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Internal Medicine

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ABSTRACT & COMMENTARY

Another Reason Why Sitting is Just No Darn Good For You

By Martin S. Lipsky, MD

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Dr. Lipsky is a retained consultant for Health Solutions & Strategies.

SYNOPSIS: Reducing sedentary time could have a protective effect and reduce the prevalence of BPH.

SOURCE: Lee HW, et al. The study about physical activity for subjects with prevention of benign prostatic hypertrophy. *Int Neurourol J* 2014;18:155-162.

Although not a life-threatening condition, benign prostatic hypertrophy (BPH) is one of the most annoying and troublesome problems that plagues aging males. Traditional risk factors, such as age, family history, and hormones, are considered the main risk factors for BPH, but lifestyle elements, such as physical activity (PA), smoking, and drinking, likely also play a role in developing BPH.[1,2] In this study, Lee and colleagues investigated the effects of PA on the risk of BPH in men older than age 40.

This Korean study used a cross-sectional survey performed annually for 3 years by trained interviewers to identify men with BPH and to collect information about their smoking, drinking, diet, and PA habits. Of an initial 779 men, 582 with urinary symptoms underwent a digital rectal exam, PSA screening, and rectal ultrasonography (US) to assess prostate size and to identify prostate cancer. BPH was defined as a prostate volume of 25 mL or more (by US) and a score of eight or more using the International Prostate Symptom Score. PA was broken into several variables, and levels of PA were assessed using questionnaires validated in previous studies.[3,4] The association of PA and BPH was analyzed by logic regression analysis using multivariable regression models.

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Internal Medicine
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Among the variables for PA selected, regular exercise, frequency of exercise, nonsedentary time, and leisure time PA did not show a statistically significant association with BPH. Sedentary time (hrs/day) was divided into three groups (low, medium, and high). Analysis showed that BPH was higher among those with the highest sedentary time (> 7 hours/day) and demonstrated a trend toward significance for a *P* value of 0.05 (OR, 1.72; 95% confidence interval, 0.96-3.09).

The authors concluded that reducing sedentary time could have a protective effect and reduce the prevalence of BPH.

■ COMMENTARY

More and more research is demonstrating that prolonged sitting raises the risk of dying from cardiac and metabolic diseases, even if you work out.[5,6] While one might not necessarily connect BPH with being sedentary, this study adds to the growing body of literature about the dangers of sitting. Even though this study is small and the results only trended toward significance, the benefits of avoiding prolonged sitting are accumulating, and it would seem beneficial to advise men with sedentary occupations to become more active at work. Suggestions might include standing more at work by using a standing desk, standing whenever talking on the telephone, trying to get up to walk a bit for a few minutes every hour, and if one must sit, consider using a "stability ball" to engage the core muscles while sitting. ■

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ABSTRACT & COMMENTARY

You Have Type I Diabetes ... Now The BAD News!

By Jeff Unger, MD

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

SYNOPSIS: A nationwide Swedish observational study of 33,915 patients with type 1 diabetes and 169,249 age and sex-matched controls demonstrated that patients with targeted A1C levels at or below 6.9% had a two-fold increase in cardiovascular mortality. A1C levels above 9.7% increased cardiovascular mortality 8- to 10-fold.

SOURCE: Lind M, et al. Glycemic control and excess mortality in type 1 diabetes. *N Engl J Med* 2014;371:1972-1982.

Type 1 diabetes is associated with an increased risk of mortality, secondary to microvascular (neuropathy, nephropathy) and macrovascular (coronary artery disease, stroke, peripheral vascular disease) complications. Mortality in patients younger than age 30 is most often explained by acute complications such as diabetic ketoacidosis and

hypoglycemia, whereas cardiovascular disease is responsible for death later in the lives of those with type I diabetes. The American Diabetes Association (ADA) recommends targeting the A1C level in "most patients" to <7 %. Patients with hypoglycemia unawareness, with limited life span, in nursing homes, with advanced complications, or with known cardiovascular disease should be treated to less stringent A1C levels of 7.5-8%. This study suggests that mortality rates in patients with type 1 diabetes is almost entirely secondary to cardiovascular disease, even among those individuals who are achieving their recommended levels of glycemic control. The authors noted that "unlike patients with type 2 diabetes, those with type 1 diabetes generally do not have excess rates of obesity, hypertension, or hypercholesterolemia; thus, the increased risks of death from … cardiovascular causes in those who have good glycemic control is unexplained."

One possible cause of the increased cardiovascular mortality in patients with diabetes achieving their targeted A1C levels involves the induction of oxidative stress. Vascular endothelial cells form physical and biological barriers between the vessel wall and circulating blood cells, with the endothelium playing an important role in the maintenance of vascular homeostasis. Central to this role is the endothelial production of nitric oxide (NO). Daily fluctuations in glucose levels result in oxidative stress, which impairs NO bioactivity. Endothelial cells exposed to oxidative stress generate reactive oxygen species, which, in turn, activate biochemical pathways, favoring microvascular and macrovascular complications. Patients in whom the hexosamine pathway has been activated will likely develop cardiovascular disease.

Although A1C remains the standard by which clinicians determine the efficacy of various antidiabetes regimens, we should now evaluate the means by which postprandial excursions might be mitigated in patients with type 1 diabetes. Off-label use of GLP-1 receptor agonists in combination with SGLT2 inhibitors might prove to be an intriguing means by which glycemic variability may be improved, saving the lives of our patients with type 1 diabetes. ■

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ABSTRACT & COMMENTARY

Peri-procedural Management of New Oral Anticoagulants

By Michael H. Crawford, MD

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

SOURCE: Beyer-Westendorf J, et al. Peri-interventional management of novel oral anticoagulants in daily care: Results from the prospective Dresden NOAC registry. *Eur Heart J* 2014;35:1888-1896.

Due to the short half-life and rapid onset of action of the new oral anticoagulants (NOACs), peri-procedural anticoagulant free time intervals should be shorter than with warfarin. Thus, there is uncertainty about the use of heparin bridging. These investigators from Germany analyzed the Dresden NOAC registry data to assess peri-procedural NOAC management and safety until 30 days post-procedure. The primary effectiveness outcome was a combination of centrally adjudicated cardiovascular events, including death. The primary safety outcome was the rate of major bleeding events.

Among the 2179 patients, 27% underwent procedures (16% minimal, 74% minor, and 10% major). Most of the patients were on rivaroxaban (76%) for stroke prevention in atrial fibrillation (81%). Peri-procedure, 1% of these patients had a major cardiovascular event and 1.2% had major bleeding. The rates of these complications were highest for major procedures (5% and 8%, respectively). During the 863 procedures, NOACs were continued in 22%, temporarily stopped in 49%, or stopped with heparin bridging in 29%. The median time of NOAC interruption was 3 days (2 days before and 1 day after the procedure). Major cardiovascular event rates were similar for those with and without heparin bridging (1.6% vs 0.8%, P = NS), but major bleeding complications were higher with heparin bridging (2.27% vs 0.5%, $P = 0.01$). However, on multivariate analysis, major procedures were independently associated with major bleeding (odds ratio [OR], 16.8; $P < 0.001$), but heparin bridging, which was more commonly used with major procedures, was not. The authors concluded that continuation or brief interruptions in NOAC therapy for most procedures is safe, but heparin bridging may be useful in selected high-risk patients.

■ COMMENTARY

This is the first report of the use of NOACs peri-procedurally and provides reassuring data about their safety and effectiveness. The data are similar to a post-hoc analysis of the RE-LY trial of dabigatran vs warfarin, looking at the patients that had a procedure done. Like the RE-LY analysis, this study shows low cardiovascular event rates, which in RE-LY were similar to warfarin. However, this study shows lower major bleeding rates (1.2%) vs RE-LY (4-5%), despite the fact that heparin bridging rates were higher in this study (30%) vs RE-LY (16%). Whether this difference is just due to the different study designs or to the different drugs used is unknown. RE-LY used dabigatran and this registry mainly represented rivaroxaban use (76%) with some dabigatran (23%) and apixaban use (1%).

The data on heparin bridging were also informative in that it did not reduce thromboembolic events, but did seem to increase major bleeding events. These results are somewhat similar to a meta-analysis of warfarin use with heparin bridging that showed reduced thromboembolic events, but increased bleeding (OR = 5). Thus, heparin bridging has been questioned recently. In this study, heparin bridging increased the absolute major bleeding rate, but it was not an independent factor in the multivariate analysis by the authors' definition. A major surgical procedure was the strongest predictor of major bleeding (OR, 16.8; $P < 0.001$); whereas heparin bridging was second (OR, 5; $P = 0.02$). So, concern about the bleeding risks of heparin bridging with NOACs persists and the authors suggest a case-by-case approach. In practice, the main reason to heparin bridge on warfarin therapy has been mechanical prosthetic valves, but NOACs are not indicated for this use, so presumably were not used for such patients in this German study. Thus, the need for heparin bridging with NOACs should be infrequent.

The limitations of this study are that it is observational. Also, the physicians were given no instructions on how to use NOACs. So there could be selection biases. In addition, event rates were low, especially for death. The strengths of the study include the large number of procedures (863), central adjudication of events, and a low rate of lost to follow-up (1%). Thus, until randomized trials are done (unlikely), this study represents the best current data we have on the use of NOACs peri-procedurally. It suggests that it is safe to either continue NOACs for more minor procedures or briefly stop them for more major procedures, and that heparin bridging is usually not needed and may increase bleeding risks. ■

ABSTRACT & COMMENTARY

Aortic Prosthetic Valve Type and Survival

By Michael H. Crawford, MD

SOURCE: Chiang YP, et al. Survival and long-term outcomes following bioprosthetic vs mechanical aortic valve replacement in patients aged 50 to 69 years. *JAMA* 2014;312:1323-1329.

This article originally appeared in the November 2014 issue of *Clinical Cardiology Alert*.

Bioprosthetic aorta valves are recommended for those > 70 years of age because of their reduced durability compared to mechanical valves and mechanical prostheses, which are recommended for those < 60 years because bioprosthetic valves deteriorate more rapidly in younger individuals. Those between ages 60 and 70 represent a gray zone, yet this is a decade in which most valve surgery is done. Thus, these investigators from Mount Sinai Medical Center in New York performed a retrospective cohort

analysis of primary, isolated aortic valve replacement in New York State over a recent 6-year period in patients aged 50-69 years. Patients with concomitant coronary or thoracic aortic surgery were excluded. The primary endpoint was all-cause mortality. Secondary endpoints included stroke, reoperation, and major bleeding. Follow-up was stopped at the end of 2012. Among the 4253 patients identified, 35% received bioprosthetic valves and 65% mechanical prostheses. Propensity score matching was done to adjust for differences in baseline characteristics and variations in practice between surgeons. This resulted in 1001 pairs of patients receiving the two valve types. There was no difference in 30-day mortality between the two groups (both 3%). Over a median follow-up of 11 years (range 0-17), there was no difference in survival. Actualized 15-year survival was 61% in the bioprosthetic group and 62% in the mechanical prosthesis group (HR mechanical vs bio 0.97; 95% CI, 0.83-1.14). Also, no difference in stroke rates were observed (8% bio vs 9% mechanical). Reoperation was significantly more common with bioprostheses (12% vs 7%). Major bleeding was more frequent with mechanical prostheses (7% bio vs 13% mechanical). The authors concluded that in patients aged 50-69 years there was no difference in 15-year survival with a bioprosthetic valve vs a mechanical prosthetic valve, but bioprosthetic valve patients had more reoperations and mechanical valve patients had more major bleeding. These findings suggest that bioprosthetic valves may be acceptable in patients aged 50-70 years.

■ COMMENTARY

The choice of a prosthetic valve type in the 50- to 70-year age range is always challenging, especially since people are living longer. Durability favors mechanical prostheses, but many patients balk at taking warfarin. In fact, as shown in this study, over the course of the study a shift toward bioprosthetic valves occurred. At the start of their study in 1997, 15% of patients had bioprosthetic valves. By 2012, it was 74%. Perhaps their cardiologists were saying what I have been saying: If your bioprosthesis deteriorates faster than you do, you will be able to have a percutaneous one put in. It is nice to see this study exhibit a relatively low 15-year reoperation rate for bioprostheses of 12%. The mortality for reoperation in this study was 9%, but some high-volume centers in New York had rates in the 2-5% range. Transaortic valve replacement mortality should be even lower in this group.

The current AHA/ACC guidelines recommend a mechanical valve for those < age 60, but these results would suggest that the bioprosthetic valve range can be extended to age ≥ 50 years, and this is what has been happening, at least in New York. The guideline recommendations are based on older randomized trials. Since then, prosthetic valve mortality and resistance to thrombosis have improved. It is unlikely that new randomized trials will be done, but I am comfortable going with this compelling data and patient desires to have bioprosthetic valves. The early successes of non-surgical valve replacement have also bolstered my confidence that this is a reasonable strategy.

Of course, there are limitations to this study. Not all potential confounders were accounted for in their model. Notably left out were important factors such as frailty, etiology of aortic valve disease, presence of other valve disease, extent of coronary artery disease, and left ventricular ejection fraction. Also, surgeons tend to put biological valves in sicker patients. In addition, they couldn't account for patients who moved out of state and didn't die. Despite these limitations, the study is in line with other smaller recent observational studies and with the trends in valve surgery and replacement today. Perhaps it's time to update the guidelines. ■

PHARMACOLOGY UPDATE

Hydrocodone Bitartrate Extended-release Tablets (Hysingla ER) CII

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 FDA has approved the first abuse-deterrent, extended-release form of hydrocodone. The extended-release formulation provides similar bioavailability to the immediate-release formulation

but with a lower maximum plasma concentration at steady state. This product is marketed by Purdue Pharma as Hysingla™ ER.

INDICATIONS

Hydrocodone extended-release tablets are indicated for the management of severe pain that requires around-the-clock, long-term opioid treatment and for which alternative options are inadequate.[1]

DOSAGE

The recommended starting dose for opioid-naïve patients is 20 mg every 24 hours.[1] Dose may be titrated every 3 to 5 days. To convert to hydrocodone ER tablets, a conversion factor is provided in the package insert. The total calculated hydrocodone daily dose is reduced by 25% for interpatient variability in relative potency of different opioids.[1]

Hydrocodone ER tablets are available as 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, and 120 mg.

POTENTIAL ADVANTAGES

This formulation is designed to reduce abuse. The tablet is difficult to crush, break, or dissolve. It forms a viscous hydrogel when tampered with that makes it difficult to inject or inhale.

POTENTIAL DISADVANTAGES

The drug should be used with caution in patients with difficulty swallowing.[1] Most common side effects are constipation, nausea, vomiting, upper respiratory inections, dizziness, headache, and somnolence.[1]

COMMENT

Hydrocodone is formulated to resist crushing, breaking, and dissolution and still retain some extended-release properties.[1] The approval of hydrocodone ER tablets was based both on its abuse-deterrent properties as well as its efficacy and safety.[1] In a non-dependent opioid abuser, the median drug liking score was 56 for the manipulated hydrocodone ER tablets for intranasal use compared to 100 for hydrocodone powder. For oral (chewed), the median score was 66, compared to 100. The scores were similar for likeliness to take the drug again. The efficacy and safety were shown in subjects (both opioid-naïve and experienced) with chronic low back pain (n = 905) who were adequately treated with their prior analgesic treatment. These patients entered into an open-label dose titration phase with hydrocodone ER. Rescue oxycodone immediate-release tablets (up to 10 mg) were permitted. Sixty-five (65%) reached a stable dose of hydrocodone ER and were subsequently randomized to the stable dose or matching placebo with hydrocodone taper. Hydrocodone ER provided statistically significant improvement in (30% or 50%) pain management compared to placebo at 12 weeks. The wholesale cost for Hysingla ER is approximately $3 per 10 mg.

CLINICAL IMPLICATIONS

This is the first abuse-deterrant form of hydrocodone to be marketed. The FDA approved a non-abuse-deterrant, long-acting form of hydrocodone last year (Zohydro, Zogenix Inc), and the FDA was roundly criticized because of the potential for abuse of the drug. For the new abuse-deterrant form, the FDA is requiring post-marketing studies on the effect of the abuse-deterrant properties on the risk of abuse and "consequences of that abuse in the community."[2] Drug abuse is a significant public health problem. As such, the FDA has encouraged manufacturers to produce abuse-deterrent opioid products.[3] Abuse-deterrent can be categorized in several ways: 1) physical/chemical barriers that can prevent chewing, crushing, cutting, etc.; 2) agonist/antagonists combinations; 3) aversion (product unpleasant effects; 4) delivery systems; 5) prodrugs; and 6) combinations of the above methods. Currently, several opioid products on the market use the physical/chemical barriers. These include oxycodone (Oxycontin), oxymorphone (Opana ER), and hydromorphone (Exalgo). In a survey of opioid-dependent subjects, oxycodone and hydrocodone were regarded as abuse drugs of choice (75%), with preference favoring oxycodone over hydrocodone (45% vs 29%) because of a better high.[4] ■

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Clinical Briefs

By Louis Kuritzky, MD

When Basal Insulin is Not Enough: Add Prandial Insulin or a GLP-1 Agonist?

SOURCE: Digenio A, et al. *Postgraduate Medicine* 2014;126:49-59.

Because of its strong efficacy, long-term durability, and predictability when titrated with algorithms employed in clinical trials, basal insulin remains a mainstay of treatment for type 2 diabetes patients who are not able to attain or maintain glycemic control with oral agents alone. Because diabetes is a progressive disorder, even patients who are initially well-controlled on basal insulin will likely require "fine tuning" of their diabetes regimen, usually with agents that preferentially affect postprandial glucose levels.

GLP-1 agonists (e.g., albiglutide, dulaglutide, exenatide, liraglutide) can impact postprandial glucose levels by means of blunting glucagon release, as well as modulating gastric emptying. In patients who have achieved fasting glucose control on basal insulin — when postprandial glucose is the target — would prandial insulin or a GLP-1 agonist better serve their needs?

Digenio et al reported on a "real-world" data analysis that looked retrospectively at a large population of General Electric Centricity electronic health records (n = 33,848) from persons who had either prandial insulin or a GLP-1 agonist added to basal insulin when glucose control was not adequate.

At follow-up 6 months to 1 year later, GLP-1 agonists and prandial insulin provided similar A1c reductions, but there were substantial differences in weight (gain with rapid acting insulin vs loss with GLP-1 agonist) and hypoglycemia (more frequent with insulin).

Current American Diabetes Association/ European Association for the Study of Diabetes guidelines include weight gain and risk of hypoglycemia as critical considerations for advancement of therapy. These data support the concept that in "real-world settings," GLP-1 agonists perform essentially as well as rapid-acting insulin, with less hypoglycemia and weight loss instead of gain. ■

Performance of Lorcaserin, a 5-HT2c Receptor Agonist, for Weight Loss

SOURCE: Aronne L, et al. *Postgraduate Medicine* 2014;126:7-18.

Clinicians may have some ambivalence about employing pharmacologic therapies for weight loss based on several reality-based observations: 1) some weight-loss drugs have been taken off the market after a brief sojourn due to serious toxicity (e.g., dexfenfluramine, of notorious Fen-Phen history); 2) some weight-loss drugs have been taken off the market after sustained use, even though early utilization seemed safe enough (e.g., sibutramine [Meridia]); and 3) many patients who embark on pharmacotherapeutic courses of weight-loss medication do not lose an amount of weight that is meaningful to them cosmetically (essentially all currently available medications).

One of the primary reasons that patients become dissatisfied with weight-loss pharmacotherapy is that the amount of weight lost does not typically result in achievement of ideal body weight or anything even close to that. Our role in the use of weight-loss agents should include re-orientation of the patient to include not just cosmetic effects of overweight/obesity, but long-term health consequences such as metabolic derangement, hypertension, diabetes, and cancer risks.

Currently available anorectic agents do perform well enough to achieve meaningful thresholds of weight reduction that lead to favorable metabolic changes. Two placebo-controlled clinical trials of lorcaserin (Belviq [BLOOM and BLOSSOM, combined n = 6380]) can inform us about what type of impact to anticipate with this 5-HT2c agonist.

At 1 year of lorcaserin treatment, 47% had lost at least 5% of their body weight and 22% had lost at least 10% of their body weight. As has been observed in numerous prior interventions that achieve this degree of weight loss, improvements in glycemic status, blood pressure, and lipids were also seen. Although an oral "magic bullet" to assist patients in attaining ideal body weight would be desirable, lorcaserin provides modest — but clinically relevant — weight loss. ■

Comparing GLP-1 Agonists: Dulaglutide vs Liraglutide

SOURCE: Dungan K, et al. *Lancet* 2014;384:1349-1357.

All currently available GLP-1 agonists (albiglutide, dulaglutide, exenatide, liraglutide) have four attributes in common: glucose-dependent stimulation of insulin secretion, glucose-dependent blunting of glucagon secretion, improved satiety, and delay in gastric emptying. These physiologic effects are associated with improved glucose control, less risk for hypoglycemia, and weight loss. Head-to-head trials can inform us about potential differences among these agents, but within this class, there is much more similarity than difference.

To date, head-to-head comparisons of GLP-1 agonists have suggested a modest A1c reduction advantage for liraglutide (Victoza). The most recently FDA-approved GLP-1 agonist, dulaglutide (Trulicity), is the subject of this head-to-head trial vs liraglutide. In the AWARD-6 trial, patients (n = 599) were randomized (open-label) to maximum as per-labeling dose of once-weekly dulaglutide 1.5 mg or once-daily liraglutide 1.8 mg.

The degree of A1c reduction at 26 weeks with dulaglutide (1.42%) was slightly greater than liraglutide (1.36%), which did meet the threshold for non-inferiority (the primary outcome of the study). The adverse effect profiles were very similar, except for a substantially lesser degree of hypoglycemia (0.34 vs 0.52 events/year) with dulaglutide.

Maximum dose once-weekly dulaglutide is non-inferior to maximum dose once-daily liraglutide. ■

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CME QUESTIONS

1. The cause of increased cardiovascular mortality in patients with type 1 diabetes is:

a. due to oxidative stress.
b. unknown
c. secondary to obesity.
d. correlated with hypertension.

2. Sitting is associated with which of the following diseases?

a. Cardivascular disease
b. Diabetes
c. Hypertension
d. BPH
e. All of the above

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