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Internal Medicine

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ABSTRACT & COMMENTARY

Diastolic Blood Pressure Goals

By Michael Crawford, MD

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

SYNOPSIS: An analysis of the community-based ARIC study showed that low diastolic blood pressures were associated with higher baseline and subsequent troponin T levels and adverse cardiac events, but not stroke.

SOURCES: McEvoy JW, Chen Y, Rawlings A, et al. Diastolic blood pressure, subclinical myocardial damage, and cardiac events: Implications for blood pressure control. *J Am Coll Cardiol* 2016;68:1713-1722.

Bhatt DL. Troponin and the J-curve of diastolic blood pressure: When lower is not better. *J Am Coll Cardiol* 2016;68:1723-1726.

Aggressively lowering systolic blood pressure (SBP) also will lower diastolic blood pressure (DBP). The level at which DBP is too low for adequate coronary artery blood flow is unclear. Thus, investigators from the Atherosclerosis Risk in Communities (ARIC) study, after excluding those with known cardiovascular (CV) disease, studied 11,565 community living subjects, including a subgroup of 1,403 who met the entry criteria for the Systolic Blood Pressure Intervention Trial (SPRINT). High-sensitivity cardiac troponin T (hsT) was measured at visits two, four, and five over a span of 21 years (1990-2003). A hsT value ≥ 14 ng/L was chosen as the cutoff for subclinical myocardial damage (99th percentile in healthy adults). BP was measured after five minutes of rest sitting, and the mean of the last two to three measures over five minutes was the BP used for this analysis. Risk factors for CV disease were recorded and clinical endpoints, such as coronary events, stroke, and mortality, were noted. The study evaluated the relationship between DBP and hsT values and clinical events. The study population mean baseline age was 57 years, 57% were female, and 25% were black. Compared to those with a baseline DBP between 80-89 mmHg, the adjusted odds ratio (OR) of having a hsT ≥ 14 ng/L at baseline was 2.2 (95% confidence interval [CI], 1.2-4.1) for a DBP < 60 mmHg and 1.5 (95% CI, 1.0-2.3) for a DBP of 60-

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69 mmHg. Similar results were observed in the SPRINT eligible subgroup (OR = 1.7 for DBP < 60 mmHg, and OR = 1.2 for DBP 60-69 mmHg), but these results were not statistically significant. Also, a low DBP at baseline was associated with increased hsT release over follow-up compared to the baseline DBP 80-89 mmHg group (+1.5 ng/L/year in the < 60 DBP group, and +1.0 ng/L/year in the 60-69 mmHg group). In addition, a DBP < 60 mmHg as compared to 80-89 mmHg was associated with more coronary heart disease events and mortality, but not stroke. These associations were strongest in those with elevated hsT (≥ 14 ng/L) at baseline and those with a baseline SBP ≥ 120 mmHg. The authors concluded that low DBP, particularly in those with an SBP ≥ 120, was associated with subclinical myocardial damage and coronary heart disease events.

■ COMMENTARY

Concern over the potential downside to pushing BP targets lower, a la SPRINT, continues. This study looked at the large ARIC database, which collected hsT data and clinical outcomes over 21 years in community living subjects. Their analysis showed an association between low DBP and subclinical myocardial injury at baseline and during follow-up. Also, low DBP was associated with coronary heart disease events and all-cause mortality. In addition, the association of low DBP and adverse outcomes was strongest in those with evidence of myocardial injury at baseline (hsT ≥ 14ng/L). These findings are consistent with other studies that have suggested a J-shaped curve for DBP and coronary events. Furthermore, since coronary blood flow largely is in diastole, this makes sense physiologically. Notably, low DBP was not associated with increased strokes, which serves as a negative control in this study, because an increase in strokes would not be biologically plausible. Finally, the findings were independent of whether the lower DBP was naturally occurring or potentially caused by antihypertensive medications, which lends more strength to the conclusions.

McEvoy et al examined DBP in isolation, but of course it is related to SBP. The association between DBP and outcome was strongest at SBPs > 120 mmHg, which suggests that the adverse effects of low DBP are more important when myocardial energy requirements (systolic load) are higher. Other studies have emphasized the predictive ability of pulse pressure (difference between systolic and diastolic pressure) and mean BP. In this study, it appears that pulse pressures > 60 are potentially detrimental, but more work needs to be done on this area. Also, elevated SBP was associated with elevated hsT and worse outcomes, which would be expected based on other studies. All these observations make determining BP targets challenging.

[The authors concluded that low diastolic blood pressure, particularly in those with a baseline systolic blood pressure ≥ 120, was associated with subclinical myocardial damage and coronary heart disease events.]

The authors suggested that when treating hypertension, try to keep the DBP > 70 mmHg but certainly keep it above 60 mmHg. Of course, if you try to drive the SBP < 120 mmHg, as suggested by SPRINT, it may be difficult to keep the DBP in a safe range. This would be especially important in patients with known coronary heart disease. Unfortunately, the SPRINT eligible subgroup in this study was underpowered, but the trend was similar to the overall study results. This suggests that there may be a cost to driving the SBP < 120 mmHg, even in the relatively healthy SPRINT group. Patients with left ventricular hypertrophy also may suffer with lower DBP. They clearly need higher DBPs as they can have myocardial ischemia without coronary artery disease when BP is low. The editorial by Dr. Bhatt emphasizes that picking BP targets for individual patients requires careful thought, considering all the factors discussed above and others. One goal for all may not be wise. ■

ABSTRACT & COMMENTARY

Cranberry Capsules Are Not Effective in Preventing Bacteriuria with Pyuria in Elderly Women in Nursing Homes

By Richard R. Watkins, MD, MS, FACP, FIDSA

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Dr. Watkins reports that he has received research support from Actavis.

SYNOPSIS: A randomized, double-blind, placebo-controlled trial found that giving cranberry capsules to elderly women residing in nursing homes did not result in any significant benefits, including no reduction in symptomatic urinary tract infections.

SOURCE: Juthani-Mehta M, Van Ness PH, Bianco L, et al. Effect of cranberry capsules on bacteriuria plus pyuria among older women in nursing homes: A randomized clinical trial. *JAMA* 2016 Oct 27. doi: 10.1001/jama.2016.16141. [Epub ahead of print].

Preventing urinary tract infections (UTIs) in elderly women is a frequent clinical problem. Unfortunately, options are limited and sometimes costly, leading to frustration for patients and physicians alike. Juthani-Mehta et al aimed to determine whether daily cranberry capsules would be beneficial in this patient population for preventing UTIs.

The study was a double-blind, randomized, placebo-controlled trial of the efficacy of two cranberry capsules daily compared to two placebo capsules daily. Inclusion criteria included female sex, long-term care residents, English speaking, and age 65 years or older. Exclusion criteria included patients not expected to be in the nursing home for at least a month, those taking chronic antibiotics for UTI prevention, hemodialysis, inability to produce a clean-catch urine sample, taking warfarin, history of nephrolithiasis, having an indwelling Foley catheter, allergy to or treatment with cranberry products, and nursing home residence for less than four weeks. The primary outcome was the presence of bacteriuria plus pyuria, which was measured every two months after randomization for a total of six assessments over 12 months. The secondary outcomes were symptomatic UTI, all-cause mortality, all-cause hospitalization, all multidrug-resistant organisms, antibiotics for suspected UTI, and total antibiotic prescriptions.

Of 5,045 nursing home residents who were screened, 185 were randomized, including 92 to the treatment group and 93 to the control group. The mean age of the participants was 86.4 years. There were 10 symptomatic UTIs in the treatment group and 12 in the control group. For the primary outcome of bacteriuria plus pyuria, the adjusted analysis showed no significant differences between the two groups (29.1% vs. 29.0%; odds ratio [OR], 1.01; 95% confidence interval [CI], 0.61-1.66; $P = 0.98$). Regarding the secondary outcomes, there were no significant differences in mortality, hospitalization, bacteriuria from multidrug-resistant gram-negative bacilli, or antibiotic use between the treatment and control groups ($P > 0.05$ for all). Finally, the frequency of adverse events was similar in both groups.

■ COMMENTARY

The use of cranberry juice, more precisely the quinic acid in cranberries that is metabolized to hippuric acid in the bladder, is an attractive strategy for preventing UTIs. It is inexpensive, widely available, and avoids the potential risks associated with antibiotics, such as disruption of the microbiome and the promotion of antibiotic resistance. Previous clinical trials that investigated the efficacy of cranberries for preventing UTIs produced mixed results. The report by Juthani-Mehta et al appears to have settled the debate. Their well-designed and conducted study found no differences in any of the outcomes between the use of cranberry capsules and placebo. While disappointing, these results signal it is time to move past using cranberries in elderly women and explore novel approaches for UTI prevention.

So why were the cranberry capsules ineffective? There are a couple of possible explanations. As the authors noted, during the first six months of treatment there was a decrease in bacteriuria with pyuria in the group that received cranberry capsules, but it was not sustained for the next six months. This

may have been due to a decrease in adherence. Another issue relates to the fact that some previous studies that found a benefit used cranberry juice instead of capsules. Hydration may be an important benefit with cranberry juice that is lacking with the capsules. For example, a study in which subjects took cranberry capsules with 8 ounces of water twice a day over six weeks found a 50% reduction in UTIs.[1] Moreover, drinking water with the cranberry capsules avoids the high glycemic load from cranberry juice, which can be deleterious in diabetic elderly patients. Finally, incontinence and changes in the vaginal microbiome with age may have made the capsules less effective. Additional studies using cranberry capsules in younger women with recurrent UTIs should be conducted to determine if there are any benefits in this population. ■

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BRIEF REPORT

How Safe Is Your Honey?

By Carol A. Kemper, MD, FACP

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

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

SOURCE: ProMED-mail post, Sept. 15, 2016. Contaminated honey — USA: Glyphosate. Available at: www.promedmail.org. Accessed Nov. 12, 2016.

Weeds. Weeds. Anyone with a garden understands. Even my neighbor, with his "organic" pinot vineyard, has given up, and uses Roundup, which contains the active weed killer glyphosate. Of course, his vineyard worker only sprays it "between" the vines (while he is wearing a Hazmat suit). Commercial agriculture depends on Roundup, and crop seeds have been genetically modified to withstand its use. While there is not much research on the effects of Roundup on bees, the chemical may remain in the ground for some time, and the spray creates an aerosol, which can be carried by the wind. I tried keeping bees for years on the property, but they kept vanishing.

Now, the FDA reports finding small amounts of the weed killer glyphosate in samples of U.S. honey. The amount of glyphosate found was as much as 107 parts per billion in some samples, which is small but nonetheless more than that permitted by the European Union (< 50 parts per billion). The FDA has not stipulated a limit for glyphosate in food substances, such as honey. And, up until this year, no testing for this chemical was performed on food substances in the United States. Independent agencies, which have identified Roundup in cereal, oatmeal, and flour samples, may have focused the FDA's attention on this concern. Obviously, the bees are collecting it with their nectar, and bringing it back to the hive. How much is a risk to humans is not clear. ■

BRIEF REPORT

Benefits of TB Screening Confirmed

By Carol A. Kemper, MD, FACP

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

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

SOURCE: Screening for latent tuberculosis infection in adults. U.S. Preventive Services Task Force Recommendation Statement. *JAMA* 2016;316:962-969.

If corporate America wishes to embrace globalization, they should heed the global disease burden, at least to the degree that it puts their own workforce at risk from tuberculosis exposure. Too often in Silicon Valley, we see another case of active tuberculosis (TB) in a visiting student, or a young high-tech worker on an H-1B visa, or in an elderly immigrant, none of whom have been screened and treated for latent TB (LTBI).

This updated statement from the United States Preventive Services Task Force (USPSTF) advocates, with "moderate certainty," for a "moderate net benefit" for the screening and treatment of persons at increased risk for TB. Based on a current assessment of the benefits and harms, screening and treatment of individuals with latent TB is of overall benefit, regardless of age, even if they are currently asymptomatic or considered lower risk.

Based on 2011-2012 National Health and Nutrition Examination Survey data, the prevalence of LTBI in the United States is estimated to be between 4.7-5.0%. Approximately 5-10% of these will progress to active TB or reactivation disease. Rates of progression to active disease are higher in the elderly, and in those with diabetes, kidney disease, and immunosuppression. Not only does the risk of reactivation increase to 20-25% by the time you are in your 80s, but the risk of mortality also is considerably increased. Although active TB is considered a treatable disease, it is important to recognize the overall mortality for active TB is approximately 4%, even with treatment.

In 2015, 66% of cases of active TB occurred in foreign-born persons, and the case rate of active TB was approximately 13 times higher in foreign-born persons compared with those born in the United States. More than half of those who develop active TB are from five countries: the Philippines, Vietnam, India, China, and Mexico. The prevalence of LTBI also is greater in the homeless, persons in long-term care facilities, and those in correctional facilities.

The USPSTF concluded that the two types of screening tests (skin test and IGRA tests) are fairly sensitive and specific, and the evidence for harm in being screened is nil. The risk for harm in the treatment of LTBI has been well characterized, and is comparatively less than the risk of harm from developing active or reactivation TB. In concrete numbers, if 100,000 persons at increased risk for TB were screened and treated for LTBI, 52 to 146 cases of active TB would be prevented, seven to 67 cases of hepatotoxicity would occur, and 111 persons would discontinue treatment for adverse effects. To prevent one case of active TB, approximately 111-314 persons (depending on risk factors) would need to be treated for LTBI. In contrast, the number of persons needed to cause one case of hepatotoxicity from LTBI treatment would range from 279-2,531 (depending on the treatment).

Make it your job — and the job of your primary care colleagues — to screen persons at risk for LTBI, especially anyone born in a foreign country endemic for TB, regardless of age, and make an effort to target those individuals who are allowed to enter this country without screening for LTBI. ■

PHARMACOLOGY UPDATE

Prasterone Vaginal Insert (Intrarosa)

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

Dr. Elliott is Medical Director, Pharmacy, Northern California Kaiser Permanente, and Assistant Clinical Professor of Medicine, University of California, San Francisco. Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

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

The FDA has approved prasterone (dehydroepiandrosterone [DHEA]) as a vaginal insert to treat moderate to severe pain during sexual intercourse in postmenopausal women.

Although available as a dietary supplement for years, prasterone represents the first FDA-approved version of DHEA. Prasterone is marketed as Intrarosa.

INDICATIONS

Prasterone is indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.[1]

DOSAGE

The recommended dose is one vaginal insert daily at bedtime.[1] Each vaginal insert contains 6.5 mg of

prasterone.

POTENTIAL ADVANTAGES

Prasterone administered intravaginally does not significantly alter the levels of sex hormones beyond normal post-hormonal values.[2]

POTENTIAL DISADVANTAGES

Vaginal discharge and abnormal Pap smear findings may occur with prasterone administrations.[1]

COMMENTS

Prasterone is metabolized intracellularly into active sex steroids, namely estradiol and testosterone. The effectiveness of the vaginal insert was evaluated in two similar randomized, double-blind, placebo-controlled, 12-week trials in postmenopausal women between 40-75 years of age with moderate to severe dyspareunia.[1,3]

Study participants presented with dyspareunia as their most bothersome symptom of vulvar and vaginal atrophy. In the two studies, 406 subjects were randomized to prasterone and 234 to placebo. They also had ≤ 5% superficial cells on vaginal smear and a vaginal pH > 5. At baseline, the mean dyspareunia severity scores ranged from 2.54-2.63, percent superficial cells, 0.68-1.04, percent parabasal cells, 52-68, and vaginal pH 6.32-6.51. Co-primary endpoints, assessed for improvement at 12 weeks from baseline, were the most bothersome moderate to severe symptoms of dyspareunia, the percent of vaginal superficial cells, the percentage of parabasal cells, and vaginal pH.[1]

Mean difference in change between prasterone and placebo in severity of dyspareunia were -0.40 (-1.27 vs. -0.87) and -0.35 (-1.42 vs. -1.06) (P = 0.013) respectively in the two studies. Mean difference increase in percent superficial cells were 4.71 (5.6 vs. 0.9) and 8.46 (10.2 vs. 1.75), mean decrease in percent parabasal cells, 45.8 (-47.4 vs. -1.62) and 29.5 (-41.5 vs. -12), and decrease in vaginal pH, -0.83 (-1.04 vs. -0.21) and -0.67 (-0.94 vs. -0.27).

Prasterone showed significant increase over placebo on the Female Sexual Function Index questionnaire in terms of desire, arousal, lubrication, orgasm, satisfaction, and pain at sexual activity.[4] An open-label study suggested that the benefit of prasterone is maintained for 52 weeks.[5]

When male partners were polled, 36% did not feel vaginal dryness of the partner who received prasterone at the end of the 12-week treatment, compared to 7.8% who received placebo.[6]

CLINICAL IMPLICATIONS

Dyspareunia is a symptom of vulvar and vaginal atrophy due to menopause and associated with the decline in level of estrogen. Circulating DHEA provides the substrate for the production of estrogen and androgens in postmenopausal women. Intravaginal prasterone (DHEA) provides a source of exogenous substrate to increase the level of sex hormones. It provides an option to various formulations of estrogens and oral ospemifene, a selective estrogen receptor modulator, which is FDA-approved for this indication.

Currently, there are no published comparative trials with any of these drugs and prasterone. Cost for prasterone was not available at the time of this review. ■

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Internal Medicine [ALERT]

Clinical Briefs

By Louis Kuritzky, MD

10-year Outcomes for Localized Prostate Cancer

SOURCE: Hamdy FC, Donovan JL, Lane JA, et al. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med* 2016;375:1415-1424.

For the past three decades, the majority of prostate cancer (PRCA) detection has resulted from prostate-specific antigen (PSA) screening. As compared to pre-PSA modes of detection, the population of PSA screening-detected PRCA is predominantly comprised of earlier, prostate-localized disease. Is there a clear advantage to one path of long-term intervention than another in long-term management of localized PRCA?

From a population of 84,429 PSA-screened men in the United Kingdom, 2,664 were diagnosed with localized PRCA and randomized to active surveillance vs. radical prostatectomy vs. external beam radiation. Although prostatectomy and external beam radiation probably are self-explanatory, the method of "active surveillance" differs from the "watching waiting" in two other prostate cancer trials. That is, active surveillance entailed PSA measurement every three months for a year, and then every six to 12 months going forward. Any 12-month PSA increase of 50% or greater prompted a case review and reconsideration of intervention; ultimately, 56 men in the active surveillance group ended up receiving an intervention secondary to increases in PSA.

At 10 years of follow-up, there was no statistically significant difference in either PRCA-specific death or all-cause mortality between the three groups. Although these results are heartening in that the three methods demonstrated similar (and low) levels of mortality, the relatively younger age of these men (mean age = 62 years) and the fact that disease progression over 10 years was more common in the surveillance group indicates that even longer-term follow-up will be needed to fully inform men on how to make optimum choices. ■

Secondary Prevention of Stroke by Pioglitazone in Prediabetes

SOURCE: Inzucchi SE, Viscoli CM, Young LH, et al. Pioglitazone prevents diabetes in patients with insulin resistance and cerebrovascular disease. *Diabetes Care* 2016;39:1684-1692.

The Insulin Resistance After Stroke (IRIS) trial randomized patients with recent ischemic stroke or transient ischemic attack to pioglitazone (PIO) or placebo for approximately five years. The rationale for selecting PIO was that these patients were all prediabetic, as defined by the homeostatic model assessment-insulin resistance score, further supported by their mean A1c (5.8). To be clear: diabetics were *excluded* from the trial; only prediabetics were included.

The primary endpoint of the IRIS trial indicated a significant 24% reduction in new stroke with PIO. This follow-up report detailed the ability of PIO to prevent development of diabetes in this population of prediabetics.

Over a five-year interval, 7.7% of placebo recipients progressed from prediabetes to diabetes, compared with 3.8% of the PIO group (hazard ratio = 0.48). Predictably, those prediabetics with the greatest degree of fasting blood glucose perturbation and highest baseline A1c showed the greatest degree of benefit.

PIO reduces vascular events in insulin-resistant stroke victims, as well as reduces risk of progression from prediabetes to diabetes by > 50%. ■

Linking Psoriasis to Vascular Health

SOURCE: Chiu HY, Lo PC, Huang WF, et al. Increased risk of aortic aneurysm (AA) in relation to the severity of psoriasis: A national population-based matched-cohort study. *J Am Acad Dermatol* 2016;75:747-754.

Approximately 15,000 people per year die in the United States from ruptured abdominal aortic aneurysms (AAA). The commonly recognized risk factors for AAA include hypertension, smoking, male sex, and age. While the link between inflammatory disorders, such as rheumatoid arthritis and psoriasis, and coronary vascular disease has received increasing attention in the last decade, little cognizance exists of a relationship between psoriasis and AAA.

To define this relationship further, Chiu et al reviewed the medical records of 34,301 patients with psoriasis in a Taiwanese database. When age and sex matched with controls (n = 137,204), a surprisingly strong association between psoriasis and risk for AAA emerged.

Patients with psoriasis were almost twice as likely (hazard ratio = 1.8) to be diagnosed with AAA as controls. Further substantiating the relationship, psoriasis severity was associated linearly with increasing risk for AAA. The strong association was independent of the already recognized risk factors for vasculopathy such as hypertension, smoking, and dyslipidemia. The authors suggested consideration of screening for AAA in psoriasis patients because of increased risk. Current U.S. Preventive Services Task Force guidelines suggest a one-time ultrasound screening for men between 65-75 years of age who are ever smokers (≥ 100 lifetime cigarettes). ■

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CME QUESTIONS

1. **A diastolic blood pressure of < 60 mmHg is associated with:**

   a. reduced mortality.

   b. increased stroke rates.

   c. increased coronary heart events.

   d. reduced high sensitivity troponin values.

2. **The study by Juthani-Mehta et al found that giving cranberry capsules to elderly women residing in nursing homes led to reductions in symptomatic urinary tract infections.**

   a. True

   b. False

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.

[IN FUTURE ISSUES]

Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease

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