DRUGMonitor

Brief summaries of recent drug approvals, interactions, and adverse events

Disparities in Adherence

Women and black patients with cardiovascular disease have markedly higher mortality rates than that of white men and are less likely to undergo cardiovascular procedures, such as cardiac catheterization after acute myocardial infarction. Women also have very different patterns of adherence: Black patients are 67% more likely to stop statin therapy, for instance, and women have 10% lower odds of adhering to antihypertensive and lipid-lowering therapy.

These differences are likely to be clinically significant, but little attention has been given to the problem, say researchers from Brigham and Women's Hospital and Harvard Medical School in Boston, Massachusetts; Columbia University Medical Center in New York, New York; CVS Caremark, Inc. in Woonsocket, Rhode Island; and the University of Toronto in Ontario, Canada. They conducted a study to help determine why, because nonadherence is potentially something that can be fixed.

The researchers reviewed 53 studies presenting data on more than 2.5 million patients, focusing on the relationship between race or gender and statin adherence. They chose statins because of this class of medication's central role in cardiovascular risk reduction and because of the many studies evaluating them.

Patient follow-up ranged from 3 months to > 5 years. Average adherence in all studies was 48%. Crude rates of nonadherence were higher among women than that among men (53% vs 50%). When the rates were pooled across studies, women were 10% more likely to be nonadherent to their prescribed statin (odds ratio 1.10, 95% CI, 1.07-1.13). The risk persisted in studies using multivariable methods as well as those that adjusted for race and socioeconomic status.

Nonwhite patients had higher crude rates of nonadherence than that of white patients (50% vs 45%). When the rates were pooled across studies, nonwhite patients were 53% more likely to be nonadherent, and that held true in the 5 studies that adjusted for socioeconomic status, insurance status, and copayment amount. However, things may be improving: Nonwhite patients were 67% less adherent than white patients in studies published before 2008, compared with 22% less adherent in studies published in 2008 or later.

The findings persisted in studies that adjusted for levels of insurance and income, militating against the idea that the lower quality care received by women and nonwhite patients is a reflection of their socioeconomic status, the researchers say.

Why the differences? The researchers suggest a variety of reasons. One reason is that women and ethnic minorities may be more likely to experience adverse effects from statins. A second reason may be that a misconception about women having lower risk for cardiovascular disease means clinicians and the women themselves don't put the same priority on prevention. And, finally, women are often caregivers, and caregivers often have lower rates of medication adherence.

The reasons behind the low adherence for nonwhite patients are more complex, the researchers say. These patients are less likely to have a consistent relationship with a primary care provider, and they are more likely to receive care from health care facilities that provide lower quality of care. These factors "may aggravate patient-level beliefs and attitudes that influence adherence," the researchers suggest, "such as mistrust of the health care system, lack of knowledge of how to best use the health care system, and misunderstanding of provider instructions."

Ongoing patient education, medication reminders, and reinforcement can help keep patients on their regimens. However, the authors add, another important step is to increase diversity in clinical training to boost the chances of a cultural match between patients and their health care professionals.

Source: Lewey J, Shrank WH, Bowry ADK, Kilabuk E, Brennan TA, Choudhry NK. *Am Heart J.* 2013;165(5):665-678.e1. doi: 10.1016/j.ahj.2013.02.011.

Preventive Dutasteride in Asymptomatic BPH

Studies of the 5α reductase inhibitor dutasteride have shown that it reduces urinary tract symptoms in men with benign prostatic hyperplasia (BPH), particularly men with an enlarged prostate. But what about men who are asymptomatic, or who have minimal symptoms? Should they be given dutasteride as preventive treatment?

Researchers from the University of Toronto in Canada conducted what they say is the first study to explore the benefits of dutasteride in this asymptomatic group. Their post hoc analysis of the 4-year, double-blind Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study examined data from 792 men taking dutasteride and 825 taking a placebo.

A total of 297 patients on placebo (36%) and 167 patients taking dutasteride (21%) experienced clinical progression of BPH ($P < .001$). The drug significantly reduced the incidence of clinical progression of BPH over

4 years, with a relative risk reduction of more than 50%.

Treating asymptomatic patients is not an uncommon approach in medicine, the researchers note, and preventing urinary symptoms can have a dramatic effect. While not as lethal as cardiovascular disease, which is treated preventively, acute urinary retention has a 10-year cumulative risk estimated to be twice that of stroke or myocardial infarction. Moreover, research has found it has a substantial impact on quality of life.

The trade-offs include cost of treatment and adverse effects (AEs). The most common AEs were erectile dysfunction (9% vs 5% with placebo; $P = .02$), and decreased or no libido (7% vs 2% with placebo; $P < .001$). Acknowledging that some men will not be receptive to preventive treatment, the authors say that the magnitude of risk reduction seen in their study "warrants further study of patient preferences for choosing optimal management."

Source: Toren P, Margel D, Kulkarni G, Finelli A, Zlotta A, Fleshner N. *BMJ.* 2013;346:f2109. doi: 10.1136/bmj.f2109.

Antioxidants and Heart Failure

Do antioxidants help prevent heart failure (HF)? Studies have been limited, and none have looked at the role of all antioxidants in the diet, according to researchers from Brigham and Women's Hospital, Harvard Medical School, and Beth Israel Deaconess Medical Center, all in Boston, Massachusetts; Karolinska Insitute in Stockholm, Sweden; and University of Alabama at Birmingham. Their study, the first to do so, they say, assessed the association between total antioxidant capacity of diet—all the antioxidant compounds in food and the interactions between them—and the effects on the incidence of HF. Apparently, even coffee and chocolate can help reduce the risk.

The study included 33,713 women (aged 49-83 years) from the Swedish Mammography Cohort. The women completed a 96-item questionnaire about how often they consumed various foods. The mean intake of fruits and vegetables was 4.8 servings per day (compared with 3 servings per day among U.S. adults).

During 11 years of follow-up, the researchers identified 769 incident cases of HF and 125 deaths from HF. A diet high in total antioxidant capacity was associated with a lower rate of HF. Fruits and vegetables contributed the majority of the antioxidants, but whole grains, coffee, and chocolate also played a role. In fact, when the researchers adjusted for fruit and vegetable consumption, they found antioxidants from other sources had an "important impact." They also cite a previous study that found women who consumed 1 to 2 servings of chocolate per week had the lowest risk of HF.

Total antioxidant capacity was inversely associated with the incidence of hospitalization or death due to HF: Women in the top quintile of antioxidant consumption had a 42% lower risk. After adjusting for smoking, body mass index, physical activity, and educational level, the results remained statistically significant.

Source: Rautiainen S, Levitan EB, Mittleman MA, Wolk A. *Am J Med.* 2013;126(6):494-500. doi: 10.1016/j.amjmed.2013.01.006.

A Faster Way to Get Back to Sleep?

Zolpidem, used to treat patients who wake in the middle of the night and have trouble getting back to sleep, is available in many formulations—immediate release (IR), controlled release, nonbuffered sublingual, and oral mist. In 2011, it was approved as a buffered sublingual tablet (ZST) as well.

Researchers from Tufts University in Boston, Massachusetts; Henry Ford Hospital in Detroit, Michigan; Transcept Pharmaceuticals, Inc. in Port Richmond, California; and Purdue Pharma L.P. in Stamford, Connecticut, compared the pharmacokinetic profile of 3.5-mg ZST with 10-mg IR oral zolpidem in 33 healthy, nonsmoking adults. Each participant was treated with 3 dosing regimens: 3.5-mg ZST after fasting, 3.5-mg ZST after a high-fat meal, and 10-mg IR after fasting. The participants remained seated or in bed for the first 4 hours after each dose.

The ZST was absorbed faster than the IR version by patients at all observed time points. The mean plasma concentration at 15 minutes and $AUC_{0\text{-}15\ min}$ were "substantially" larger for ZST than that for IR. Although sleep-inducing effects have not been clearly linked to absorption or systemic exposure, the researchers say, it can be anticipated that ZST might be more likely than IR to promote more rapid sleep resumption.

Plasma levels were notably higher in women than those in men. The researchers note that a similar gender-dependent pharmacokinetic profile has been reported for zolpidem in other studies, but the mechanism has not been established. Moreover, at 3 to 5 hours after dosing, plasma concentrations were substantially higher with IR compared with ZST. The 5-mg dose of IR cannot be assumed to be clinically equivalent to ZST at approved dosages, the researchers caution. If 5 mg of IR is substituted, plasma zolpidem concentrations at 4 to 5 hours after dosing will be much higher, raising the possibility of potentially hazardous residual sedative effects at the time of planned awakening. Thus, the researchers advise, the dose should be lower for women.

Source: Greenblatt DJ, Harmatz JS, Roth T, et al. *Clin Ther.* 2013;35(5):604-611. doi: 10.1016/j.clinthera.2013.03.007.

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