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Evidence-based summaries on cancer treatment and research

## ABSTRACT & COMMENTARY

# Aromatase Inhibitor-induced Arthralgia

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

SYNOPSIS: Aromatase inhibitor-induced arthralgia develops by week 6 of initiating aromatase inhibitor (AI) therapy, and does not appear to resolve. In fact, it usually worsens over the first year of AI therapy. Women who have severe menopausal symptoms or existing joint-related conditions at the time they start taking AIs had worse arthralgia.

SOURCE: Castel LD, et al. Time course of arthralgia among women initiating aromatase inhibitor therapy and a postmenopausal comparison group in a prospective cohort. Cancer 2013;119:2375-2382.

This prospective cohort study measured joint pain in 91 women beginning adjuvant aromatase inhibitor (AI) therapy for postmenopausal breast cancer. These women were asked to rate pain in eight joint pair groups (bilateral fingers, wrists, elbows, shoulders, hips, knees, ankles, and toes) at baseline and 2, 4, 6, 8, 12, and 52 weeks after they started taking the AI. A comparison group of 177 postmenopausal women without breast cancer completed the same surveys, using the same time frame, to assess the background rate of arthralgia in menopause.

At baseline, the AI and comparison groups did not differ in their composite arthralgia score, but, by week 6, the AI-initiating group had more severe arthralgia than did the comparison group (ratio of means, 1.8; 95% confidence interval, 1.24-2.7; $P = 0.002$). Arthralgia did not appear to resolve with time, but continued to worsen in the AI group over the entire 1-year period of the study.

Menopausal symptom severity and existing joint-related comorbidity at baseline among women initiating AI were associated with more severe arthralgia over time. Additional clinical, demographic, and health-related quality of life variables were assessed, but none of these appear to be risk factors for aromatase inhibitor-induced arthralgia (AIA).

With regard to adherence, over the 1-year course of the study, 83% of the women initiating AI were reported as still taking either the AI they initiated or another AI; 12% were reported switched to tamoxifen; and 5% were reported as having discontinued adjuvant endocrine therapy entirely.

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## COMMENTARY

Despite the fact that AIs improve breast cancer disease-free survival in postmenopausal women with early-stage, hormone-receptor-positive breast cancer, only 50-70% of women are adherent to their AI medication at 3 years,[1] well short of the 5-year course of therapy that is the standard of care. Although the reasons for nonadherence are not clear, AIA is common, and, in conjunction with the vasomotor and bone-health side effects, likely plays a significant role in explaining this significant dropout rate. Even for those who remain compliant with the prescribed course of therapy, the negative impact of AIs on their quality of life may be profound.

The prevalence of AIA is said to range between 5% and 35%. AIA usually presents with symmetrical joint pains, most commonly affecting the wrists, hands, and knees. Complaints of carpal tunnel syndrome and trigger finger symptoms are not uncommon, as are morning stiffness, myalgia, and decreased grip strength.[1]

Although nearly all oncologists appreciate the significance of AIA, the paucity of prospective studies designed specifically to elucidate this problem has left clinicians without a clear understanding of the risk factors for AIA and its natural history. The Castel study was intentionally designed to longitudinally assess arthralgia, clinical and patient-reported arthralgia predictors, and other clinical and patient-reported outcomes. Accordingly, its findings have practical implications for clinicians.

It is no surprise to learn that women taking AIs have more severe arthralgia than women in the postmenopausal comparison group. That these symptoms continue to worsen with time and do not appear to resolve over the first year is, however, useful new information that was not made clear by previous studies that had less rigorous design and outcome measurements. It suggests that women should return for their initial follow-up 6 weeks after initiating AI therapy, the time that it usually takes for AIA to develop, and that they should be monitored for worsening symptoms throughout the entire first year of AI therapy.

By the end of her study, Castel found that 27% of women had stopped taking an AI and 5% had discontinued adjuvant hormonal therapy altogether (12% switched to tamoxifen after experiencing unacceptable AI-related side effects). Although this number is below the 30-50% 3-year dropout rate reported in other studies, it suggests that AIA and other side effects continue to worsen with the passage of time. If women are to realize the maximum effect of these agents, physicians will need to monitor and treat these symptoms throughout the course of therapy. AIs may continue to adversely impact the health and quality of life of a breast cancer patient for years after she has completed therapy, and "survivorship plans" should be constructed accordingly. Future research should extend the observation period beyond the 1-year studied by Castel and should add a therapeutic focus.

Although AIA is a common problem, there have been surprisingly few prospective, randomized, controlled studies to explore management strategies. Most treatments, including NSAIDs, have been based on extrapolations from the management of osteoarthritis and rheumatoid arthritis. These include counseling and education, lifestyle modifications like exercise and weight loss, massage, relaxation techniques, and hypnosis. Calcium and vitamin D, opioid and non-opioid analgesics, and other pain modifiers, like tricyclic antidepressants or anticonvulsants, are among the various pharmacologic interventions that have been used.

One of the few prospective, randomized, controlled clinical trials explored the role of acupuncture in managing AIA, and found that women who received true acupuncture twice weekly for 6 weeks had less pain and pain-related symptoms than those who received sham acupuncture. Although this study was small (43 women) it raises interesting possibilities for treating AIA and for future research.[2]

The ATOLL study showed that women who do not tolerate one AI because of AIA might be able to tolerate an alternative AI. In this study, women who stopped taking anastrozole because of AIA were switched to letrozole and reported less pain and

better quality of life. However, it is important to note that these women were observed for only 6 months, and though the letrozole was better tolerated, 74% of the women still had significant arthralgia after 6 months of letrozole therapy.[3] It is essential that the strategy of "switching AIs" be studied over a longer period of time in light of what Castel has demonstrated about the natural history of AIA.

Another "switching strategy" is to prescribe tamoxifen in women who have unacceptable AIA. Although tamoxifen is associated with a lower incidence of AIA, tamoxifen does have a significantly higher risk for deep venous thrombosis, pulmonary embolism, and stroke when compared with AI. This risk may not be insignificant in the older postmenopausal woman who frequently suffers from comorbidities that increase her risk for these tamoxifen-related thromboembolic side effects.

Finally, it is important to highlight Castel's finding that women taking AIs with more severe menopausal symptoms or existing joint-related conditions at the time of AI initiation had worse arthralgia over time. Targeted interventions in these at-risk groups may improve AI compliance and improve quality of life. Knowing who may be at risk for AIA, oncologists are better able to help their patients make informed decisions about the benefits and burdens of AI therapy and compare these to alternative adjuvant approaches. ■


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## ABSTRACT & COMMENTARY

# Modern Radiation Therapy and ADT for High-risk Prostate Cancer Result in Improved Survival


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



SYNOPSIS: Historically, men with high risk prostate cancer were believed to have low survival rates after definitive treatment with either surgery or radiation. However, long-term results of dose-escalated radiotherapy of doses ≥ 75.6 Gy, along with long-term androgen deprivation therapy (ADT), demonstrate 5-year survival rate of 92%, 5-year biochemical control rate of 82%, and symptomatic local failure rate of 0%. Death from prostate cancer was only 5.5% at 10 years in men treated with high-dose radiation therapy and ADT.


SOURCE: Nguyen Q, et al. Long-term outcomes for men with high-risk prostate cancer treated definitively with external beam radiotherapy with or without androgen deprivation. *Cancer* 2013;119:3265-3271.

Historically, disease-free survival rates have been disappointing with external beam radiotherapy alone. Over the last 30 years, significant technological improvements in the delivery of radiotherapy have resulted in the successful and safe delivery of escalating doses. In addition, studies in the 1990s demonstrated improvement in outcomes with long-term androgen deprivation therapy (ADT) in high-risk prostate cancer patients. This led to the hypothesis that the combination of long-term ADT and dose-escalated radiotherapy would likely produce at least an additive effect.

To address the question of whether high doses of radiotherapy combined with long-term ADT results in improved outcomes, Nguyen and colleagues performed a retrospective analysis of 741 men with high-risk prostate cancer treated at M.D. Anderson Cancer Center between 1987 and 2004. High-risk disease was defined as T3 disease, Gleason score 8-10, or PSA > 20 ng/mL. Patients were typically staged with CT scans and bone scans. The median PSA for the cohort was 15.6 ng/mL and the median age was 68 years old. Three hundred seventy-five men were treated with low-dose radiation defined as < 75.6 Gy, 122 men were treated with ADT and low-dose radiation therapy, 71 men were treated with high-dose radiation therapy without ADT, and 173 men were treated with ADT and high-dose radiotherapy (> 75.6 Gy). ADT was started 2 months prior to radiotherapy and continued for a median of 2.9 years. The target for radiotherapy was the prostate and the seminal vesicles and did not include the pelvic lymph nodes.

Compared with low-dose radiotherapy alone, ADT combined with high-dose radiation therapy resulted in improved 5-year overall survival (82% vs 92%), 5-year prostate cancer survival (93% vs 96%), and

5-year clinical failure-free survival (67% vs 92%). There were no local failures in men treated with ADT and high-dose radiotherapy. The 10-year symptomatic local failure rate was only 2% for all patients. High-dose radiotherapy resulted in a 5% absolute benefit in 5-year survival either with or without ADT. Prostate cancer specific deaths were rare among all cohorts at 5.5% at 10 years. The use of ADT improved local failure rates, overall survival rates, and biochemical control.

## COMMENTARY

High-risk prostate cancer represents between 13% and 21% of newly diagnosed patients.[1] A number of randomized trials done in the United States including RTOG 92-02 have demonstrated improved overall survival in patients with high-risk prostate cancer treated with long-term hormones and radiation compared to short-term hormones and radiation.[2] These trials have essentially outlined the standard of care for the last decade in the management of high-risk prostate cancer. Many of these trials including RTOG 92-02 used lower doses of radiation therapy (65-70 Gy). Several trials have demonstrated a benefit to a higher dose of radiation therapy in high-risk patients, which results in improved outcomes when compared to lower doses.[3]

So what have I learned from this trial as a radiation oncologist who treats prostate cancer patients? Every radiation oncologist is likely already giving dose of at least 75.6 Gy using Intensity Modulated Radiation Therapy (IMRT), so my radiation dose will likely remain unchanged. However, the debate as to what areas need to be irradiated continues to rage on. It is very interesting in this study that there were no local failures in men treated to only the prostate and seminal vesicles. Many radiation oncologists continue to treat the pelvic nodes as well as the prostate and seminal vesicles based on other RTOG trials demonstrating a small benefit early on in progression-free survival.[4] There are still questions remaining to be answered. Should men with high-risk prostate cancer be offered surgery when the risk of prostate cancer mortality is < 5% even in high-risk populations or should the standard of care be radiation and hormones? What about the use of combination external beam radiation and brachytherapy? In my opinion, it's hard to argue against the combination of hormones and high-dose modern radiation therapy in this high-risk population with such excellent results. The alternative is a prostatectomy with a high likelihood of requiring postoperative radiation therapy because of positive margins or extracapsular penetration. Why treat with two treatment modalities when you can treat with one? ■


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# ABSTRACT & COMMENTARY

# Sorafenib + TACE for Advanced HCC


***By William B. Ershler, MD***



SYNOPSIS: In an observational cohort of 222 hepatocellular cancer patients treated in China, transarterial chemoembolization (TACE) combined with sorafenib resulted in outcomes in terms of response rates and survival that compare favorably with prior series of sorafenib used alone. Although TACE is not typically used in U.S. patients with advanced disease, this series would indicate that it may prove an effective and safe adjunct to sorafenib and is worthy of exploration by prospective clinical trial.



SOURCE: Zhao Y, et al. Sorafenib combined with transarterial chemoembolization for the treatment of advanced hepatocellular carcinoma: A large-scale multicenter study of 222 patients. *Ann Oncol* 2013;24:1786-1792.


Worldwide, hepatocellular carcinoma (HCC) remains a major cause of cancer-related deaths and its incidence is increasing in the United States.[1,2] Surgical excision remains the best chance for cure but unfortunately patients frequently present with advanced, unresectable disease. Patients with intermediate-stage disease are frequently treated with transarterial chemoembolization (TACE), and studies have indicated angiogenesis inhibitors such as sorafenib provide additional response rate and survival advantage[3,4] Until recently, TACE was considered inappropriate for patients with advanced disease. However, there has been a rationale presented that combining systemic and localized therapy (e.g., TACE) would improve outcomes even for patients with advanced disease.[5] To investigate this hypothesis, Zhao and colleagues at seven treatment centers in China reviewed their collective experience with TACE plus sorafenib in patients with advanced HCC. For this study, data on 222 consecutive patients with advanced HCC treated from June 2008 through July 2011 were retrospectively analyzed.

HCC was diagnosed according to the criteria from the European Association for the Study of Liver Disease/American Association for the Study of Liver Disease and staging was per Barcelona Clinic Liver Cancer criteria.[6] The inclusion criteria for the study population were as follows: an ECOG performance status of ≤ 2, Child-Pugh class A or B, HCC stage B or C, a baseline CT obtained just prior to therapy, an elapsed time of < 60 days between the beginning of sorafenib treatment and the first TACE procedure, and treatment and follow-up in one of the seven participating centers. All consecutive patients who met these criteria were included unless they had any of the following conditions: main portal vein obstruction, second primary malignancy, sorafenib discontinuation due to patient compliance, or a known transjugular intrahepatic portosystemic shunt. Chronic hepatitis B was causally related in 86% of enrolled subjects. Eighty percent of patients were at stage C, and 86% patients were in Child-Pugh class A.

In all cases, TACE consisted of an injection containing a mixture of chemotherapeutic agents followed by embolization with gelatin foam until complete stasis was achieved in the tumor-feeding vessels. The chemotherapeutic agents used concurrently included doxorubicin (10-50 mg), epirubicin (10-50 mg), cisplatin (10-110 mg), and/or mitomycin (2-10 mg); they were selected according to the preferred practices at each center. Tumor-feeding vessels were selected whenever possible. TACE was repeated as tolerated and indicated by radiological response. Sorafenib treatment was initiated at a dose of 400 mg twice daily and was administered continuously with no breaks before or after TACE. Standard follow-up evaluations (including CT) were carried out during weeks 4 and 8 after initiation of treatment and every 8 weeks thereafter. Overall survival (OS) was measured from the time treatment started until the time of death from any cause. Time to progression (TTP) was defined as the time from the baseline CT scan to radiological disease progression according to RECIST criteria.

During the study period, 302 patients received combined TACE/sorafenib. Of these, 222 met the inclusion criteria for this analysis. The majority of patients were male (84%) and the mean age was 51 years (range 23-80 years).

The overall median survival was 12 months (95% confidence interval [CI], 10.1-13.9). The rates of CR, PR, SD, and PD were 2%, 25%, 60%, and 14% respectively. The median TTP was 8.5 months (95% CI, 6.4-10.6 months). For patients with stage C disease, factors influencing OS included performance status, the number of nodules, Child-Pugh score, and macrovascular invasion.

The overall incidence of adverse events (AEs) was 87%. Most frequently observed were diarrhea (50%), hand-foot skin reaction (44%), rash (39%), and fatigue (33%). The most frequent grade 3 or 4 AEs were diarrhea (5%), hand-foot skin reaction (5%), and rash (4%).

## COMMENTARY

This was a retrospective, observational series of consecutive HCC patients treated with combined local and systemic therapy at several centers in China. Distinct from HCC in the United States, the great majority (approaching 90%) of included patients had evidence for hepatitis B. However, what makes this study unique and of value is the advanced stage of the majority of patients included. Historically, and most notably in treatment centers outside of Asia, TACE has been generally reserved for those with earlier-stage disease and those with more advanced disease are often treated with single-agent sorafenib or a similar drug.[7,8] Yet, there is an evolving rationale that for those with preserved liver function despite advanced stage HCC, TACE might be equal or even superior to sorafenib used alone.[9] In fact, although comparisons between series of patients are imprecise, the outcomes for patients included in this study are at least comparable, if not superior to those observed for advanced HCC patients treated with sorafenib alone.[7,8] Certainly, we have a long way to go in optimizing care for this group of patients with advanced HCC, but strategies that incorporate the use of TACE with sorafenib should be considered for further study in prospective, randomized trials. ■

[Strategies that incorporate TACE with sorafenib for advanced HCC should be considered for future RCTs.]


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## ABSTRACT & COMMENTARY

# Two-step Ovarian Cancer Screening: A 'Scissor-step' Forward?

***By Robert L. Coleman, MD***

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

**This article originally appeared in the October 2013 issue of *OB/GYN Clinical Alert*.**

SYNOPSIS: An 11-year prospective screening trial in 4051 menopausal women (age 50-74) demonstrates that the risk of ovarian cancer algorithm probability index, along with ultrasound and gynecologic oncology consultation of "high-risk" cases, produces high specificity and positive predictive value leading to the identification of higher than expected incident early-stage ovarian cancers.

SOURCE: Lu KH, et al. A 2-stage ovarian cancer screening strategy using the risk of ovarian cancer algorithm (ROCA) identifies early-stage incident cancers and demonstrates high positive predictive value. Cancer 2013; Aug 26. Doi: 10.1002/cncr.28183 [Epub ahead of print].

Ovarian cancer is a highly lethal disease of low prevalence in the general population and associated with advanced stage presentation in more than 70% of incident diagnoses. Strategies to identify these clinical features early in the disease process have included a focus on symptomatology, blood-based biomarkers, imaging (predominately ultrasonography), and physical exam with little success.

In this study, a two-stage ovarian cancer screening strategy was evaluated that incorporates change of CA125 levels over time and age to estimate risk of ovarian cancer. Women with high-risk scores were referred for transvaginal ultrasound (TVS). The prospective study included postmenopausal women (age 50-74) with at least one retained ovary, no personal history of ovarian cancer, and no family history of a first- or second-degree relative with breast or ovarian cancer. Patients were also not allowed to have had another malignancy, other than breast cancer, within 5 years of enrollment. Participants underwent an annual CA125 blood test. Based on the Risk of Ovarian Cancer Algorithm (ROCA) result, women were triaged to a subsequent annual CA125 test if deemed low risk, a repeat CA125 test in 3 months if intermediate risk, or TVS and referral to a gynecologic oncologist if high risk. A total of 4051 eligible women participated over 11 years, accounting for 16,832 screen years. The average annual rate of referral to a CA125 test in 3 months was 5.8%, and the average annual referral rate to TVS and review by a gynecologic oncologist was 0.9%. Ten women underwent surgery on the basis of TVS triage, which identified four invasive ovarian cancers (one with stage IA disease, two with stage IC disease, and one with stage IIB disease), two ovarian tumors of low malignant potential (both stage IA), one endometrial cancer (stage I), and three benign ovarian tumors, providing a positive predictive value of 40% (95% confidence interval [CI], 12.2%, 73.8%) for detecting invasive ovarian cancer. The specificity was 99.9% (95% CI, 99.7%, 100%). All four women with invasive ovarian cancer were enrolled in the study for at least 3 years with low-risk annual CA125 test values prior to rising CA125 levels (CA125 change point). The authors concluded that ROCA followed by TVS demonstrated excellent specificity and positive predictive value in a population of U.S. women at average risk for ovarian cancer.

## COMMENTARY

Some may recall the children's game "Mother may I?" in which participants follow instructions from a leader (mother) trying to guess the progress of the participants (children) toward a goal (home). Granted requests, such as "baby steps" or "scissor steps," afford minor advancements toward progress. The current study, while offering hope and promise of bridging the gap between early detection and mortality from ovarian cancer, essentially represents a minor, albeit positive, step forward. It clearly demonstrates that the process will involve several key elements such as good biomarkers, good probability estimate algorithms, motivated follow-up, access to secondary triage and gynecologic oncology consultation, and ultimately validation by documentation of reduction in mortality. However, to reach this zenith, studies assessing the merits of the individual steps forward are necessary and build confidence in the process.

It is clear that a screening program's best opportunity to reduce disease mortality is to identify a pre-invasive state where intervention will prevent disease.[1] Currently, we have no such marker for ovarian cancer, which likely also consists of a high proportion of fallopian tube abnormalities that form the primary site of disease.[2] Thus, the next best

opportunity to affect mortality in ovarian cancer is "stage migration;" that is, diagnosing the disease at earlier stages than what is currently observed in the general population. This can measurably impact survival as early-stage disease is curable at rates two- to three-fold that of advanced disease. Since more than 70% of ovarian cancer diagnosed in 2013 is stage IIIC/IV, there is significant opportunity to vastly alter its natural history and expected disease-specific mortality under a screening program that results in significant stage migration. The performance of the two-step screening algorithm used in this trial is remarkably consistent with the initial prevalence report presented by the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)[3] group in 2009 (also reviewed in *OB/GYN Clinical Alert*).[4] Although incidence was not reported in that study, the general specificity and positive predictive value of the two-step algorithm (which is similar to current study) were very consistent and, fortunately for screening participants, required only two to three operations from "positive screens" to identify cases of ovarian cancer — all in "early-ish" stages (Stage IC-IIB).

It was also of interest that two of the four cancers identified in this study had "normal" CA-125 values but met the criteria for a significant CA125 change point while remaining within the normal range. This highlights the value of establishing a normal baseline and the power of serial investigation. In addition, nearly 85% of all participants just went on getting annual CA-125 tests, demonstrating the low overall specificity of the program. The 200,000 person UKCTOCS trial's primary endpoint is disease-specific mortality; it is hoped that the preliminary results will be confirmed, offering practice changing policies in the management of screening menopausal women. ■


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## ABSTRACT & COMMENTARY

# Physician Communication and Prostate Cancer Screening


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

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SYNOPSIS: A brief web intervention improved shared decision making regarding prostate cancer screening.

SOURCE: Feng B, et al. Physician communication regarding prostate cancer screening: Analysis of unannounced standardized patient visits. *Ann Fam Med* 2013;11:315-323.

Prostate cancer screening is no longer recommended by the U.S. Preventive Services Task Force for average risk men.[1] Feng et al[2] explored how physicians communicate this recommendation to patients and how shared decision making is used by clinicians for prostate cancer screening. The authors defined shared decision making as a communication process through which clinicians collaboratively help patients understand medical information to reach value-congruent medical decisions.

To explore clinicians' communication styles, this study used a standardized patient methodology. Standardized patients are actors trained to role play a clinical scenario in a reproducible and standardized manner. Each standardized patient visited a clinician and during the course of the visit was trained to ask about prostate cancer screening.

The study group physicians were divided into a control and intervention group. The control group received a brochure on prostate cancer screening published by the Centers for Disease Control and Prevention and the intervention group was exposed to an interactive, 30-minute, web-based curriculum that included interactive roulette wheels, illustrative video vignettes, and other content to illustrate the risk and benefits of prostate cancer screening. They also received education about methods to enhance shared decision making.

Each encounter was audio recorded and physician behaviors were analyzed for: 1) engagement of a discussion about prostate cancer screening after prompting, 2) degree of decision making, and 3) recommendations for prostate cancer screening. The study group included 43 physicians in the control group and 77 in the intervention group. After prompting, 90% of the physicians discussed prostate cancer screening. The intervention group was somewhat more likely to engage in more shared

decision-making behaviors, were more likely to mention no screening as an option (63% vs 26%, $P < 0.05$), to encourage patients to consider different screening options (62% vs 39%, $P < 0.05$), and to mention no screening as an option (63% vs 26%, $P < 0.05$).

Based on their findings, the authors concluded that a brief web-based interactive education intervention can improve shared decision making, neutrality of recommendation, and in the case of prostate cancer, reduce prostate-specific antigen (PSA) testing.

## COMMENTARY

Prostate cancer screening is no longer recommended for average risk men. Despite this, 40-50% of men are still screened.[3] Shared decision making is touted as a method of discussing prostate testing and making better decisions about testing, especially when a test is of equivocal value. In the case of prostate cancer, shared decision making has the potential to reduce costs and improve patient care. However, most men in the United States report little shared decision making with their doctor regarding PSA screening.[4]

The findings reported by Fang et al suggest that a brief web-based intervention has the potential to impact shared decision making, and in the case of prostate cancer, perhaps improve care and reduce costs. While the improvement in shared decision making was modest, the number of physicians who mentioned the option of no screening in the intervention group was more than double the control group. While this study only examined prostate cancer among a relatively small group of primary care physicians working in five health care systems in California, the fact that even a brief, low-cost intervention improved shared decision making seems promising. Future studies to validate these findings and to explore other methods of improving patient involvement in decisions will be valuable. ■

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## Continuing Education Questions

**1. Aromatase inhibitor-induced arthralgia:**
a. usually occurs within 1 month of initiating AI therapy.
b. usually improves after 2-3 months.
c. is more common in women with pre-existing joint-related conditions.
d. None of the above

**2. High-dose radiation therapy and ADT result in a local failure rate of:**
a. 10%.
b. 5%.
c. 2%.
d. 0%.

**3. HCC patients with which of the following pretreatment criterion were *not* included in the analysis of TACE + sorafenib treatment?**
a. Hepatitis B
b. Child Pugh score of C
c. Stage C (by Barcelona staging)
d. Age > 65 years

**4. Which of the following is a stated eligibility or exclusion criteria for women in the ovarian cancer screening trial?**
a. Age > 50 years
b. At least one intact ovary
c. Previous history of ovarian cancer
d. No evidence of another cancer within 5 years of initial screening

**5. In reference to prostate cancer screening, Feng et al define shared decision making as:**
a. when a primary care physician works closely with a specialist to decide on a course of care.
b. when the public and health fields collaborate to arrive at a consensus regarding screening.
c. when the family meets to decide on whether it is best to be aggressive in treatment or adopt watchful waiting.
d. when clinicians use a communication process to collaboratively help patients understand medical information to reach value-congruent medical decisions.

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Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

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## Our Newest Pharmacologic Class for Treatment of Diabetes: SGLT2 Inhibitors

**Source:** Polidori D, et al. *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. *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. *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 (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. ■

## Osteoporosis: Are Two Drugs Better Than One?

**Source:** Tsai JN, et al. *Lancet* 2013;382: 50-56.

Most women today who are receiving pharmacotherapy for treatment of osteoporosis receive oral bisphosphonates (e.g., alendronate, risedronate). Other effective treatments, like teriparatide (TERI) and denosumab (DENO) are usually reserved for more severe cases, in some part because they require parenteral administration.

Even though osteoporosis treatments have shown risk reduction for fracture and improved bone mineral density (BMD), restoration of full bone integrity remains a challenge. As one of the few anabolic tools (as opposed to anticatabolic tools like bisphosphonates), some investigators have tried to augment the favorable activity of TERI by combination with bisphosphonates, but the results have been disappointing. Whether the addition of DENO to TERI might be beneficial was the subject of investigation by Tsai et al. Postmenopausal women with osteoporosis (n = 100) were randomized to DENO, TERI, or both for 6 months. The primary outcome of the study was improvement in BMD.

Combination TERI+DENO appeared to be synergistic, with improvements in BMD greater than either agent alone and arithmetically greater than the anticipated benefit of combined monotherapies. For example, BMD increases at the hip were 4.2% for TERI+DENO, 0.8% for TERI, and 2.1% for DENO. These data support the consideration of TERI+DENO in highest-risk patients, those unable to take other treatments, or patients who fail to respond to other regimens. ■

## Long-Term Impact of Weight Management on Blood Pressure

**Source:** Tyson CC, et al. *J Clin Hypertens* 2013;15:458-464.

The weight loss maintenance (WLM) trial randomized adults (n = 741) with hypertension (HTN) and/or dyslipidemia — but without evidence of cardiovascular disease — to one of several weight loss management programs. Although the initial outcome reports from WLM addressed the relative efficacies of different weight loss strategies over time, this report stratified study participants into those who lost, maintained, or gained weight over the 5-year study period. Tyson et al compared blood pressure effects between the three categories of weight impact, irrespective of which particular method of weight loss had been applied.

At study end, the weight-stable group had gained 0.6 kg, as compared with a 9.1 kg increase in the weight-gain group, and a 7.1 kg decrease in the weight-loss group. The weight-stable and the weight-gain groups were noted to have similar increases in systolic blood pressure (SBP) over 5 years (SBP increase mean 4.2 mmHg), whereas the weight-loss group SBP was not statistically significantly changed.

In contrast to some other trials that report a "legacy effect" (prolonged beneficial impact of early intervention, even after the intervention has ceased), initial weight loss in WLM was not associated with favorable SBP effects if weight was regained. On the other hand, sustained modest weight reduction (< 10% of baseline BMI) had a sustained effect to maintain SBP. Although simply maintaining weight over the long term might appear to be a laudable goal, it is apparently insufficient to favorably affect SBP. ■

## The WEAVE Study: Does Special Training in Domestic Violence Improve Outcomes?

**Source:** Hegarty K, et al. *Lancet* 2013; 382:249-258.

Intimate partner violence (IPV) is a public health problem that knows no boundaries of age, country of residence or origin, economic status, or education. Primary care clinicians, particularly family physicians, are often the first point of clinical contact for victims of IPV, but may lack confidence in their ability to identify and/or address IPV. Hegarty et al report on a trial from Australia in which women who screened positive for concerns about fear of their partner (n = 272) received care from family physicians who were randomized to receive special training in IPV or no intervention. The intervention group physicians participated in the Healthy Relationships Training program, which is intended to provide the ability to respond effectively to women who have experienced IPV and give brief counseling. The primary outcomes of the trial were changes in quality of life (as per the WHO QOL-BREF), safety planning and behavior, and mental health (as per the SF-12) at 1 year.

At 1 year, there was no difference in the primary endpoint between the intervention group and controls. A favorable impact on depression (a secondary endpoint) was seen. However, since the primary endpoint was not achieved, the potential for benefits on depression must remain considered as hypothesis generating. ■

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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. ■