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INSIDE

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Fluoroquinolones and the Risk of Acute Kidney Injury

ABSTRACT & COMMENTARY

By Rahul Gupta, MD, MPH, FACP

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

Synopsis: *In men taking oral fluoroquinolone antibiotics, the risk of acute renal failure is doubled, and when combined with renin-angiotensin-system blockers, the risk increases by 4.5 fold.*

Source: Bird ST, et al. Risk of acute kidney injury associated with the use of fluoroquinolones. *CMAJ* 2013;185:E475-E482.

FLUOROQUINOLONES ARE COMMONLY PRESCRIBED BACTERICIDAL AGENTS with a wide spectrum of activity. In addition to the coverage against conventional gram-negative organisms, newer agents in this class have an expanded spectrum of activity against a variety of gram-positive and atypical organisms. One agent, moxifloxacin, even has increased activity against anaerobic bacteria. Additionally, fluoroquinolones are a promising new class of drugs for the treatment of tuberculosis.[1] Fluoroquinolones are also associated with a variety of known adverse effects. These include gastrointestinal, neurological, dermatological, respiratory, and cardiovascular effects. Similar to other antimicrobials, it is not uncommon to observe newer side effects with more extensive clinical use after regulatory approval. Case reports of tendon rupture and retinal detachment have indicated that these drugs may damage collagen and connective tissue.[2] Similarly, reports of acute kidney injury with the use of fluoroquinolones have been published, and it is often included in the product label in the list of potential, but uncommon, adverse reactions.[3] Since acute kidney injury is serious and potentially a fatal adverse event, it is essential that we attempt to quantify this risk.

In their study, Bird et al analyzed a Health Plan Claims Database that contained fully adjudicated medical and pharmacy claims for more than 68 million patients from U.S. health care plans. A nested case-control design of men aged 40-85 years between 2001 and 2011 was used for

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primary analysis. Data were extracted for 2 million men who had both prescription and medical coverage. Those men who met the inclusion criteria between January 1, 2001, and June 30, 2011, and who had 365 days of enrolment with no acute kidney injury were included. Men with a history of chronic kidney disease or dialysis were excluded since they may be more prone to acute kidney injury. Cases were defined as those admitted to hospital for acute kidney injury, and controls were admitted to hospital with a different presenting diagnosis. Drug exposure to oral fluoroquinolones such as ciprofloxacin, gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin, and norfloxacin was included. Ophthalmic, topical, and intravenous fluoroquinolones were excluded as the study was focused on outpatient-dispensed preparations with significant systemic absorption. Current use was defined as having a supply of or stopped taking a fluoroquinolone within a week of hospitalization. Recent users were those who had a prescription termination up to 60 days before admission and no drug taken within the week prior to admission. Past users had a prescription termination 61-180 days prior to admission and had no active prescriptions during days 0-60.

Researchers found that current fluoroquinolone use was associated with a 2.18 fold (95% confidence interval [CI] 1.74-2.73) higher adjusted relative risk (RR) of acute kidney injury compared with no use. The study researchers did not find any association between acute kidney injury and recent or past fluoroquinolone use. The researchers observed one additional case per 1529 patients given fluoroquinolones. Additionally, the dual use of fluoroquinolones and renin-angiotensin-system blockers was associated with a 4.46 fold (95% CI, 2.84-6.99) higher adjusted RR for acute kidney injury. The use of amoxicillin or azithromycin was not associated with acute kidney injury.

The limitations of this study included a lack of information on kidney injury severity, an inability to assess the risk associated with the dosage or duration of treatment, and residual confounding inherent in observational research.

■ COMMENTARY

There is no doubt that when serious infections occur, a variety of wide-spectrum antibiotics, including fluoroquinolones, are appropriate and required to be prescribed in order to save lives. However, this study finds more than a two-fold increased risk of acute kidney injury requiring hospital admission with the use of fluoroquinolone antibiotics among adult men. In clinical practice, when oral fluoroquinolones are prescribed, the potential for acute kidney injury is generally not a clinical consideration. However, the study results mean that physicians need to be aware of the risks of acute kidney injury when prescribing these drugs, albeit much lower in prevalence. Additionally, it is also a concern that a strong interaction with concurrent use of fluoroquinolones and renin-angiotensin-system blockers was found. Renin-angiotensin-system blockers are a widely prescribed and popular class of cardiovascular medications used for a variety of diagnoses. This certainly requires taking a cautious approach against the concomitant use of these two drug classes when possible. Interestingly enough, the findings of absence of an increased risk of acute kidney injury with other antibiotics such as amoxicillin and azithromycin would support the hypothesis that this potential adverse association of fluoroquinolones with acute kidney injury is not a class effect of all antibiotics. That would allow physicians to use other classes of antibiotics in high-risk patients such as those on renin-angiotensin-system blockers or with pre-existing renal disease. ■

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MORES Power to You

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

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

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

Synopsis: *A simple decision support tool can help identify which men should be screened with dual-energy x-ray absorptiometry (DEXA) for osteoporosis.*

Source: Cass AR, Shepherd AJ. Validation of the Male Osteoporosis Risk Estimation Score (MORES) in a primary care setting. *J Am Board Fam Med* 2013;26:436-444.

THIS CROSS-SECTIONAL STUDY'S PURPOSE WAS TO VALIDATE THE Male Osteoporosis Risk Estimation Score (MORES) in a primary care setting; it had been previously validated in the National Health and Nutrition Examination Survey (NHANES) III.[1] The subjects were men who were attending the University of Texas Medical Branch, Galveston, family medicine, general internal medicine, and geriatric medicine outpatient clinics from 2008-2011. Inclusion criterion was age ≥ 60 years. Excluded were men with a history of osteoporosis, bone disease, or bilateral hip replacement; men who were taking bone-conserving medications (e.g., bisphosphonates); and men who weighed > 300 pounds (the DEXA scanner couldn't handle them).

The investigators enrolled 386 men: 40, who did not report for the DEXA scan, were excluded, leaving 346. They were an average age of 70 years with a mixed ethnic population (white, black, Hispanic, and Asian). The criterion for osteoporosis was a T-score ≤ -2.5 at the femoral neck or the total hip. Using this, 15 men (4.3%) met the criterion. An additional 19 had severe osteopenia. The rates of other potential risk factors for osteoporosis (previous fragility fracture, history of rheumatoid arthritis, heavy alcohol use, chronic obstructive pulmonary disease [COPD], and glucocorticoid use) were all < 10%.

How did MORES perform? The table below gives the raw data from which the sensitivity and specificity were calculated.

Table 1
MORES Performance Data

	Osteoporosis present	Osteoporosis absent
MORES positive	12	99
MORES negative	3	232

The sensitivity was 0.80 (95% confidence interval [CI], 0.52-0.96), and the specificity was 0.70 (95% CI, 0.64-0.74). About one-third (32.1%) of all subjects were MORES positive. The authors calculate that the number needed-to-screen (NSS) and to be referred for DEXA to prevent one additional hip fracture (assuming treatment over 10 years) was 654 (95% CI, 485-1132). Universal DEXA screening had an NSS of 1604.

■ COMMENTARY

MORES has been around for 7 years now. The authors of that study, two of whom authored this one, did logistic regression modeling to choose the variables that yielded a good fit to the data, and then simplified it. MORES is ridiculously easy to score. It considers just three variables: age, weight, and history of COPD. Points are awarded as described in the table below. A positive score is ≥ 6.

Table 2
MORES Scoring

Risk Factor	Points
Age (years)	
≤ 55	0
56-74	3
≥ 75	4
Weight (kg)	
≤ 70	6
71-80	4
> 80	0
COPD	3

As we have previously discussed in *Internal Medicine Alert*, a really good clinical decision tool is 95% sensitive and 95% specific.[2] Sensitivity (or true positive rate) measures the proportion of people identified with a condition to those who truly have it. Specificity (or true negative rate) measures the proportion of people identified as not having a condition to those who truly don't. MORES doesn't quite make the grade of "really good," coming up short on the specificity side. (The 95% CI for sensitivity contains 95%, so it is possible that sensitivity could be "really good.")

This is a good time to review what, according to the Frame Criteria, makes a good screening test.

1. The disease must have a significant effect on quality or quantity of life.
2. Acceptable methods of treatment must be available.
3. The disease must have an asymptomatic period during which detection and treatment significantly reduce morbidity and/or mortality.
4. Treatment in the asymptomatic phase must yield a therapeutic result superior to that obtained by delaying treatment until symptoms appear.
5. Tests must be available at reasonable cost to detect the condition in the asymptomatic period.
6. The incidence of the condition must be sufficient to justify the cost of screening.[3]

How do osteoporosis and MORES stack up? Osteoporosis, especially if it results in a fracture, can have a significant effect on quality and quantity of life. In fact, men do worse than women after a hip fracture.[4] Acceptable methods of treatment are available for women,

but the evidence that the same methods are effective in men is not as extensive.[5] Osteoporosis does have an asymptomatic period, and treating it during this period is better than waiting for a fracture, at least in women. Administering MORES is very inexpensive, especially if it's self-administered or done by a medical assistant; a DEXA costs about $200 if your patient doesn't have insurance.[6] In this study, the incidence of osteoporosis was 4.3%. In the NHANES 2005-2006, it was 2% at the femoral neck in men and 10% in women.[7] Whichever number you choose, the low cost of administering MORES makes screening cost-effective. Although one-third of the subjects would have been referred for DEXA, two-thirds wouldn't have and < 1% (3/346) would have been missed.

The U.S. Preventive Services Task Force, my go-to source for screening advice, has currently concluded that there is not enough evidence to recommend for or against male osteoporosis screening.[8] Ideally, before I would recommend adopting it, there would be a number of randomized, controlled studies of MORES to "pre-screen" for osteoporosis in men, and they would have fracture prevention as the primary outcome. That would be a long wait. In the meantime, I think we can extrapolate from the screening and treatment trials of osteoporosis in women and use MORES for men. ■

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Poor Sleep Quality May Predict Preclinical Alzheimer's Disease

ABSTRACT & COMMENTARY

By Alan Z. Segal, MD

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Dr. Segal reports no financial relationships relevant to this field of study. This article originally appeared in the July 2013 issue of Neurology Alert.

Synopsis: *Poor sleep quality may predict future Alzheimer's disease and may play a pathogenic role in its etiology.*

Source: Ju YE, et al. Sleep quality and preclinical Alzheimer disease. *JAMA Neurol* 2013;70:587-593.

Insomnia is a common complaint among adults and it is well recognized that mental performance can be impaired by poor sleep. Both difficulty falling asleep and trouble staying asleep have been associated with poor cognitive function in cross-sectional elderly cohorts. Sleep impairments leading to excessive daytime sleepiness also have been shown to contribute to cognitive decline. Getting more sleep, however, clearly is not the solution. The quantity of sleep has been shown to have variable effects, with some studies showing a U-shaped relationship between sleep duration and cognition. The Nurse's Health Study, for instance, suggested that subjects getting 7 hours of sleep had optimal functioning compared to those getting 5 or 9 hours of sleep. Sleep may be further compromised by obstructive sleep apnea, which not only causes oxidative stress, but also disrupts sleep architecture and has been shown to increase the risk of dementia. Snoring itself, in the absence of documented sleep apnea, has shown similar results.

Most prior studies have used subject self-report surveys or sleep diaries to assess variables such as sleep efficiency — defined as the actual time asleep divided by the total time in bed. Formal polysomnography eliminates the imprecision introduced by such patient estimates, but is an artificial environment which itself limits sleep efficiency. Sleep may be measured at home using movement detection (actigraphy) as in the current study or with increasingly available technologies, such as smartphone apps that capitalize on embedded accelerometers and movement detectors to create modestly accurate sleep maps.

In the current study, cognitively normal subjects wore actigraphs for 2 weeks to measure total sleep time and efficiency. Sleep was then correlated with levels of cerebrospinal fluid (CSF) ß-amyloid (Aß) 42. It has been shown that low soluble Aß42 levels in the CSF are suggestive of insoluble amyloid deposition in brain senile plaques. This decrease in CSF Aß42 may predate clinical Alzheimer's disease by 15 years. Low Aß42 levels have also been correlated with positive findings on amyloid PET imaging.

Among subjects with Aß42 levels < 500 pg/mL, sleep efficiency was 80.4% compared with those having Aß42 levels > 500 pg/mL, who had a sleep efficiency of 84.7% (P = 0.04). Frequent napping (3 or more days per week) was also associated with amyloid deposition (31.2% among low Aß42 subjects compared with 14.7% in the high Aß42 group, P = 0.03). Total sleep time did not differ between

the two groups; however, low Aß42 subjects spent a longer total time in bed in order to obtain adequate sleep.

Because the relationship between sleep efficiency and Aß42 could be bidirectional, the investigators also used Aß42 as an outcome variable and dichotomized sleep into poor (< 75% efficiency) vs good (> 89% efficiency) groups. Subjects with poor sleep had a 5.6-fold increased risk of having low Aß42 levels compared to subjects with good sleep quality.

As the authors nicely demonstrate in a cyclical flow diagram, these data clearly suggest a two-way street. Aß accumulation may be disruptive of sleep and conversely impaired sleep may promote Aß deposition. There are multiple mechanisms by which amyloid plaques may disrupt sleep circuits in the basal forebrain. This pathogenesis is supported by transgenic mouse models prone to amyloid plaques. These animals have markedly impaired sleep-wake cycles. Interestingly, when such mice are immunized with Aß, preventing plaque formation, sleep architecture is restored. Because Aß is secreted during active neuronal activity, the investigators further hypothesize that prolonged wakefulness results in a higher concentration of amyloid and therefore an increased plaque burden.

Multiple other behavioral factors that impair sleep in the elderly may further amplify the relationship between poor sleep and Aß. Depression, schedule changes related to retirement (due to cognitive decline or merely due to age), lack of exercise, and institutionalization (impairing regular light exposure) all may potentially contribute to Aß deposition. As the authors note, however, Aß secretion also may have a strong circadian influence. This would vary independent of the subject's sleep-wake state.

■ COMMENTARY

These data confirm that poor sleep efficiency may play a pathogenic role in Alzheimer's disease. This study has important strengths in its use of actigraphy to quantify sleep and also its use of Aß42 as a biomarker of Alzheimer's disease risk in place of psychometric data. Of note, these subjects all underwent exhaustive neuropsychiatric testing, confirming them to all be normal. Aß42 in a cognitively normal person, however, is not equivalent to a future diagnosis of Alzheimer's disease. Low CSF levels of Aß42 may not consistently correlate with pathologically confirmed amyloid plaques, and these plaques may not be uniformly predictive of Alzheimer's disease. As the authors observe, the use of amyloid imaging and the inclusion of individuals with elevated CSF tau, planned in future studies, could further strengthen the connection between sleep disruption and preclinical Alzheimer's disease.

Despite these limitations, it is clear that addressing reversible sleep disorders, such as obstructive sleep apnea, may be an important step toward addressing Alzheimer's disease in its earliest stages. Sleep disorders, including sundowning, excess daytime napping, and insomnia occur in up to 40% of patients with Alzheimer's disease. Although these phenomena may be the consequence of Alzheimer's disease, they might also mark a population of people for whom Alzheimer's disease is in the future and might be prevented. ■

Pharmacology Update

Dolutegravir Tablets (Tivicay®)

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.

DOLUTEGRAVIR, A ONCE DAILY HIV-1 INTEGRASE STRAND transfer inhibitor (INSTI), has been approved by the FDA. The drug joins raltegravir and elvitegravir as the three INSTIs currently marketed. These drugs exert their antiviral activity by inhibiting the insertion of viral genome into the chromosome of the host cell. Both raltegravir and dolutegravir are available as single agents. Elvitegravir is only available as part of a four-drug combination (Stribild). Dolutegravir is manufactured by GlaxoSmithKline for ViiV Healthcare and marketed as Tivicay.

Indications

Dolutegravir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infections in adults and children 12 years of age or older weighing at least 40 kg.[1]

Dosage

The recommended dose is 50 mg once daily taken without regard to meals.[1] However, it should be taken 2 hours before or 6 hours after taking a cation (e.g., aluminum, magnesium) containing antacid or laxative, sucralfate, oral iron supplement and calcium supplement, or buffered medications. The dose is 50 mg twice daily in patients coadministered with potent UGT1A/CYP3A inducers: efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin. The dose is also 50 mg twice daily in patients who have been treated with an integrase inhibi-

tor with selected INSTI-resistance associated mutations. The pediatric dose is 50 mg once daily or 50 mg twice daily if UGT1A/CYP3A inducer is coadministered.

Dolutegravir is available as 50 mg tablets.

Potential Advantages

Dolutegravir may have limited cross-resistance to raltegravir and has shown activity in treatment-experienced subjects with raltegravir-resistance.[1,2] In vitro data suggest that it may have a higher genetic barrier to resistance compared to raltegravir and elvitegravir.[3] Dolutegravir is generally dosed once daily compared to twice daily for raltegravir.

Potential Disadvantages

Dolutegravir has been associated with elevated (grade 2-4) ALT (8%), AST (6%), cholesterol (8%), lipase (8%), hyperglycemia (12%), and elevated serum creatinine (mean change of 0.11 mg/dL).[1] Adverse events include nausea, diarrhea, nasopharyngitis, upper respiratory infections, and headache.[4,5]

Comments

Dolutegravir is a HIV-1 integrase inhibitor similar to raltegravir and elvitegravir. The efficacy and safety of dolutegravir were studied in five clinical trials, including two treatment-naïve, one treatment-experienced, one integrase inhibitor-experienced, and one pediatric trial.[1,4,5] In treatment-naïve subjects, dolutegravir (50 mg once daily, n = 403) was compared to raltegravir (400 mg twice daily, n = 405) in combination with tenofovir/emtricitabine or abacavir/lamivudine with a non-inferiority margin of 10%.[1,4] At 48 weeks, the proportion of subjects with virologic response (HIV-1 RNA < 50 copies/mL) was 88% for dolutegravir and 86% for raltegravir. No treatment-emergent resistance occurred with dolutegravir. However, one patient had integrase inhibitor resistance (6%) and four had NRTI resistance (21%).[4] In the second treatment-naïve study, subjects were randomized to dolutegravir and abacavir/lamivudine (n = 414) or efavirenz/emtricitabine/tenofovir (n = 419). The proportion of subjects achieving virologic response was 88% and 81%, respectively.[1] In the treatment-experienced study, subjects were randomized to dolutegravir (n = 354) or raltegravir (n = 361) with investigator-selected background therapy.[1,5] At 48 weeks, virologic response was 79% and 70%, respectively, suggesting an advantage for dolutegravir. The study with integrase inhibitor-experienced subjects included those who had virological failure and current or historical evidence of raltegravir and/or elvitegravir resistance (n = 183). In this study, subjects received dolutegravir 50 mg twice daily while continuing a failing regimen for 7 days, then dolutegravir with an optimized regimen from day 8. Mean reduction from HIV-RNA at day 8 was 1.4 $\log_{10}$ and response at week 24 was 63%. The response rate was 36% with integrase inhibitor resistance substitution (mutation) at Q148 at baseline. Efficacy was evaluation in a small pediatric population (n = 24) showing a 70% response rate.[1] The adverse reaction profile of dolutegravir and raltegravir appears to be similar. The rate of discontinuation due to adverse events was 2% for dolutegravir and raltegravir.[1,4]

Clinical Implications

Dolutegravir provides another INSTI for the treatment of HIV-1 infections as an alternative to raltegravir. Currently, the combination of raltegravir/tenofovir/emtricitabine is one of the recommended regimens with strong evidence for treatment-naïve patients.[6] The quad pill (elvitegravir/cobicistat, emtricitabine/tenofovir) was recommended with moderately strong evidence.[7] The wholesale cost for dolutegravir (50 mg once daily) is $1175 per 30-day supply compared to $1074 for raltegravir (400 mg twice daily). ■

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CME Questions

1. **In the study by Bird et al, intake of oral fluoroquinolones increases the risk of acute kidney injury by:**
   a. by two-fold.
   b. by three-fold.
   c. by four-fold.
   d. has no impact.

2. **Which of the following statements about the MORES clinical decision tool is true?**
   a. It assigns points for gender, age, weight, and COPD to calculate a risk score.
   b. It correctly identified the proportion of men without osteoporosis as 70%.
   c. It has been shown to reduce the morbidity and mortality of osteoporotic fractures.
   d. About one-third of the subjects had osteoporosis.

Clinical Briefs

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

Dr. Kuritzky is an advisor for Endo, Kowa, Pricara, and Takeda.

Our Newest Pharmacologic Class for Treatment of Diabetes: SGLT2 Inhibitors

Source: Polidori D, et al. Canagliflozin lowers postprandial glucose and insulin by delaying intestinal glucose absorption in addition to increasing urinary glucose excretion: Results of a randomized, placebo-controlled study. *Diabetes Care* 2013;36:2154-2161.

The role of the kidney in glucose regulation has been underappreciated. Although perhaps counterintuitive, after persistent exposure to elevated glucose levels in the glomerular filtrate presented to the proximal renal tubule, the kidney adapts by reabsorbing *increased* amounts of glucose, thereby *increasing* blood sugar. The sodium glucose cotransporter (SGLT2) receptor is the primary pathway for renal tubular glucose reabsorption; blockade of this receptor results in enhanced urinary glucose excretion. Currently, the only FDA-approved agent for blockade of the SGLT2 receptor is canaglifozin.

In addition to potent SGLT2 receptor blockade, it has been suspected that canaglifozin might affect intestinal absorption of glucose by its modest inhibition of intestinal SGLT1. Polidori et al tested the impact of canagliflozin SGLT1 inhibition by examining the rate of gastrointestinal glucose absorption in healthy volunteers following a 600-kcal mixed-meal tolerance test.

Canagliflozin produced a very modest reduction in glucose absorption over a 6-hour interval (about 6%). The effects were accentuated in the early postprandial intervals, indicating a slowed absorption of glucose that was not attributable to delayed gastric emptying. Blunting of early postprandial glucose absorption should have a favorable effect on postprandial glucose excursions in diabetics.

Although enhanced urinary glucose excretion is the primary mechanism of plasma glucose lowering by SGLT2 inhibitors, modest gastrointestinal SGLT1 inhibition also appears to impact postprandial glucose excursion. ■

Bariatric Surgery vs Intensive Medical Therapy for Diabetes

Source: Kashyap SR, et al. Metabolic effects of bariatric surgery in patients with moderate obesity and type 2 diabetes: Analysis of a randomized control trial comparing surgery with intensive medical treatment. *Diabetes Care* 2013;36: 2175-2182.

The benefits of bariatric surgery (BAS) are increasingly recognized for obese patients with type 2 diabetes mellitus (T2DM). Indeed, the mechanisms by which diversionary surgery (e.g., gastric bypass) produces such prompt and dramatic remission in diabetic patients are still being elucidated. Long-term observational data on BAS for persons with severe obesity (body mass index [BMI] > 40) confirm durable weight reduction, improved control of diabetes, and even suggest reduced mortality.

Few trials have directly compared the efficacy of BAS with intensive medical treatment (IMT). Kashyap et al randomized T2DM subjects (n = 60) with moderate obesity (mean BMI = 36) to one of two BAS interventions (gastric sleeve or gastric bypass) or IMT in the Surgical Therapy And Medications Potentially Eradicate Diabetes (STAMPEDE) trial. Currently reported data include outcomes at 24 months.

In essentially every category assessed, BAS patients had superior outcomes to IMT. No BAS-related deaths occurred. At 2 years, degree of A1c control, LDL, HDL, total cholesterol, triglycerides, and CRP were all more improved in the BAS patients than in the IMT patients.

When comparing outcomes in the two BAS groups, even though weight loss was similar between gastric sleeve and bypass surgery, the latter achieved greater improvements in truncal fat reduction, leptin, insulin sensitivity, beta cell function, and incretin responses. BAS is more effective for multiple metabolic markers than IMT over the long term in T2DM patients. ■

Psoriasis and Risk for New Onset Diabetes

Source: Khalid U, et al. Psoriasis and new-onset diabetes: A Danish nationwide cohort study. *Diabetes Care* 2013; 36:2402-2407.

Inflammatory disorders like rheumatoid arthritis (RA) and psoriasis (PSOR) have recently been confirmed to be risk factors for adverse cardiovascular (CV) events, although the precise pathways through which such risk occurs remain controversial. Some have even gone so far as to say that RA should be considered an independent CV risk factor of equal potency to the already registered risk factors like hypertension, history of premature cardiovascular death, etc. Since PSOR and RA share common inflammatory pathways, it's perhaps not surprising that both are associated with CV adversity.

To date, the relationship between PSOR and diabetes mellitus (DM) has been controversial. Since DM is a major contributor to CV events, if PSOR and DM are related, that would account for some of the increased CV risk.

Khalid et al report on an analysis of the PSOR-DM relationship discerned through a 12-year follow-up of Danish persons ≥ 10 years of age (n = 4,614,807). They studied the incidence of new-onset DM in PSOR subjects vs controls. A graded linear association between PSOR and new onset DM was found. Compared to the reference population, the incidence of DM in persons with mild PSOR was almost doubled, and in severe PSOR, nearly tripled. ■

Mobitz I or Mobitz II AV Block?

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

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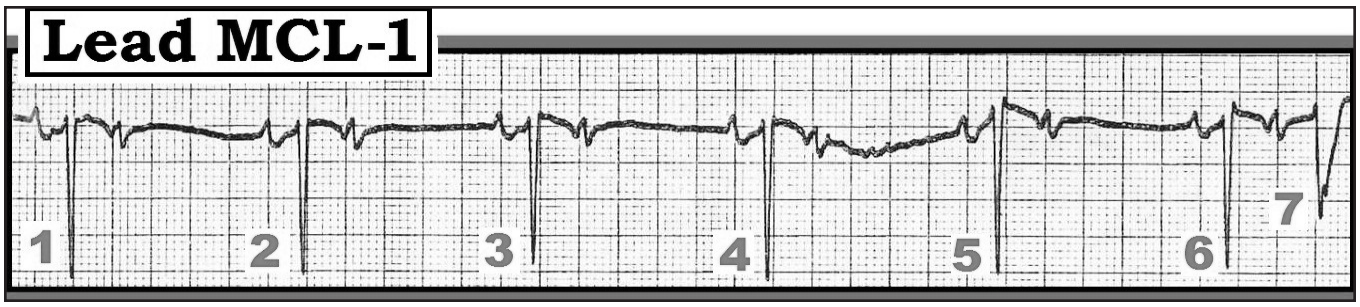

Figure — Lead MCL-1 rhythm strip. Is this Mobitz I or Mobitz II?

Scenario: Interpret the lead MCL-1 rhythm strip shown in the figure. Does this rhythm represent Mobitz I (*Wenckebach*) or Mobitz II AV block? Is a pacemaker likely to be needed?

Interpretation: Neither Mobitz I nor Mobitz II is present. Rather than AV block, the rhythm in the figure represents an insightful example of the "mischief" that *blocked* premature atrial contractions (PACs) can cause, especially when PACs are frequent.

All forms of AV block are characterized by the presence of similar morphology P waves that occur with a regular (or at least fairly regular) P-P interval. Requiring similar P wave morphology when assessing an arrhythmia for AV block eliminates other potential causes of bradycardia such as wandering pacemaker, sinus pauses, and sinus arrest. So while occasional PACs with differing P wave morphology may be seen, the presence of constantly changing P wave morphology should suggest some phenomenon other than AV block.

With regard to regularity of the atrial rate, slight variation in the P-P interval may be seen with AV block when there is underlying sinus arrhythmia. However, gross variation in the P-P interval is usually *not* seen when the primary problem is AV block.

Keeping these two points in mind allows us to rule out AV block as the cause of the rhythm disturbance in the figure. The P-P interval is clearly irregular. In fact, there is a pattern to this P-P variation (alternating *short-long* cycles) produced by the finding that every other P wave is early (premature). The underlying rhythm is atrial bigeminy (every other beat is a PAC). In addition, P wave morphology changes from one beat to the next. Sinus P waves are seen as a biphasic (positive-then-negative) deflection preceding beats 1, 2, 3, 4, 5, and 6. In contrast, P waves buried within the ST-T wave of beats 1 through 6 are triphasic (small negative, then positive, then narrow negative), deflections that clearly look *different* in morphology than the sinus P waves. These triphasic P waves arise from an atrial site other than the sinus node.

In summary, the underlying rhythm in the figure is atrial bigeminy. The very early occurring PACs (buried within the T waves of beats 1 through 5) are non-conducted because they occur during the absolute refractory period. In contrast, the PAC that occurs within the T wave of beat 6 *is* conducted, albeit with aberration (because it presumably occurs during the relative refractory period). No AV block is present. No pacemaker is needed. Clinically, blocked PACs are much more common than any form of heart block. They may be recognized by careful attention to P wave regularity, morphology, and careful search for the "telltale" notching of a hidden PAC within T waves preceding a relative pause on the tracing.

For more information on the basics of AV block, please visit: https://www.kg-ekgpress.com/av_block_pdf_file/. ■

In Future Issues:

Antibiotic Prescribing for Adults in Ambulatory Care

Effect of Dabigatran on Referrals to and Switching from Warfarin

PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

More Side Effects of Fluoroquinolones Coming to Light

In this issue: New side effects of fluoroquinolones; probiotics and antibiotic-related diarrhea; prostate cancer risk and 5-ARIs; and FDA actions.

New study finds dysglycemia risk

Fluoroquinolones, such as levofloxacin, ciprofloxacin, and moxifloxacin, are useful broad-spectrum antibiotics, but they have been associated with tendinopathy, including tendon rupture and QT interval prolongation. Now, two new potential side effects are coming to light. In a new study from Taiwan, more than 78,000 diabetic patients who received fluoroquinolones were monitored for dysglycemia, including hyperglycemia and hypoglycemia. The study looked at users of levofloxacin, ciprofloxacin and moxifloxacin, cephalosporins, and macrolides. The absolute risk of hyperglycemia was 6.9 per 1000 for moxifloxacin and 1.6 for macrolides. The risk for hypoglycemia was 10.0 for moxifloxacin and 3.7 for macrolides. The adjusted odds ratios for hyperglycemia compared to macrolides were: moxifloxacin 2.48 (95% confidence interval [CI], 1.50-4.12), levofloxacin 1.75 (95% CI, 1.12-2.73), and ciprofloxacin 1.87 (95% CI, 1.20-2.93). For hypoglycemia, the adjusted odds ratios were moxifloxacin 2.13 (95% CI, 1.44-3.14), levofloxacin 1.79 (95% CI, 1.33-2.42), and ciprofloxacin 1.46 (95% CI, 1.07-2.00). The risk of hypoglycemia associated with moxifloxacin was even higher if patients were taking insulin. The authors suggest that fluoroquinolones, especially moxifloxacin, are associated with severe dysglycemia in diabetic patients and that clinicians should "prescribe quinolones cautiously" in diabetic patients (*Clin Infect Dis* published online August 14, 2013. DOI: 10.1093cid/cit439). In related news, the FDA is requiring labeling changes for fluoroquinolones regarding the risk of neuropathy. The FDA Drug Safety Communication states that "serious nerve damage potentially caused by fluoroquinolones may occur soon after these drugs are taken and may be permanent." The warning is for both oral and parenteral forms of the drugs, but not topicals. The FDA recommends that if a patient develops symptoms of peripheral neuropathy associated with a fluoroquinolone, the drug should be stopped immediately and the patient should be switched to a non-fluoroquinolone antibiotic. Further information can be found at the FDA's website at www.fda.gov/Safety/MedWatch. ■

Probiotics and antibiotic-related diarrhea

Probiotics may not prevent antibiotic-associated diarrhea (AAD), including *Clostridium difficile* infections. That was the finding of a randomized, double-blind, placebo-controlled trial in nearly 3000 inpatients aged ≥ 65 years who were exposed to one or more oral or parenteral antibiotics. Patients were randomized to a multistrain preparation of lactobacilli and bifidobacteria or placebo for 21 days. The rate of AAD was 10.8% in the probiotic group and 10.4% in the placebo group ($P = 0.71$). *C. difficile* was uncommon and occurred in 0.8% of the probiotic group and 1.2% of the placebo group ($P = 0.35$). The authors state that "we identified no evidence that a multistrain

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preparation of lactobacilli and bifidobacteria was effective in the prevention of AAD or CDD." (*Lancet* published online August 8, 2013. doi: 10.1016/S0140-6736(13)61218-0). An accompanying editorial wonders if this study can tip the balance of probiotic evidence, as it was a rigorously performed study vs previous small studies showing a positive effect. But, the current study used only two types of non-pathogenic bacteria (doi: 10.1016/S0140-6736(13)61571-8). Still, the cost effectiveness of routine probiotic use must be questioned based on this study. ■

Prostate cancer risk and 5-ARIs

The debate regarding 5-alpha reductase inhibitors (finasteride [Proscar] and dutasteride [Avodart]) and the risk of prostate cancer continues. Despite good evidence that the drugs reduce the overall risk of prostate cancer, there is also evidence that the drugs may increase the risk of high-grade prostate cancers (Gleason score 7-10). This was a finding of the Prostate Cancer Prevention Trial (PCPT) that was published in 2003. That finding was recently questioned in a study published in the *British Medical Journal* that found no risk of higher-grade prostate cancers (*BMJ* 2013;346:f3406, reported in the August *Pharmacology Watch*). Now, 10 years after the PCPT was originally published as an 8-year study, the 18-year follow-up has been published in the *New England Journal of Medicine*. Of the nearly 19,000 men who underwent randomization in the PCPT, prostate cancer was diagnosed in 10.5% of the finasteride group and 14.9% of the placebo group, a 30% reduction in the rate of prostate cancer (relative risk 0.70; 95% CI, 0.65-0.76; $P < 0.001$). But all of the reduction was in lower-grade prostate cancers. There was a slightly higher rate of high-grade cancer in the finasteride group (3.5% vs 3.0%, $P = 0.05$), but there was no difference in overall mortality. There was also no increase in mortality in men diagnosed with high-grade prostate cancer. The authors conclude that finasteride reduced the risk of prostate cancer by about one-third, and although high-grade cancer was more common in the finasteride group, there was no difference in overall mortality or survival after the diagnosis of prostate cancer (*N Engl J Med* 2013;369:603-610). Dutasteride was also studied in the REDUCE trial and similarly found lower rates of low-grade prostate cancers but increased rates of higher-grade cancers (*N Engl J Med* 2010;362:1192-1202). Some have argued that the higher rate of high-grade cancers is due to higher surveillance and "detection bias," but regardless of the cause, it is reassuring to know that there is no higher risk of mortality, at least in the PCPT. The FDA changed the labeling to both finasteride and dutasteride in 2011 regarding the increased risk of high-grade prostate cancers. ■

FDA actions

The FDA has issued a Drug Safety Communication regarding a case of progressive multifocal leukoencephalopathy (PML) in a patient who was taking fingolimod (Gilenya) for the treatment of multiple sclerosis. This is the first reported case of PML associated with fingolimod in patients who had not previously taken natalizumab (Tysabri). The patient, who lives in Europe, had been on the drug for about 8 months and had previously taken interferon beta-1a, azathioprine, and steroids. Novartis, the manufacturer of fingolimod, indicated it is possible that the patient had PML prior to starting the drug. PML is a rare neurologic disease caused by latent infection with the JC virus. It has been associated with immunosuppressive drugs, including natalizumab.

The FDA has approved a new topical agent to treat facial redness in adults with rosacea. Brimonidine, an alpha-2 agonist, is currently used as an ophthalmic preparation for treating glaucoma. The drug constricts dilated facial blood vessels for up to 12 hours. It is approved in a 0.33% topical gel that is applied once daily. Patients with depression, coronary artery disease, Raynaud's, or other conditions that may be exacerbated by an alpha agonist should use the drug with caution. Brimonidine gel is marketed by Galderma as Mirvaso.

The FDA has approved dolutegravir, a new once-daily HIV integrase inhibitor. It is the third integrase inhibitor on the market after raltegravir and elvitegravir. The drug is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infections in adults and children ≥ 12 years of age weighing at least 40 kg. It may be used in treatment-naïve patients or treatment-experienced patients, including those who have previously taken an integrase inhibitor. Approval was based on four trials in more than 2500 patients that showed efficacy in combination with other antiretrovirals. A fifth trial showed efficacy in HIV-infected children as young as 12 who had not taken an integrase inhibitor. Dolutegravir is marketed by ViiV Healthcare as Tivicay. ■