INTERNAL MEDICINE ALERT®

Evidence-based summaries of the latest research in internal medicine

Providing Evidence-based Clinical Information for 35 Years

AHC Media Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com
www.cmecity.com

AHC Media

INSIDE

Financial Disclosure: *Internal Medicine Alert's* editor, Stephen Brunton, MD, serves on the advisory board for Abbott, Amarin, Boehringer Ingelheim, Duchesnay, Janssen, Lilly, Novo Nordisk, Sunovion, and Teva; he serves on the speakers bureau of Boehringer Ingelheim, Janssen, Lilly, Novo Nordisk, and Teva. Peer reviewer Gerald Roberts, MD; executive editor Leslie Coplin; and managing editor Neill Kimball report no financial relationships relevant to this field of study.

Is it 'Low T' or 'Low E' or Both?

ABSTRACT & COMMENTARY

By Rahul Gupta, MD, MPH, FACP

Clinical Assistant Professor, West Virginia University School of Medicine, Charleston, WV

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

Synopsis: *In men 20-50 years of age, testosterone deficiency accounted for decreases in lean muscle mass, size, and strength while estrogen deficiency primarily accounted for increases in body fat, and both contributed to the decline in sexual function.*

Source: Finkelstein JS, et al. Gonadal steroids and body composition, strength, and sexual function in men. *N Engl J Med* 2013;369:1011-1022.

It is well documented that serum testosterone levels decline modestly with age in men. A variety of age-related changes are considered to be related to the physiologic lowering of testosterone. Existing evidence suggests that based on free testosterone levels, up to 20% of men > age 60, 30% > age 70, and 50% > 80 years of age may be hypogonadal.[1] Aging in men is associated with declines in bone mineral density and consequent increase in risk for fractures, lean muscle mass and strength decline with fat mass increases, reduced sexual function, anemia, mood, and cognitive changes. As a result, declining levels of testosterone are often blamed as the culprit and millions of American men are prescribed testosterone therapy each year. Coupled with widespread marketing for conditions named "Low T," there has been a recent rapid expansion in the market for demand of testosterone replacement therapy. It is common for the clinician to prescribe this type of therapy when a patient presents with nonspecific symptoms, such as fatigue or decline in libido, coupled with laboratory findings of serum testosterone levels below the reference range. However, unlike the case for menopause in women, there still remains a certain degree of uncertainty in establishing a link between the physiological decline of androgens in males and the symptoms of late-stage hypogonadism. Therefore, it is unclear if increasing the serum testosterone concentrations of elderly men to those of young men will prevent or reverse these changes. Nonetheless, this has not halted the use of testosterone

VOLUME 35 • NUMBER 19 • OCTOBER 15, 2013 • PAGES 145-152

INTERNAL MEDICINE ALERT IS AVAILABLE ONLINE
www.internalmedicinealert.com

replacement as an anti-aging or sexual tonic among aging men. While the consequences of male hypogonadism are routinely attributed solely to testosterone deficiency, there are two additional active metabolites in males, dihydrotestosterone and estradiol, that are also significant in the metabolic processes. Through 5-alpha reductase, testosterone is converted into its more potent form, dihydrotestosterone. Estradiol is also produced as an active metabolic product of testosterone through aromatization. There is evidence to suggest that men require some locally synthesized estradiol in tissues.[2] While the potential role of this type of estrogen deficiency in certain processes such as bone loss is clear, that is not the case for others such as sexual function, muscle, and fat mass.

In their study, Finkelstein et al recruited 400 healthy men between the ages of 20 and 50 years who were given monthly shots of goserelin acetate to suppress endogenous testosterone and estradiol production to pre-puberty levels. At this time, one cohort (198 men) was randomly assigned to receive a placebo gel or 1.25 g, 2.5 g, 5 g, or 10 g of testosterone gel daily for 16 weeks. The other cohort (202 men) additionally received anastrozole (to suppress the conversion of testosterone to estradiol). Primary study outcomes measured were percentage change in body fat and lean muscle mass. Sexual function, physical function, vitality, and overall health status were also assessed with a self-administered questionnaire at each visit. The researchers found that the percentage of body fat increased in groups receiving placebo or low-dose daily testosterone (1.25 g or 2.5 g) without anastrozole. Lean mass and thigh-muscle area were found to be decreased in men receiving placebo and the lowest daily testosterone dose of 1.25 g (eliciting a mean serum level of approximately 200 ng/dL) without anastrozole. Leg-press strength fell only with placebo administration. Overall, the sexual desire declined as the testosterone dose was reduced. The researchers also found that in the cohort of men in whom the aromatization of testosterone to estradiol was inhibited with anastrozole, the percentage of body fat increased in all groups. The magnitudes of these increases were similar with all doses of testosterone, suggesting a predominantly estrogenic effect. In further comparison analysis conducted between the two cohorts, researchers found that receiving testosterone with inhibition of estrogen synthesis, as compared with intact estrogen synthesis, was associated with significant increases in the percentage of body fat ($P < 0.001$), subcutaneous-fat area ($P < 0.001$), and intra-abdominal-fat area ($P = 0.002$), as well as significant decreases in sexual desire ($P < 0.001$) and erectile function ($P = 0.022$).

■ COMMENTARY

In this remarkable study, the authors conducted what I consider groundbreaking research on a significant issue related to male aging. By employing an ingenious study design, they found that testosterone levels regulate lean body mass, muscle size, and strength, while estrogen levels regulate fat accumulation in healthy men 20-50 years of age. On the other hand, sexual function, including the desire and erectile function, seems to be regulated by both hormones. So, it seems that both "Low T" and "Low E" may be an issue in the aging male patient.

There are several contributions and implications of this study to our current understanding of the concept of male menopause. First and most obvious is the fact that estrogens play a fundamental role in the regulation of body fat and sexual function. Second, since muscle loss and erectile dysfunction were not seen until serum testosterone dropped to approximately 200 ng/dL in the study, not everyone with levels between 200-300 may require testosterone replacement. This is especially significant since the impact of testosterone replacement in older men with low serum testosterone and hypogonadal symptoms remains unclear. Finally, when prescribing testosterone replacement, it may be worthwhile to ensure that the particular supplement should be capable of being aromatized into estrogen. However, while there is no compelling need to taper patients off existing testosterone replacement regimens or start prescribing estrogen to men, I would anxiously await further research on this issue since it seems we are heading for a new era — one of better understanding the complicated physiology in male menopause! ■

Internal Medicine Alert, ISSN 0195-315X, is published monthly by AHC Media LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326.

EXECUTIVE EDITOR: Leslie G. Coplin.
MANAGING EDITOR: Neill L. Kimball.
INTERIM EDITORIAL DIRECTOR: Lee Landenberger.

GST Registration Number: R128870672.

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

POSTMASTER: Send address changes to ***Internal Medicine Alert,*** P.O. Box 550669, Atlanta, GA 30355.

Back Issues: $21. 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: neill.kimball@ahcmedia.com
Online: www.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)

Multiple Copies
Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

Canada
Add 7% GST and $30 shipping.

Elsewhere
Add $30 shipping.

Accreditation

AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of 45 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This enduring material activity, *Internal Medicine Alert*, has been reviewed and is acceptable for up to 24 Prescribed credit(s) by the American Academy of Family Physicians. AAFP certification begins January 15, 2013. Term of approval is for one year from this date with the option of yearly renewal. Each issue is approved for 1 Prescribed credits. Credit may be claimed for one year from the date of each issue. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity is intended for the internist/family physician. It is in effect for 36 months from the date of the publication.

AHC Media

Questions & Comments
Please call **Neill Kimball**, Managing Editor, at (404) 262-5404.

References

1. Harman SM, et al. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. *J Clin Endocrinol Metab* 2001;86:724-731.
2. Vanderschueren D, et al. Androgens and bone. *Endocr Rev* 2004;25:389-425.

Hyperglycemia, Insulin Resistance, and the Risk of Pancreatic Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD

INOVA Fairfax Hospital Cancer Center, Fairfax, Virginia; Director, Institute for Advanced Studies in Aging, Washington, DC

Dr. Ershler reports no financial relationships relevant to this field of study. This article originally appeared in the August 2013 issue of Clinical Oncology Alert.

Synopsis: *There is a known association of obesity and glucose intolerance with pancreatic cancer but whether this is due to the effect of high glucose itself, insulin resistance, or pancreatic β-cell dysfunction is unknown. In an epidemiological, nested, case-control analysis drawn from five large prospective cohorts, measures of insulin resistance were independently associated with pancreatic cancer risk, but this was not true for measures of hyperglycemia or β-cell dysfunction alone.*

Source: Wolpin BM, et al. Hyperglycemia, insulin resistance, imparired pancreatic ß-cell function, and risk of pancreatic cancer. *J Natl Cancer Inst* 2013;105:1027-1035.

Pancreatic cancer remains both a challenge to diagnose and an even greater challenge to effectively treat. In fact, only patients discovered early and with resectable disease have a chance for long-term survival. Unfortunately, the majority of patients (> 85%) have unresectable disease by the time disease-associated symptoms occur and a diagnosis is made.[1] Patients who have the greatest chance for curative resection are those who have their tumors diagnosed when under evaluation for other problems and the pancreatic mass is discovered before symptoms occur. The timeline for progression of pancreatic cancer from resectable to unresectable is unknown. Glucose intolerance is known to occur in a substantial percentage of pancreatic cancer patients and it may occur earlier than other signs or symptoms of disease.[2-5] Yet the relationship between glucose metabolism and pancreatic cancer remains unclear, and an observed associated risk could be secondary to consequences of peripheral insulin resistance, pancreatic ß-cell dysfunction, or hyperglycemia itself. Hemoglobin A1c (HbA1c) is a measure of hyperglycemia, whereas plasma insulin and proinsulin are markers of peripheral insulin resistance,[6] and the proinsulin to insulin ratio marks pancreatic ß-cell dysfunction.[7]

Capitalizing on data from five prospective U.S. cohorts followed through 2008, Wolpin and colleagues performed a nested, case-control study of 449 pancreatic cancer patients and 982 control subjects, all of whom had prediagnostic blood samples but no prior diagnosis of diabetes. Two or three control subjects were matched to each case patient by year of birth, cohort, smoking, and fasting status. Pancreatic cancer risk was assessed by prediagnostic HbA1c, insulin, proinsulin, and proinsulin to insulin ratio with multivariable-adjusted logistic regression.

The data were analyzed in quintiles and it was found that the highest vs lowest quintiles of HbA1c, insulin, and proinsulin were associated with an increased risk for pancreatic cancer (odds ratio [OR], 1.79; 95% confidence interval [CI], 1.17-2.72 for HbA1c; OR, 1.57; 95% CI, 1.08-2.30 for insulin; and OR, 2.22; 95% CI, 1.50-3.29 for proinsulin). The proinsulin to insulin ratio was not associated with pancreatic cancer risk. To evaluate whether subclinical malignancy influenced results, the authors performed analyses with exclusion of patients whose tumor developed < 10 years after their samples were drawn. For those with cancers developing ≥ 10 years after blood collection, the associations with insulin and proinsulin became stronger (highest vs lowest quintile: OR, 2.77; 95% CI, 1.28-5.99 for insulin; and OR, 3.60; 95% CI, 1.68-7.72 for proinsulin). In mutually adjusted models including HbA1c, insulin, and proinsulin, only proinsulin remained statistically significant (highest vs lowest quintile, OR, 2.55; 95% CI, 1.54-4.21).

■ COMMENTARY

The association of obesity, diabetes, and pancreatic cancer has been well described but the mechanism accounting for this association has yet to be established. Although the current study does not definitively answer this, it is valuable in providing direction. The analysis demonstrated statistically significant positive associations between risk of pancreatic cancer and prediagnostic circulating markers of hyperglycemia (HbA1c) and peripheral insulin resistance (plasma insulin and proinsulin). However, the risk for pancreatic cancer was not associated with plasma proinsulin to insulin ratio (a marker of impaired ß-cell function). Furthermore, when evaluated in joint models, high levels of plasma proinsulin (a marker of peripheral insulin resistance) were associated with a nearly 2.5-fold increase in risk for pancreatic cancer, whereas HbA1c (a marker of hyperglycemia) was no lon-

ger associated with risk. Thus, insulin resistance existent over a decade or more was found to be a key pancreatic cancer risk factor.

The implications of these findings are important at several levels. Studies that examine how insulin resistance and hyperglycemia mediate pancreatic neoplastic transformation would allow a better understanding of the early steps in the development of this devastating illness. And, in the short run, physicans should be aware that early recognition and reversal of insulin resistance, aside from the obvious immediate health benefits, may be effective in preventing pancreatic cancer. ■

References

1. Jemal A, et al. Cancer statistics, 2009. *CA Cancer J Clin* 2009;59:225-249.
2. Chari ST, et al. Probability of pancreatic cancer following diabetes: A population-based study. *Gastroenterology* 2005;129:504-511.
3. Gapstur SM, et al. Abnormal glucose metabolism and pancreatic cancer mortality. *JAMA* 2000;283:2552-2558.
4. Grote VA, et al. Diabetes mellitus, glycated haemoglobin and C-peptide levels in relation to pancreatic cancer risk: A study within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. *Diabetologia* 2011;54:3037-3046.
5. Huxley R, et al. Type-II diabetes and pancreatic cancer: A meta-analysis of 36 studies. *Br J Cancer* 2005; 92:2076-2083.
6. Kahn SE, et al. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature* 2006;444:840-846.
7. Roder ME, et al. Disproportionately elevated proinsulin levels reflect the degree of impaired B cell secretory capacity in patients with noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 1998;83:604-608.

Brief Reports

An Old Disease Returns: Syphilis in North America

By Carol A. Kemper, MD, FACP

Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases, Santa Clara Valley Medical Center

Dr. Kemper does research for Abbott Laboratories and Merck. The article originally appeared in the August 2013 issue of Infectious Disease Alert.

SYPHILIS IS MAKING A RESURGENCE IN THE U.S. AND CANada, especially in urban areas, where the rates of newly diagnosed infection have soared, especially in men-who-have-sex-with-men (MSM). The problem has begun "spilling over" into the heterosexual community. This epidemic may be largely attributed to the availability of Internet hook-ups and networking mobile smartphone apps, such as Grindr, the increased use of methamphetamines, as well as what is termed "prevention fatigue." San Francisco County has recorded spikes in all STDs for 6 straight years — and the number of early syphilis cases rose from 659 in 2010 to 682 in 2011 (the last year for which unofficial numbers are available). It is estimated that each new case of syphilis results, on average, in exposure to 10 additional people.

Grindr is a gay social networking application launched in 2009 and available worldwide — it runs on the iPhone, Blackberry, and Android. The app allows users to meet other men within close proximity who are interested and available for whatever specified sexual activity using the phone's mobile location services. We tried it in our Santa Clara county HIV clinic the other day and someone was available and interested in having sex not more than 75 feet away — they were in the same building!

Some public health officials are now recommending syphilis screening of high-risk individuals every 3-6 months. This might make good sense — in our HIV clinic, we routinely screen on an annual basis — but based on these figures, screening at even shorter intervals makes sense. ■

Women Are at Greater Risk of Dying from Stroke Than Men

By Matthew E. Fink, MD

Professor and Chairman, Department of Neurology, Weill Cornell Medical College, and Neurologist-in-Chief, New York Presbyterian Hospital

Dr. Fink is a retained consultant for MAQUET. The article originally appeared in the August 2013 issue of Neurology Alert.

Source: Zhou G, et al. Sex differences in stroke case fatality: A meta-analysis. *Acta Neurol Scand* 2013;128:1-8.

THERE IS ONGOING CONTROVERSY REGARDING GENDER DISparity in stroke treatment and outcomes. Many small studies suggest that women have worse outcomes than men after stroke, and some authors have suggested that women are less likely to receive thrombolysis or other interventions than men. However, there is a dearth of large, population-based studies that have examined gender differences in treatment and outcome. Zhou et al investigated sex differences in stroke case fatality in all published studies based on a comprehensive meta-analysis. A systematic search of all published databases was made for papers

published from 1992 through 2009, groups were pooled, and a random effects model was used to find sex differences in cases of fatality of stroke with a Mantel-Haenzel method. A meta-regression analysis was also performed.

Thirty six population-based studies, along with three randomized clinical trials (RCTs), representing 125,227 men and 115,511 women, were included and analyzed. For the pooled group, there was an overall hazard risk of 1.13 for women compared to men. In the RCTs subgroup, there was a hazard risk of 1.27 for women and in the population-based studies a risk of 1.12. Although these data support the hypothesis that stroke case fatality is higher in women, more large, multicenter clinical trials are needed to determine this with more certainty. ■

Pharmacology Update

Afatinib Tablets (Gilotrif™)

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.

An irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) has been approved for first-line treatment of non-small cell lung cancer (NSCLC) with certain EGFR mutations. Afatinib is marketed by Boehringer Ingelheim Pharmaceuticals as Gilotrif.

Indications

Afatinib is indicated as first-line treatment for metastatic NSCLC in tumors with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.[1]

Dosage

The recommended dose is 40 mg orally once daily at least 1 hour before a meal or 2 hours after a meal.[1] The dose should be reduced by 10 mg if coadministered with a P-glycoprotein inhibitor (e.g., phenytoin, rifampin) and increased by 10 mg if coadministered with a p-glycoprotein inducer (e.g., cyclosporine, itraconazole, erythromycin). Afatinib is available as 20 mg, 30 mg, and 40 mg tablets.

Potential Advantages

Afatinib is associated with prolongation of progression-free survival (PFS) compared to standard chemotherapy (cisplatin and pemetrexed) as well as better control of cough and dyspnea.[1,2,3] Afatinib is an irreversible tyrosine kinase inhibitor with increased inhibition of common EGFR-activating mutations compared to reversible inhibitors such as erlotinib and gefitinib.[4] Afatinib does not interact with the cytochrome P450 isoenzymes.

Potential Disadvantages

Afatinib is associated with a higher frequency of diarrhea, rash, stomatitis, and paronychia compared to chemotherapy (cisplatin/pemetrexed).[1,2] Grade 3 severity adverse events ranged from 11-15%.

Comments

Afatinib irreversibly binds to the kinase domains of EGFR, HER2, and HER4 as well as tyrosine kinase autophosphorylation.[1] This results in down regulation of ErbB signaling, resulting in inhibition of tumor growth. The efficacy and safety of afatinib were evaluated in 345 treatment-naïve subjects with EGFR mutation positive metastatic NSCLC.[1,2] These subjects had Stage IV and Stage III b disease with pleural and/or pericardial effusion. They were randomized (2:1) to afatinib (40 mg daily; n = 230) or up to six cycles of cisplatin 75 mg/m^2/pemetrexed (500 mg/m^2 × 21 days) (n = 115). Mutation-positive subjects were stratified by mutation type (exon 19 deletion, L858R, or other) and race (Asian or non-Asian). The primary endpoint was PFS and secondary endpoints were overall survival and tumor response. Median PFS was 11.1 months for afatinib and 6.9 months for cisplatin/pemetrexed (hazard ratio, 0.58; 95% confidence interval, 0.43, 0.78; $P < 0.001$). Subgroup analysis showed that those with exon 19 deletion had the best response (PFS 13.7 vs 5.6). Asians tended to respond better than non-Asians.[2] Objective tumor response (complete + partial) was 50.4% for afatinib and 19.1% for cisplatin/pemetrexed. There was no difference in overall survival (50.4% vs 51.2%), although those with exon 19 deletion showed survival benefit. Afatinib delayed the time to deterioration for cough and dyspnea as well as improvement in dyspnea score compared to cisplatin/pemetrexed. Dose reductions were required in 57% of subjects randomized to afatinib. The most common adverse events were diarrhea, rash, paronychia, and stomatitis. The discontinuation rate was 14%. Uncommon but serious adverse events included interstitial lung disease (1.5%) (which appears to be more common in Asians [2.1%]) and left ventricular dysfunction (2.2%).[1] In patients previously treated with erlotinib or gefitinib (n = 585), the addition of afatinib to best supportive care improved NSCLC-related symptoms compared to placebo.[5] In a subgroup analysis with known EGFR mutations (n = 96), PFS favored afatinib vs placebo (4.5 months vs 1 month).[4,6]

Clinical Implications

NSCLC is the most common type of lung cancer and exon 19 deletions and exon 21 single amino acid substitutions (L585R) are the most common mutations.[4] Approximately 50% of Asians have this mutation compared to 10-15% of Caucasians. Currently, erlotinib is first-line treatment for NSCLC with EGFR exon 19 deletion or exon 21 substitution mutation.[4,7] Unfortunately, a significant percentage of patients develop secondary resistance within 9-12 months after initiation of therapy with reversible TKIs.[4,8] Afatinib offers a new option as first-line treatment and may have a role in patients who develop resistance to erlotinib. More clinical experience is needed to define the ultimate role of afatinib in NSCLC. The wholesale cost of afatinib 40 mg is $5555 for 30 days compared to $5752 for erlotinib 150 mg. ■

References

1. Gilotrif Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals; July 2013.
2. Sequist LV, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 2013;31:3327-3334.
3. Yang JC, et al. Symptom control and quality of life in LUX-Lung 3: A phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 2013;31:3342-3350.
4. Nelson V, et al. Afatinib: Emerging next-generation tyrosine kinase inhibitor for NSCLC. *Onco Targets Ther* 2013;6:135-143.
5. Hirsh V, et al. Symptom and quality of life benefit of afatinib in advanced non-small-cell lung cancer patients previously treated with erlotinib or gefitinib: Results of a randomized phase IIb/III trial (LUX-Lung 1). *J Thorac Oncol* 2013;8:229-237.
6. Miller VA, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): A phase 2b/3 randomised trial. *Lancet Oncol* 2012;13:528-538.
7. http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed September 22, 2013.
8. Cadranel J, et al. Therapeutic strategy for advanced EGFR mutant non-small-cell lung carcinoma. *Crit Rev Oncol Hematol* 2013; Jul 30. [Epub ahead of print.]

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.

CME Instructions

To earn credit for this activity, follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. You will no longer have to wait to receive your credit letter! ■

CME Questions

1. **In the study by Finkelstein et al, as opposed to low serum testosterone levels, which of the following effects are attributed exclusively to low estrogen in men?**
   a. Low muscle mass
   b. Low muscle strength
   c. Low libido
   d. High body fat

2. **From epidemiological analysis, which of the following measures proved to be an independent risk factor for the development of pancreatic cancer?**
   a. Fasting blood sugar
   b. HbA1c (as an indicator of hyperglycemia)
   c. Insulin and proinsulin levels (as an indicator of insulin resistance)
   d. Proinsulin to insulin ratio (as an indicator of pancreatic ß-cell dysfunction)

Clinical Briefs

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.

Finasteride for Prevention of Prostate Cancer: 18 Years of Follow-up

Source: Thompson IM, et al. Long-term survival of participants in the prostate cancer prevention trial. *N Engl J Med* 2013;369:603-610.

The prostate cancer prevention trial (PCPT) was a randomized, double-blind, placebo-controlled trial (n = 18,880) performed to evaluate the efficacy of the 5-alpha-reductase inhibitor finasteride (FIN) for prevention of prostate cancer. At the end of 7 years, the good news was a 25% reduction in total prostate cancer; the bad news was that there was a 27% *increase* in higher-grade prostate cancers, intimating that although the total amount of prostate cancer was reduced, overall outcomes could possibly be worsened by the increase in more aggressive cancers. Mitigating explanations for the increased risk of higher-grade tumors included alpha-reductase inhibitor-induced shrinkage of healthy prostate tissue (thereby increasing the likelihood of biopsy-positive results) and alteration of tissue architecture induced by FIN; insufficiently reassured by these explanations, most primary care clinicians have opted not to use FIN for prostate cancer prevention.

The outcomes of this population in very long-term follow-up can better answer the question of whether the risk-benefit balance was indeed unfavorably tipped by high-grade prostate cancers. Reviewing the outcomes of patients originally enrolled in PCPT, the survival rates at 18 years were essentially identical among men who had been randomized to FIN or placebo. Although FIN treatment did not appear to reduce mortality, the increased incidence of higher-grade Gleason scores among FIN-treated patients did not appear to increase mortality either. In the absence of mortality improvement, unless men are seeking alpha-reductase treatment for symptomatic benign prostatic hyperplasia, FIN treatment for prevention of prostate cancer would appear unwarranted, albeit otherwise safe. ■

Addressing Diabetic Neuropathy

Source: Tesfaye S, et al. Mechanisms and management of diabetic painful distal symmetrical polyneuropathy. *Diabetes Care* 2013;36:2456-2465.

Type 2 diabetes (T2DM) remains the No. 1 cause of atraumatic limb loss in the United States. Neuropathy is a primary culprit in the process beginning with undetected foot injury that progresses to deep-seated infection and, ultimately, limb loss. Hence, it is hoped that early identification and management of diabetic peripheral neuropathy (DPN) might improve outcomes. Unfortunately, of the microvascular consequences of T2DM, neuropathy appears to be the most recalcitrant to glucose control: Glucose control appears to forestall progression of neuropathy, but not improve nerve function or reverse neuropathy.

In clinical practice, it is recommended that the diagnosis of DPN should be based on typical symptoms and physical examination (e.g., lower extremity deep tendon reflex changes). On the other hand, clinical trials usually employ sophisticated techniques such as nerve conduction testing. Comparison of tuning fork testing vs monofilament testing found the former to be the most sensitive test for identification of neuropathy. The postulated pathophysiology of DPN is uncertain and may be multifactorial, but there is some support for dysfunction of the neural microvasculature.

FDA-approved agents for DPN pain are duloxetine and pregabalin, although venlafaxine, gabapentin, carbamazepine, and alpha-lipoic acid have also demonstrated some efficacy. A recently published algorithm created by the Toronto International Neuropathy Consensus Group suggests that when traditional agents are not effective, opioid analgesia may be considered. ■

When Metformin and Sulfonylurea Are Not Enough: Canagliflozin or Sitagliptin?

Source: Schernthaner G, et al. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: A 52-week randomized trial. *Diabetes Care* 2013; 36:2508-2515.

Many type 2 diabetes (T2DM) patients are unable to achieve or maintain their A1c goals even when appropriately treated with oral agents. Currently, the combination of metformin with a sulfonylurea (MET/SFU) is a very commonplace initial combination. Because T2DM is a progressive disorder, and because some agents lose efficacy over time, most patients must recognize that augmentation of treatment is usually required. But which next step is best when MET/SFU is insufficient?

Canaglifozin (CAN) is the first approved member of a new class of agents for T2DM, known as the SGLT2 inhibitors, which work by blocking renal reabsorption of excess glucose, leading to increased urinary glucose excretion. Sitagliptin (SIT) is one of three approved DPP-4 inhibitors that work by increasing blocking glucagon and stimulating insulin production when glucose is elevated.

In a 1-year trial comparing the addition of CAN or SIT to MET/SUF (n = 755), A1c reduction with CAN was substantially greater (-1.03 vs -0.66) and both agents were well tolerated. SGLT2 inhibitors are potentially useful when A1c goals are not attained or maintained with MET/SUF. ■

The Cause of T Wave Inversion?

By Ken Grauer, MD, *Professor Emeritus in Family Medicine, College of Medicine, University of Florida*

Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.

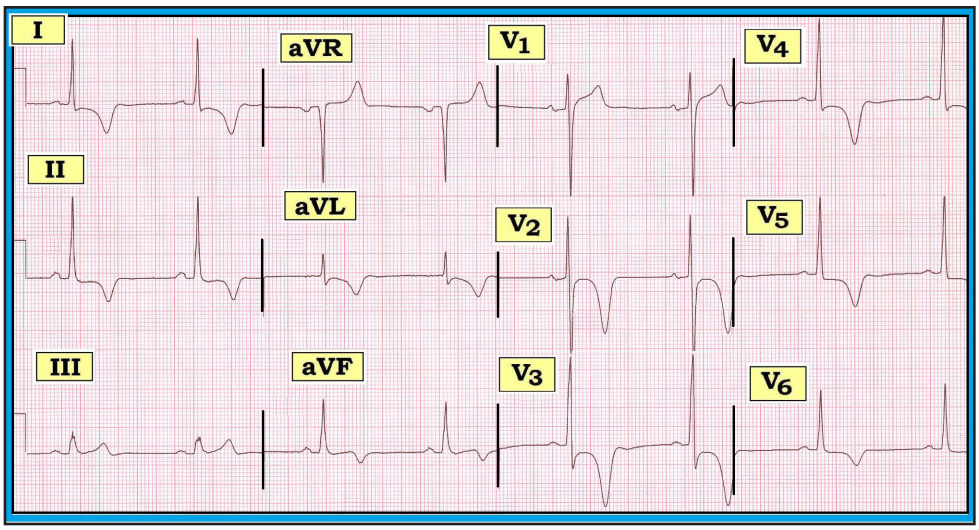

Figure — No history is available. What clinical conditions should be considered?

Scenario: No history is available for the ECG shown above. How would you interpret this tracing? What clinical conditions should be considered as the possible cause for the ST-T wave changes seen?

Interpretation: The rhythm is sinus bradycardia and arrhythmia, with an overall heart rate just under 60/minute. All intervals (PR/QRS/QT) are normal. The axis is normal at +50 degrees. Voltage for LVH is present (deepest S in V1, V2 + tallest R in V5, V6 ≥ 35 mm). With regard to Q-R-S-T changes, there are no Q waves and transition occurs early (with relatively tall R waves in leads V1, V2). The most remarkable finding on this tracing is diffuse, deep symmetric T wave inversion. T wave inversion almost attains a depth of 15 mm in leads V2, V3. Other subtle but real ST-T wave findings include 1-2 mm of J-point ST depression in multiple leads — suggestion of ST segment coving in leads I, aVL, V2, V3, V4 — and a hint of ST elevation in leads III, aVR, and V1.

The overall impression of this ECG is suggestive of giant T wave syndrome. Although some T wave inversion is common in many conditions, the term "giant T waves" is reserved for a select number of clinical entities that produce truly deep (> 5 mm amplitude) T wave inversion. When this clinical picture is seen (as it is in the figure above), one should think of the following diagnostic entities: 1) apical (Yamaguchi) cardiomyopathy, 2) severe central nervous system (CNS) disorders (increased intracranial pressure), 3) Stokes-Adams attacks (especially when due to severe bradycardia or complete AV block), 4) acute ischemia/coronary artery disease, 5) post-tachycardia syndrome, and 6) massive pulmonary embolism (with acute right heart strain).

Without any history, it is impossible to know which of the above entities is most likely. Acute CNS disorders (stroke, subarachnoid or intracranial hemorrhage, seizure, coma, brain tumors, trauma) may produce some of the most bizarre ST-T wave abnormalities. However, the QT interval will usually be prolonged with CNS disorders and there will often be manifest T wave broadening (neither of which is seen here). Other stigmata of acute right heart strain usually accompany anterior T wave inversion from a large pulmonary embolus. The history is usually revealing when Stokes-Adams attacks, tachycardia, and/or CNS catastrophe is the reason for T wave inversion. This leaves us with myocardial ischemia and/or the special form of hypertrophic cardiomyopathy that preferentially affects the left ventricular apex. Increased QRS amplitude and the ST-T wave changes described above are consistent with either of these two entities.

For more information on giant T waves, please visit: https://www.kg-ekgpress.com/ecg_-_giant_t_waves/. ■

In Future Issues:

ARBs in Diabetes — Some Good, Some Better!

PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Medications for Risk Reduction of Breast Cancer in Women

In this issue: USPSTF issues new guidelines for risk reduction of breast cancer; safety of Chantix in patients with depression; polypills for cardiovascular disease; and FDA actions.

Risk reduction of breast cancer

The U.S. Preventive Services Task Force (USPSTF) has published new guidance regarding medications for risk reduction of primary breast cancer in women. The group reviewed evidence on the effectiveness, adverse effects, and subgroup variations of medications to reduce breast cancer, specifically the selective estrogen receptor modulators tamoxifen and raloxifene (Evista). The USPSTF recommends that clinicians engage in shared, informed decision making with women who are at increased risk for breast cancer about medications to reduce the risk. Women who are at increased risk for breast cancer and have a low risk for adverse medication effects should be offered one of the risk-reducing medications (B recommendation). However, the group recommends against the routine use of these medications in women who are not at increased risk of breast cancer. High-risk women are defined as those with a 5-year risk of ≥ 3% based on the National Cancer Institute's Breast Cancer Risk Assessment Tool (www.cancer.gov/bcrisktool/). Tamoxifen and raloxifene are shown to reduce the risk of estrogen receptor-positive breast cancer, but not estrogen receptor-negative cancer, which is more difficult to treat. Tamoxifen is associated with a moderate benefit for breast cancer but a slightly higher risk of endometrial cancer. Raloxifene is associated with a slightly smaller benefit for breast cancer but no risk for endometrial cancer. Both drugs may reduce the risk of nonvertebral fractures with greater benefit for raloxifene. Both drugs also increase the risk of venous thromboembolism with the risk being age-dependent (*Ann Intern Med* published online September 24, 2013). ■

Chantix safe in patients with depression

Varenicline (Chantix) was approved in 2006 to treat smoking addiction. Since its approval, the drug has been plagued by reports of worsening depression and increases in suicidality, prompting the FDA to issue an alert in 2008 noting "serious neuropsychiatric symptoms" associated with the drug. But a new study suggests that varenicline may be safe and effective in smokers with a history of depression. In a study sponsored by Pfizer, 525 adult smokers with stably treated current or past major depression and no recent cardiovascular events were randomized to varenicline 1 mg twice daily or placebo for 12 weeks with 40 weeks of nontreatment follow-up. The primary outcome was carbon monoxide-confirmed continuous absence rate (CAR) for weeks 9-12. Other outcomes included ratings of mood, anxiety, and suicidal ideation or behavior. About two-thirds of patients in both groups completed the study. Patients treated with varenicline had double the quit rate at weeks 9-12 (CAR 35.9% vs 15.6%; odds ratio, 3.35; 95% confidence interval [CI], 2.16-5.21; $P < 0.001$). The quit rates were also approximately double from weeks 9-24 and from weeks 9-52, with the CAR at week 52 for the varenicline group at

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) 262-5404. E-mail: neill.kimball@ahcmedia.com.

20.3% vs 10.4% for placebo. There were no clinically relevant differences between groups in suicidal ideation or behavior, or overall worsening depression or anxiety. About 27% of the treatment group experienced nausea as the most frequent adverse event. The authors conclude that varenicline increased smoking cessation in smokers with stably treated current or past depression without exacerbating depression or anxiety (*Ann Intern Med* 2013;159:390-400). ■

Polypills for cardiovascular disease

Is a "polypill" the answer to adherence in patients with cardiovascular disease (CVD)? Long-term medication adherence is notoriously poor in these patients. Even in high-income countries, adherence rates are only 50% in patients with coronary disease and 35% in those with those a history of stroke. Polypills combine several cardiovascular medications in one, including aspirin, a statin, and one or more blood pressure medications. A recent study was designed to see if these fixed-dose combination (FDC) pills would improve compliance, LDL cholesterol, and blood pressure levels compared to usual care. Two polypills were evaluated in the study. The first pill contained aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, and atenolol 50 mg. The second pill substituted hydrochlorothiazide 12.5 mg for atenolol. About 1000 patients received one of the FDCs with about 1000 controls continuing on usual care. After an average follow-up of 15 months, adherence was higher with the FDC vs usual care (86% vs 65%, $P < 0.001$), but there were only modest reductions in systolic blood pressure with FDC of about 2.6 mmHg and also modest reductions in LDL cholesterol of 4.2 mg/dL vs usual care. Subgroups of patients who showed poor adherence at baseline had higher levels of improvement in blood pressure and LDL cholesterol. There was no significant difference in cardiovascular events (5% FDC vs 3.5% usual care; relative risk, 1.45; 95% CI, 0.94-2.24; $P = 0.09$). The authors conclude that among patients at high risk of CVD, use of a FDC "polypill" improved medication adherence with small improvements in systolic blood pressure and LDL cholesterol (*JAMA* 2013;310:918-929). ■

FDA actions

Treatment of chronic pain has changed dramatically in the last 3 years, shifting from concern about undertreating patients with chronic pain to concern about the safety of overuse of extended-release and long-acting opioid analgesics. With overdoses of prescription opioids skyrocketing and far outnumbering overdoses from illegal drugs, the FDA has decided to take action. The agency is requiring labeling changes and new postmarketing study requirements for these drugs, including oxycodone (Oxycontin), controlled-release and extended-release morphine (MS Contin and Avinza), and fentanyl patches (Duragesic). The labeling changes are being required to "combat the crisis of misuse, abuse, addiction, overdose, and death from these drugs that have harmed too many patients and devastated too many families and communities." The updated indications for the extended-release and long-acting opioids state that these drugs are indicated "for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate." The goal of the postmarketing studies is to further assess the known serious risks of these drugs, including misuse, abuse, hyperalgesia, addiction, overdose, and death.

The FDA is also requiring additional labeling changes to fentanyl patches due to 32 accidental pediatric exposures, including 12 deaths in the last 16 years. The labeling requirements include printing the drug's name and strength in the clearly visible, long-lasting ink on the patch, in a color that is clearly visible to the patient and caregivers. The FDA also recommends that for disposal the patch be folded in half, sticky sides together, and flushed down the toilet immediately. These labeling changes apply to both generic fentanyl patches and brand-name Duragesic patches.

The FDA has approved the first generic version of the anticancer drug capecitabine (Xeloda), an oral chemotherapy agent used to treat metastatic colorectal cancer and metastatic breast cancer. The new generic is manufactured by Teva Pharmaceuticals while the branded product is manufactured by Roche. Two years ago, Roche settled a patent infringement case against Mylan over the same drug. It is unclear whether Mylan will now also launch its own generic. ■

Pharmacology Watch is going digital!

Beginning with the January issue, *Pharmacology Watch* can be found exclusively online. It will no longer be inserted in your newsletter. You will find the same high-quality, evidence-based updates in clinical pharmacology that you know and trust. You will be able to access the online edition anywhere. We hope this transition will better meet your needs as a subscriber. Stay tuned for more information about this digital transition. We will keep you posted on all the details!