In-County Subscriptions *(Include advertiser's proof and exchange copies)*	9	0
	(3)	Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	57	48
	(4)	Other Classes Mailed Through the USPS	28	30
c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2)*			2134	1801
d. Free Distribution by Mail *(Samples, Complimentary and Other Free)*	(1)	Outside-County as Stated on Form 3541	30	33
	(2)	In-County as Stated on Form 3541	1	0
	(3)	Other Classes Mailed Through the USPS	0	0
e. Free Distribution Outside the Mail *(Carriers or Other Means)*			22	20
f. Total Free Distribution *(Sum of 15d and 15e)*			53	53
g. Total Distribution *(Sum of 15c and 15f)*			2187	1854
h. Copies Not Distributed			312	280
i. Total *(Sum of 15g, and h.*			2499	2134
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			98%	97%

16. Publication of Statement of Ownership
Publication required. Will be printed in the October 29,2008 issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: President and CEO — Date: 9/27/08

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including multiple damages and civil penalties).

Instructions to Publishers

1. Complete and file one copy of this form with your postmaster annually on or before October 1. Keep a copy of the completed form for your records.
2. In cases where the stockholder or security holder is a trustee, include in items 10 and 11 the name of the person or corporation for whom the trustee is acting. Also include the names and addresses of individuals who are stockholders who own or hold 1 percent or more of the total amount of bonds, mortgages, or other securities of the publishing corporation. In item 11, if none, check the box. Use blank sheets if more space is required.
3. Be sure to furnish all circulation information called for in item 15. Free circulation must be shown in items 15d, e, and f.
4. Item 15h., Copies not Distributed, must include (1) newsstand copies originally stated on Form 3541, and returned to the publisher, (2) estimated returns from news agents, and (3), copies for office use, leftovers, spoiled, and all other copies not distributed.
5. If the publication had Periodicals authorization as a general or requester publication, this Statement of Ownership, Management, and Circulation must be published; it must be printed in any issue in October or if the publication is not published during October, the first issue printed after October.
5. In item 16, indicate date of the issue in which this Statement of Ownership will be published.
6. Item 17 must be signed.

Failure to file or publish a statement of ownership may lead to suspension of second-class authorization.

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

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