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INSIDE

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An Evidence-Based Insulin Intensification Regimen

ABSTRACT & COMMENTARY

By Jeff Unger, MD, ABFP, FACE

Medical Director, Unger Primary Care Medicine Group, Rancho Cucamonga, CA

Dr. Unger has received research grants from Novo Nordisk and serves on the advisory board and speaker's bureau of Novo Nordisk.

Synopsis: *This study provides clinicians with valuable guidance on a technique by which insulin therapy may be intitiated and intensified using a safe, timely, and rational therapeutic approach.*

Source: Rodbard HW, et al. Treatment intensification with stepwise addition of prandial insulin aspart boluses compared with full basal-bolus therapy (FullSTEP Study): A randomised, treat-to-target clinical trial. *Lancet Diabetes Endocrinol* 2014;2:30-37.

THIS IS A 32-WEEK, RANDOMIZED, OPEN-LABEL, TWO-ARM, PARALLEL group treat-to-target study comparing the effectiveness of a stepwise prandial insulin dosing approach vs a standard basal-bolus insulin regimen in 401 patients with type 1 diabetes. The mean baseline A1C in this cohort was 7.9% and the mean duration of diabetes was 12.6 years. Basal-bolus patients received insulin aspart prior to each meal. Patients in the stepwise group received one bolus dose at a single meal. After 11 and 22 weeks, additional meals were targeted if subject's A1Cs remained ≥ 7%. The primary endpoint was non-inferiority of stepwise mealtime dosing vs basal-bolus dosing as assessed by the A1C at 32 weeks. At study end, the A1C change from baseline was -0.98% (95% confidence interval [CI], -1.09 to -0.87) for the stepwise group and -1.12% (-1.23 to -1.00) for the basal-bolus group; mean treatment difference 0.14 (95% CI, -0.02 to 0.30), non-significant (P = 0.0876). Fewer hypoglycemic episodes occurred in the stepwise group than in the basal-bolus group.

Stepwise prandial insulin intensification provides glycemic control non-inferior to a full basal-bolus regimen after 32 weeks, with significantly lower hypoglycemia risk.

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Table

Insulin Detemir Titration Schedule Using a 70-90 mg/dL Fasting Glucose Target	
Average fasting plasma glucose of 3 consecutive days (mg/dL)	Insulin detemir dose adjustment*
< 70	-3 units
70-90	0 adjustment
> 90	+3 units
*Initial detemir dose was 0.1-0.2 U/kg or 10 U at dinner or bedtime[3]	

■ COMMENTARY

Although primary care physicians appear quite competent in initiating basal insulin, the timing and titration of prandial insulin is more challenging. The initiation of basal bolus insulin requires patients to develop immediate expertise at diabetes self-management skills. Blood glucose values must be checked prior to each meal and often 2 hours after eating to assess the efficacy of the prescribed prandial insulin dose. Variables such as timing of insulin boluses in relation to ambient blood glucose values, insulin correction calculations, fat content of meals, anticipated post meal activity levels, and fear of hypoglycemia can equate a prandial dose of insulin with the famous Disneyland ride, "Mr. Toad's Great Adventure!" Rodbard points out that initiating prandial insulin slowly and meticulously over several weeks will allow patients to develop expertise in self-monitoring, avoidance of hypoglycemia, and become more adherent to the treatment regimen.

Clinicians understand the importance of insulin intensification for poorly controlled patients with type 2 diabetes mellitus (T2DM). Unfortunately, adherence to intensive insulin regimens remains an elusive target, as 89% of T2DM patients do not inject outside of the home![1,2]

During an 8-week run-in period, subjects were transferred from pre-existing therapies to insulin detemir at bedtime. Dose titration followed the protocol adapted from the TITRATE study (*see Table*).

Patients in the basal-bolus cohort of the FullSTEP study were initiated on two units of aspart insulin prior to each meal. Individuals in the stepwise group injected 4 units of aspart prior to the meal with the highest carbohydrate content as assessed by each patient at baseline. All patients used a self-titration algorithm to achieve a plasma glucose target of 72-130 mg/dL prior to the subsequent premeal glucose measurement. Subjects were advised to self-adjust their insulin aspart doses daily on the basis of the previous day's blood glucose values.

This study provides clinicians with valuable guidance on a technique by which insulin therapy may be intitiated and intensified using a safe, timely, and rational therapeutic approach. ■

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Optic Disc Cupping and Cognitive Decline: Three-year Prospective Study Demonstrates Association

ABSTRACT & COMMENTARY

By Marc Dinkin, MD

Assistant Professor of Ophthalmology, Weill Cornell Medical College

Dr. Dinkin reports no financial relationships relevant to this field of study. This article originally appeared in the January 2014 issue of Neurology Alert.

Synopsis: *This long-term epidemiological study shows an association between glaucoma and Alzheimer's disease. Cup to disc ratio, but not elevated intraocular pressure, is a risk factor for dementia.*

Source: Helmer C, et al. Is there a link between open-angle glaucoma and dementia: The three-city–Alienor cohort. *Ann Neurol* 2013;74:171-179.

From a neurologist's perspective, glaucoma is the mirror image of pseudotumor cerebri, with both diseases leading to optic atrophy due to pressure on one side of the optic nerve head. However, since neuronal degeneration in glaucoma typically occurs over decades, and may occur even in the absence of elevation in intraocular pressure (IOP), the disease is perhaps most similar to Alzheimer's disease (AD). Indeed, multiple studies have shown areas of overlap between the two diseases — diffusion tensor imaging has shown a loss of cortical white matter along the optic radiations in glaucoma patients,[1] while optical coherence tomography (OCT) has demonstrated retinal nerve fiber layer (RNFL) thinning in AD patients.[2]

The evidence linking one disease to the other has so far been conflicting, with two case-control studies demonstrating an increased risk of glaucoma in AD patients,[3,4] while several studies based on review of hospitalization records were negative.[5] The case-control studies were problematic in that the diagnosis of glaucoma could have been artifactually increased due to visual field defects secondary to the posterior cortical atrophy that may occur in some AD patients, while the negative studies, which depended on hospitalization records, may have missed either the diagnosis of AD, glaucoma, or both in some patients, since the rate of missed diagnosis of these conditions in the inpatient setting is high.

Helmer and colleagues aimed to settle the issue, with a prospective, epidemiological study, following a group of patients from one French city over a three-year period. Unlike prior studies addressing the AD-glaucoma link, patients were all actively screened for both AD and glaucoma at baseline and then again at 3 years. The results were impressive, with 17.5% of the 29 patients who developed AD at some point over the 3 years also receiving a diagnosis of glaucoma vs only 4.5% of the non-demented patients. Additionally, those patients who began the study with a diagnosis of glaucoma were four times as likely to develop AD, even when adjusting for age, sex, family history of glaucoma, education, and apolipoprotein ε4 status. Interestingly, an increased vertical cup to disc ratio (vCDR) of ≥ 0.65 and a small minimal rim to disc ratio (mRTDR), both predisposed to the development of dementia, while elevated IOP ≥ 21 and taking IOP-lowering drops did not.

■ COMMENTARY

This appears to be the first study in which a large cohort of patients were actively screened for both glaucoma and AD over several years, in search of an association. The results suggest that similar vulnerabilities of neuronal populations, perhaps determined by genetics or prior environmental exposures, may underlie the neurodegeneration in both glaucoma and AD, with the identity of the degenerating cell population determined by a secondary factor, such as elevated IOP in glaucoma patients. The finding that markers of neurodegeneration (such as a large vCDR) correlated with the risk of dementia, while elevated IOP did not, is consistent with that hypothesis. The lack of correlation of interocular cup to disc asymmetry (≥ 0.2) with dementia also supports a link through a factor predisposing to neurodegeneration, as cases with monocular or asymmetric cupping are more likely to result from a specific ocular factor.

A second interpretation of the results is that one disease actively predisposes to the other. AD, for example, has been shown to be associated with a low cerebrospinal fluid pressure,[6] which in turn would cause a higher trans-laminar pressure differential across the optic nerve head. It may be that this difference in pressure (whether it results from high IOP or low intracranial pressure) predisposes to glaucoma.

The study is limited by the relatively low number of patients diagnosed with glaucoma in the cohort, and also by the lack of OCT data to corroborate and quantify the degree of glaucoma. Furthermore, although lumbar puncture is not necessary for the diagnosis of AD, it would have been interesting to measure the opening pressure in the AD patients to see if low measurements correlated with the incidence of glaucoma. Cerebrospinal fluid analysis for AD biomarkers such as β-amyloid1-42 (Aβ1-42), total tau protein (T-tau), and hyperphosphorylated tau would have been useful as well, as an association with glaucoma would have

pointed to their role in both diseases.

While one pathological study that showed retinal degeneration in postmortem retinas of AD patients failed to show any neuritic plaques,[7] more recently curcumin angiography has allowed in vivo visualization of retinal Aβ plaques in transgenic mouse models of AD,[8] suggesting a primary degeneration of retinal neurons that could include the ganglion cells. This has been corroborated by OCT studies that have shown increased atrophy of the RNFL in AD patients. In light of this, it is possible that the results of the current study were confounded by a prior misdiagnosis of glaucoma based on AD-associated structural changes in the optic disc, especially since the definition of glaucoma in this study did not require an elevation in IOP. Of course, an alternative interpretation is that the association between glaucoma and AD demonstrated in this study explains the RNFL thinning previously demonstrated in AD patients.

Despite many remaining questions, this study makes an impressive statement on a powerful relationship between two of the most common neurodegenerative diseases in the world. The findings have significant implications for population screening of both diseases, and may even be relevant to future avenues of therapy. Further research will hopefully illuminate the cause and effect relationships subserving the observed association in this study, bringing us closer to a true understanding of both of these potentially devastating neurological conditions. ■

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Is Atrial Fibrillation Associated with Silent Cerebral Emboli?

ABSTRACT & COMMENTARY

By Edward P. Gerstenfeld, MD

Professor of Medicine, Chief, Cardiac Electrophysiology, University of California, San Francisco

Dr. Gerstenfeld does research for Biosense Webster, Medtronic, and Rhythmia Medical. This article originally appeared in the January 2014 issue of Clinical Cardiology Alert.

Synopsis: *In this study comparing the prevalence of silent cerebral ischemia (SCI) and cognitive performance in patients with paroxysmal and persistent atrial fibrillation (AF) and controls in sinus rhythm, the authors concluded that patients with AF had more SCI and worse cognitive function than matched controls in sinus rhythm.*

Source: Gaita F, et al. Prevalence of silent cerebral ischemia in paroxysmal and persistent atrial fibrillation and correlation with cognitive function. *J Am Coll Cardiol* 2013;62:1990-1997.

It is well known that patients with paroxysmal or persistent atrial fibrillation (AF) and appropriate risk factors are at increased risk of embolic stroke. However, the question of whether patients with AF on anticoagulant therapy are at higher risk of asymptomatic thomboemboli and cognitive dysfunction is unknown. In this study, patients with paroxysmal and persistent atrial fibrillation were recruited, along with matched control patients in sinus rhythm, from a cardiology clinic. All patients underwent diffusion weighted magnetic resonance imaging (MRI) of the brain, which is the best method for detecting asymptomatic or silent cerebral ischemia (SCI). The presence and number of SCIs were compared among patients with paroxysmal AF, persistent AF, and control. There were 90 patients with paroxysmal AF, 90 with persistent AF, and 90 control patients recruited. The baseline characteristics showed that 70% of paroxysmal AF patients and 73% of persistent AF patients had a CHA2DS2-VASc score ≥ 1. In addition, 43% of paroxysmal AF patients and 88% of persistent AF patients were taking oral anticoagulants. On MRI, at least one region of SCI on MRI was found in 80 (89%) patients with paroxysmal AF, 88 (98%) with persistent AF, and 41 (46%) controls. MRI lesions were bilateral in 90% of patients, suggesting an embolic etiology. The number of areas of SCI per patient was significantly higher in persistent than in paroxysmal AF, and both were greater than controls (persistent = 41.1 ± 28.0; paroxysmal = 33.2 ± 22.8; control = 12.0 ± 26.7; $P < 0.01$). On multivariate analysis, including use of oral anticoagulants and the CHA2DS2-VASc score, the presence of AF was independently associated with SCI (odds ratio, 7.2; 95% confidence interval, 2.3-22.3; *P* -0.001). The authors concluded that patients with AF had more SCI and worse cognitive function than matched controls in sinus rhythm.

■ COMMENTARY

AF remains the most common supraventricular arrhythmia, responsible for more hospitalizations and out-

patient visits than any other arrhythmia. Several large randomized studies, including AFFIRM,[1] have not demonstrated any mortality benefit to maintenance of sinus rhythm. The incidence of asymptomatic thromboemboli has come to attention after several studies found asymptomatic thromboemboli after catheter ablation of AF, and in one study, this was associated with cognitive decline.[2] However, another large, retrospective study found that patients who underwent catheter ablation and remained in sinus rhythm had a lower incidence of dementia than those remaining in AF.[3] The current study raises further suspicion that AF may lead to silent embolic events in many patients, and that these events may lead to subtle cognitive decline. This study also finds that embolic rates are higher for persistent compared to paroxysmal AF patients, a finding that makes sense, but has not been shown in prior studies. Of course there are no prospective data to suggest that maintenance of sinus rhythm, through pharmacologic or interventional means, will reduce that risk. However, the implications are provocative.

There are several limitations to this study, including the relatively small sample size and retrospective nature of the study. The high incidence of asymptomatic embolic events in the control population (46%) is difficult to explain, and may suggest that the MRI is a bit too sensitive. However, the authors convincingly argue that the pattern seen on the majority of MRIs is highly suggestive of chronic thromboembolic disease. Finally, during the study period, most patients were anticoagulated with warfarin, where time in therapeutic range (TTR) is often only ~50% and lower TTR has been associated with dementia.[4] Whether the results would be similar with patients on newer oral anticoagulants is unknown. Will there be a prospective study of the effect of rate vs rhythm control on asymptomatic thomboemboli? The ongoing CABANA study,[5] which randomizes patients to catheter ablation vs medical therapy, will examine this in a substudy. However, we are currently limited by the absence of an effective means to maintain sinus rhythm 100% of the time in AF patients, particularly those with persistent AF. So stay tuned — the relationship of asymptomatic cerebral emboli and dementia may reopen the issue of whether maintenance of sinus rhythm should be the goal in patients with AF. ■

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Special Feature

New Clinical Practice Guidelines for Preventing Heart Disease and Stroke

By Michael H. Crawford, MD

Professor of Medicine, Lucie Stern Chair in Cardiology, Director, Cardiology Fellowship Program, Chief of Clinical Cardiology, University of California, San Francisco

Dr. Crawford reports no financial relationships relevant to this field of study. This article originally appeared in the January 2014 issue of Clinical Cardiology Alert.

Synopsis: *The American College of Cardiology and the American Heart Association released new guidelines for preventing heart disease and stroke. Dr. Crawford provides expert opinion and commentary on why these new guidelines are so important.*

1. What is the significance of these new guidelines?

The new guidelines change the focus of cholesterol lowering treatment from cholesterol levels to the patient's risk of developing atherosclerotic cardiovascular disease (ASCVD). The committee recognized that despite decades of study, there are not strong data to support the use of LDL-cholesterol targets in individual patients. This is no surprise to clinicians who see myocardial infarction patients with cholesterol values in the normal range. We were taught that they still needed cholesterol-lowering therapy because their levels are too high for them. By focusing on an individual patient's risk, this problem is circumvented.

2. What are the biggest changes from the previous guidelines?

The new guidelines describe four groups of high-risk patients that need cholesterol-lowering therapy. The first three are not different from the old guidelines: patients with known atherosclerotic disease, diabetics, and those with an LDL > 190 mg/dL. The fourth is new — non-diabetic patients aged 40-75 years with LDL cholesterol between 70-189 mg/dL and a 10-year risk of ASCVD of ≥ 7.5%. The second big change is that cholesterol lowering is defined as LDL cholesterol lowering, since there is insufficient data to support other targets. The third change is that LDL lowering therapy should be statins only, since there are insufficient data to support the use of other agents alone or in combination with statins.

3. Why are these changes important?

These changes are important because they represent a shift in our assessment of how best to manage ASCVD and the risk of ASCVD. The most difficult part will be deciding who is at high risk for developing ASCVD. Once that decision is made, treatment actually becomes much simpler and straightforward.

4. What does this mean for physicians in their daily practice?

Physicians now have to assess who has a ≥ 7.5% risk of developing ASCVD in 10 years, and this is the main area of controversy with the new guidelines. The committee developed a new risk calculator that included data on African Americans, which is a defect of the commonly used Framingham risk calculator that was developed from data in largely European Americans. However, critics have commented that the new calculator overestimates risk to the extent that one-third of Americans between 40-75 years of age and every man older than 65 years would need statin therapy. Whether this is appropriate or not is debatable, but clearly more work needs to be done on risk calculation methods. In borderline risk cases, the physician should consider other factors that are not in the risk calculator, such as family history of premature ASCVD, LDL > 160 mg/dL, hs CRP ≥ 2.0, a coronary CT calcium score > 300 or the 75th percentile, and an ABI < 0.9. Second, LDL cholesterol will still need to be measured to guide therapy. The goal now is to lower LDL at least 30-50% depending on how high it is at baseline, rather than aiming for a specific numerical target. Third, the non-statin, cholesterol-lowering therapies are not necessary, but can be considered if the patient cannot take statins or can only tolerate low doses. Fourth, the new guidelines exclude patients < 40 years or > 75 years old, with symptomatic heart failure or end-stage renal disease. Physicians must use their own judgment with these patients.

5. What does this mean for patients?

Patients are going to have to lose their fixation on their cholesterol numbers and start thinking about lowering their risk in many ways. Hopefully, this new focus will encourage patients to modify risk factors beyond cholesterol. Also, patients should stop relying on unproven remedies for lowering their risk and seriously consider major lifestyle modifications and statin therapy if necessary.

6. What are the next steps physicians and patients should take?

Physicians need to develop a brief talk on the new guidelines to educate their patients. It could be given to each patient as a paper handout, posted on a website, or played on a video in the waiting room. Patients need to consider that medicine is not a static field and changes to how we manage ASCVD and the risk of ASCVD will change over time, but that these changes are for the better. ■

Pharmacology Update

Conjugated Estrogens and Bazedoxifene Tablets (Duavee®)

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

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

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

The first combination of conjugated estrogen and an estrogen agonist/antagonist (bazedoxifene) has been approved for the treatment of hot flashes. Bazedoxifene is a selective estrogen receptor modifier (SERM) that inhibits the estrogen effect on the endometrium. It is used in place of a progestin to reduce endometrial hyperplasia. Conjugated estrogens and bazedoxifene is marketed by Pfizer as Duavee.

Indications

The combination of conjugated estrogens and bazedoxifene (CE/BZA) is indicated for the treatment of moderate-to-severe vasomotor symptoms associated with menopause and for the prevention of postmenopausal osteoporosis in nonhysterectomized women.[1]

Dosage

The recommended dose is one tablet once daily. CE/BZA is available as a tablet containing conjugated estrogen 0.45 mg and bazedoxifene 20 mg.

Potential Advantages

In contrast to CE and medoxyprogesterone, CE/BZA does not increase mammographic breast density and showed lower rates of breast tenderness.[2]

Potential Disadvantages

In an animal model, BZA antagonized the atheroprotective effect of CE.[3] CE/BZA is not recommended in patients

with renal impairment and is contraindicated in those with hepatic impairment.[1] BZA may be less effective in patients with a body mass index greater than 27 kg/m^2.

Comments

The data for safety and efficacy of CE/BZA for the approved indications were from two Phase 3 Selective estrogens, Menopause and Response to Therapy (SMART) trials.[4] For moderate-to-severe vasomotor symptoms, menopause subjects (n = 318) were between 42-64 years of age and had at least seven moderate-to-severe hot flashes per day or at least 50 per week. They were randomized to CE/BZA (n = 127) or placebo (n = 63). The primary endpoint was the reduction in the number and severity of hot flashes compared to placebo at 4 and 12 weeks. From an average baseline frequency of 10.3 daily, CE/BZA showed a statistically significant treatment difference of -3.1 (95% confidence interval [CI], -4.4, 1.7) compared to placebo at week 4 and -2.7 (95% CI, -3.8, -1.6) at week 12. Severity was significantly reduced from a baseline of 2.3 by -0.5 (95% CI, -0.7, -0.3) and -0.6 (95% CI, -0.9, -0.4), respectively. Prevention of osteoporosis was shown in a 24-month study.[1,4] CE/BZA showed a difference (from placebo) in bone mineral density of 3.62% (95% CI, 2.64, 4.60) in those between 1 and 5 years postmenopausal. The difference for those who were postmenopausal longer than 5 years was 3.11% (95% CI, 2.29%, 3.93%). The incidence of endometrial hyperplasia assessed by biopsy was less than 1% at 24 months.[1,4] CE/BZA is generally well tolerated. The frequency of adverse events was 7-9%, and included nausea, diarrhea, muscle spasm, upper abdominal pain, and oropharyngeal pain.[1]

Clinical Implications

CE/BZA provided an effective and perhaps safer alternative than estrogen/progestin combinations for treating vasomotor symptoms and preventing osteoporosis. The drug combines a traditional estrogen with a SERM. The long-term effects, especially on the risk of breast cancer, are intriguing as the drug is being widely touted in the lay press as being potentially protective. There are currently no data to support this claim. The cost of CE/BZA was not available at the time of this review. ■

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CME Objectives

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

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5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. ■

CME Questions

1. Which of the following statements regarding the FullSTEP Study is *false*?

a. Subjects in the stepwise protocol were initiated on prandial insulin targeting a single meal whereas the basal-bolus cohort dosed insulin at every meal.
b. The stepwise participants experienced more hypoglycemia episodes than the basal-bolus cohort.
c. All subjects used a self-titration algorithm to achieve a plasma glucose target of 72-130 mg/dL prior to the subsequent premeal glucose measurement.
d. The intermittent addition of prandial insulin is non-inferior to basal-bolus insulin when targeting a specific glycemic target.

2. Which of the following statements is true regarding Alzheimer's disease and glaucoma?

a. Glaucoma may cause Alzheimer's disease.
b. Alzheimer's disease may cause glaucoma.
c. A common neuropathology may underlie the causes of Alzheimer's disease and glaucoma.
d. There is no relationship between glaucoma and Alzheimer's disease.

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

Dr. Kuritzky is a retained consultant for Boehringer Ingelheim, Daiichi Sankyo, Forest Pharmaceuticals, Janssen, Lilly, Novo Nordisk, Pfizer, and Sanofi.

Efficacy of Roflumilast in Asians with COPD

Source: Zheng J, et al. Roflumilast for the treatment of COPD in an Asian population: a randomized, double-blind, parallel-group study. *Chest* 2014;145: 44-52.

Site-specific phosphodiesterase (PDE) inhibition is now a standard component of pharmacotherapy. Because PDE5 is selectively located in the genital area, PDE5 inhibition (e.g., sildenafil, tadalafil, vardenafil) can improve circulatory flow and enhance sexual function. PDE3 is located dominantly in the circulation of the lower legs, enabling the PDE3 inhibitor cilostazol to improve circulation in patients with intermittent claudication. PDE6 is located in the retina, such that sildenafil (which has PDE5 and PDE6 inhibition activity) can produce blue visual effects. PDE4 is located in the pulmonary system, and PDE4 inhibition has recently been added to the pharmacotherapy of chronic obstructive pulmonary disease (COPD) in the form of roflumilast.

In the United States, roflumilast is FDA-approved for reducing COPD exacerbations. Although registration trials have shown modest bronchodilatory activity from PDE4 inhibition, the degree of bronchodilation produced by the PDE4 inhibitor roflumilast is below the threshold required by the FDA to be specifically labeled as a bronchodilator.

Ethnically diverse responses to pharmacotherapy are increasingly recognized to be of clinical significance. For instance, there are clinically meaningful differences in the metabolism of theophylline between American children and Chinese children. Zheng et al evaluated the effects of roflumilast treatment of COPD in an Asian population.

The efficacy of roflumilast in this all-Asian population was consistent with prior published results in non-Asian populations. Unless the current and evolving smoking status of much of Asia (especially men) experiences a prominent reversal — some recent reports indicate that as many as 50% of adult Chinese men are smokers — we can anticipate the need for a full complement of COPD treatments in the coming decades. ■

A More Confident 'Maybe' for the Role of Genotyping in Warfarin Therapy

Source: Pirmohamed M, et al. A randomized trial of genotype-guided dosing of warfarin. *N Engl J Med* 2013; 369:2294-2303.

It is difficult to contest the excellence of warfarin for risk reduction in atrial fibrillation (average stroke reduction approximately 66%; mortality reduction 26%). Nonetheless, maintenance therapy with warfarin is complicated by drug interactions, dietary interactions, and the foibles of inconsistent medication administration in even the best of hands. The consequences of significant bleeding — especially intracranial bleeding — have spawned a variety of plans for initial dosing and subsequent dose adjustment, each method seeking the most prompt and safe pathway for achieving a therapeutic level of anticoagulation while avoiding over-anticoagulation.

A good deal of the variation in response to warfarin is due to genetic metabolic pathways, particularly CYP2C9 and VKORC1. Identification of individual genetic makeup in reference to these pathways could help predict (at least in theory) doses of warfarin necessary to achieve therapeutic anticoagulation.

First, the good news. In the clinical trial by Pirmohamed et al (n = 455) in which genotyping was performed, there was a statistically significant increase in time in the therapeutic range (67.3%) vs traditional warfarin dosing (60.3%). Additionally, the incidence of excessive anticoagulation was less in the group whose dosing was based on genotyping.

The bad news, however, is that in the same issue of the *New England Journal of Medicine* another trial (n = 1015) that compared pharmacogenetic-based warfarin dosing vs standard dosing found no difference between methodologies (*N Engl J Med* 2013;369:2283-2293). Counterintuitively, in black patients in the latter trial, maintenance of a therapeutic INR was actually less in the pharmacogenetic-based group.

At the current time, you and I do not have to worry about sorting this out, since current guidelines do not advocate routine genetic testing. The status of pharmacogenetic warfarin management remains controversial. ■

In Future Issues:

Recommendations from the American Geriatrics Society Consensus Statement on Vitamin D for Prevention of Falls and Their Consequences