Update in Women's Health: Evidence Published in 2012

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This update summarizes 10 important studies on women's health published in 2012 that are relevant to primary care. Authors screened the literature using ACP JournalWise and Journal Watch Women's Health to identify articles for inclusion. The articles focus on 1 key theme: Clinicians should recommend preventive and therapeutic interventions that maximize patient benefit while minimizing harm.

Studies finding increased risk for myocardial infarction (MI) with calcium supplementation, hip fracture with regular use of proton-pump inhibitors (PPIs), and venous thromboembolism (VTE) and stroke with the contraceptive ring will inform discussions about the risks and benefits of these therapies. Ulipristal acetate, which seems to be as efficacious but substantially better tolerated than conventional therapies for uterine fibroids, may be an attractive new option.

In the area of screening, human papillomavirus (HPV) and cytology cotesting of women aged 30 to 60 years leads to earlier detection of clinically relevant cervical intraepithelial neoplasia (CIN) grade 2 or worse and repeated screening for osteoporosis can be extended to every 15 years for women with normal bone mineral density (BMD) at baseline. A randomized, controlled trial of screening for intimate partner violence (IPV) revealed no benefit. Screening mammography increases the diagnosis of early-stage breast cancer but does not substantially reduce late-stage diagnoses. Several guidelines that provide advice on cervical cancer screening and menopausal hormone therapy were published in 2012 and are listed in the **Table**.

Reproductive Health

The Contraceptive Patch and Ring Are Associated With an Increased Risk for VTE Compared With Nonhormonal Contraception

Lidegaard O, Nielsen LH, Skovlund CW, et al. Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001-10. BMJ. 2012;344:e2990. [PMID: 22577198]

Background: Combined oral contraceptives (COCs) increase the risk for VTE, and this risk is even greater among women who have used COCs containing newer third-generation progestins (such as gestodene, desogestrel, and drospirenone) (1). The risk for VTE associated with nonhormonal contraceptives, such as the contraceptive patch, ring, and intrauterine system, is unclear.

Findings: Researchers used several national databases in Denmark to compare the risk for VTE between nonusers of hormonal contraception and users of nonoral hormonal contraception and between users of nonoral hormonal contraception and users of a reference COC. Among the more than 1.6 million women in this study, there were 5287 new diagnoses of VTE. Compared with nonusers of hormonal contraception, women who used the contraceptive patch and vaginal ring had a significantly increased risk for VTE (relative risk [RR], 7.90 [95% CI, 3.54 to 17.65] and 6.48 [CI, 4.69 to 8.94], respectively). Conversely, no increased risk was seen among users of the implant or intrauterine system. When compared with users of a second-generation progestin COC, the RRs for VTE among users of the patch and ring were 2.31 (CI, 1.02 to 5.23) and 1.90 (CI, 1.33 to 2.71), respectively.

Cautions: The results of this observational study were not adjusted for smoking or body mass index, both of which could influence the development of incident VTE.

Implications: Women who used the contraceptive patch or ring, compared with a second-generation COC, had a 2-fold increase in the RR for VTE. There is biological plausibility for these findings because both the patch and ring have been shown to increase resistance to activated protein C and increase sex hormone–binding globulin levels (2). However, women who prefer the convenience of these methods should note that the absolute risks were small: Approximately 1250 women using the patch and 2000 women using the ring would have to switch to a second-generation COC to prevent 1 VTE per year. For women who are at high risk for VTE and desire nonoral hormonal contraception, the implant or intrauterine system are less risky options.

Hormonal Contraception Is Associated With a Low Risk for Thrombotic Stroke and MI

Lidegaard Ø, Løkkegaard E, Jensen A, et al. Thrombotic stroke and myocardial infarction with hormonal contraception. N Engl J Med. 2012;366:2257-66. [PMID: 22693997]

Background: Although several studies have shown that COCs increase the risk for VTE, studies focusing on the association with MI and stroke (cerebrovascular accident [CVA]) have had conflicting results (3, 4). Moreover, data on risk for arterial events among users of nonoral hormonal contraception are scant.

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Table. **Women's Health Clinical Guidelines Published in 2012**

Organization, by Topic	Recommendations
Cervical cancer screening	
U.S. Preventive Services Task Force (12)	Cervical cancer screening should be done in all women aged 21–65 y with cytology (Papanicolaou smear) every 3 y, or for women aged 30–65 y who want to lengthen the screening interval, screening with a combination of cytology and HPV testing every 5 y. No screening in women younger than 21 y. Screening can be discontinued in women older than 65 y who have had previous screening in which smears have been consistently normal. No screening with HPV testing in women younger than 30 y. No screening in women who have had a hysterectomy.
American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology (13)	For women aged 30–65 y, cytology and HPV cotesting every 5 y is preferred, but screening with cytology every 3 y is acceptable.
Menopausal hormone therapy for the primary prevention of chronic conditions	
U.S. Preventive Services Task Force (8)	Recommends against the use of combined estrogen and progestin for the prevention of chronic conditions in postmenopausal women. Recommends against the use of estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy.
Hormone therapy for postmenopausal women	
North American Menopause Society (9)	Individualization is of key importance in the decision to use hormone therapy and should incorporate the woman's health and quality-of-life priorities as well as her personal risk factors. Estrogen–progestin therapy duration should be limited to 3–5 y of use. Local vaginal estrogen therapy should be used when only vaginal symptoms are present. Women with premature or early menopause who are otherwise appropriate candidates for hormone therapy can use it at least until the median age of natural menopause. There is a lack of safety data supporting the use of estrogen therapy in breast cancer survivors. Both transdermal and low-dose oral estrogen have been associated with lower risks of VTE and stroke than standard doses of oral estrogen, but RCT evidence is not available.

HPV = human papillomavirus; RCT = randomized, controlled trial; VTE = venous thromboembolism.

Findings: Researchers used several national databases in Denmark to compare the risk for thrombotic stroke and MI among users of hormonal contraception (both oral and nonoral) with nonusers. The study cohort included more than 1.6 million nonpregnant women aged 15 to 49 years. Compared with nonusers of hormonal contraception, women who used COCs containing 30 to 40 mcg of ethinyl estradiol had an increased risk for both CVA (adjusted RRs, 1.17 to 2.20) and MI (adjusted RRs, 1.33 to 2.28). The risk for both outcomes was lower with COC preparations containing 20 mcg of ethinyl estradiol (adjusted RRs for CVA, 0.88 to 1.70, and for MI, 0.0 to 1.55) but did not differ significantly according to progestin type. Users of the contraceptive ring had an increased risk for CVA (RR, 2.49 [CI, 1.41 to 4.41]) but not for MI (RR, 2.08 [CI, 0.67 to 6.48]). Women who used the patch or progestin-only products (such as implant, intrauterine system, or oral contraceptives) were no more likely than nonusers to have CVA.

Cautions: Data on participants' smoking status were incomplete. Few events were noted among patch users (2 CVAs and no MIs), resulting in limited power to assess differences in risks.

Implications: Combined oral hormonal contraception is associated with a small but statistically significant increase in the risk for CVA and MI. This risk is lower with COCs that contain only 20 mcg of ethinyl estradiol versus larger amounts. In contrast to what has been seen with VTE, there is no significant difference in the risk for arterial outcomes according to progestin type. The contraceptive ring, which is used continuously, potentially results in more sustained exposure to estrogen than COCs and may explain the greater RR for CVA seen with this product. Further studies are needed to quantify the risk associated with patch use.

Ulipristal Acetate Is a Safe and Effective Alternative to Leuprolide Acetate for the Treatment of Uterine Fibroids

Donnez J, Tomaszewski J, Vázquez F, et al; PEARL II Study Group. Ulipristal acetate versus leuprolide acetate for uterine fibroids. N Engl J Med. 2012;366:421-32. [PMID: 22296076]

Background: Leuprolide acetate is a gonadotropin-releasing hormone agonist that is commonly used before fibroid surgery to reduce uterine volume, size, and intraoperative blood loss (5). However, treatment is associated with hot flashes and decreased BMD. Ulipristal acetate is a selective progesterone-receptor modulator that may be similarly efficacious in presurgical fibroid treatment but associated with fewer side effects. To date, no studies have compared these drugs.

Findings: This noninferiority trial randomly assigned 307 women aged 18 to 50 years with symptomatic uterine fibroids who were eligible for surgery to 13 weeks of either

5 or 10 mg daily of oral ulipristal acetate and a monthly placebo saline injection or daily oral placebo with monthly injection of leuprolide acetate. The primary efficacy end point was the proportion of patients who had a substantial reduction in menorrhagia, as measured by a reported Pictorial Blood Assessment Chart score less than 75 (lower scores indicate less bleeding). Coprimary safety outcomes were chosen to assess the superiority of ulipristal acetate when compared with leuprolide acetate in terms of serum estradiol levels and patients' experiences with hot flashes. In the per-protocol efficacy analysis, 90% of women in the 5-mg ulipristal acetate group, 98% of women in the 10-mg ulipristal acetate group, and 89% of women in the leuprolide acetate group reported Pictorial Blood Assessment Chart scores less than 75 after 13 weeks of therapy (difference, 1.2 [CI, −9.3 to 11.8] for 5 mg of ulipristal vs. leuprolide and 8.8 [CI, 0.4 to 18.3] for 10 mg of ulipristal vs. leuprolide). Bleeding was controlled more rapidly, mean estradiol levels were significantly greater, and hot flashes were less common in the ulipristal acetate groups. Similar numbers of women in each group subsequently had fibroid surgery.

Cautions: No black women were included, and the average body mass index of study participants was 25 kg/m^2, limiting generalizability.

Implications: Ulipristal acetate, at a daily dose of 5 or 10 mg for 13 weeks, is noninferior to leuprolide acetate for presurgical treatment of uterine fibroids and is superior in terms of side effects and tolerability. Ulipristal acetate is a welcome addition to the limited armamentarium for medical treatment of uterine fibroids, but further study is needed to determine whether it results in fewer surgical procedures.

Menopause

Hormone Therapy May Reduce the Risk for Death or Cardiovascular Events in Young, Recently Menopausal Women

Schierbeck LL, Rejnmark L, Tofteng CL, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. BMJ. 2012;345:e6409. [PMID: 23048011]

Background: In the Women's Health Initiative (WHI), women (average age, 63 years) randomly assigned to combined estrogen and progesterone therapy versus placebo had an increased risk for MI after 5 years. Reanalysis according to participants' age and years since menopause suggested that women in early menopause may actually benefit from hormone therapy (6, 7). However, controversy persists.

Findings: Researchers used data from DOPS (Danish Osteoporosis Prevention Study) to investigate the effect of triphasic estradiol–norethisterone (or estradiol for patients who have had a hysterectomy) versus placebo on the composite outcome of death or admission for MI or heart failure, death or breast cancer diagnosis, other cancer, and hospitalization for VTE. A total of 1006 women (mean age, 49.7 years [average time since menopause, 7 months]) were randomly assigned and treated with hormone therapy or placebo for 10 years. The composite outcome of all-cause mortality and admissions for heart failure or MI occurred in 3.2% of hormone users and 9.7% of placebo users (hazard ratio [HR], 0.48 [CI, 0.26 to 0.87]). Women in the hormone group were less likely to die or be diagnosed with breast cancer (4.4% vs. 7.9%; HR, 0.54 [CI, 0.32 to 0.91]). Rates of pulmonary embolism and deep venous thrombosis were low and did not differ significantly between groups.

Cautions: This open-label trial was designed to evaluate hormone therapy for the primary prevention of osteoporotic fracture, and the composite cardiovascular outcome was not prespecified (7). Only 49 composite events occurred at 10 years and 86 events at 16 years, so these findings are imprecise. The DOPS findings about other outcomes also have wide CIs that overlap respective estimates from the WHI; there was limited power to differentiate between the effects of combined hormone therapy and estrogen-only therapy; and participants had few cardiovascular risk factors and were treated with 17β-estradiol, which may be less thrombogenic than conjugated equine estrogen.

Implications: Although this osteoporosis prevention trial suggests that young, recently menopausal women who received hormone therapy for 10 years had decreased risk for death and admissions for MI or heart failure, the limitations noted above and the limited power to assess risk for thromboembolism should temper enthusiasm for hormone therapy in primary prevention of cardiovascular disease as reflected in current guidelines (8, 9).

Prevention and Screening

Screening for IPV Did Not Improve Quality of Life

Klevens J, Kee R, Trick W, et al. Effect of screening for partner violence on women's quality of life: a randomized controlled trial. JAMA. 2012;308:681-9. [PMID: 22893165]

Background: Annually, approximately 1.5 million women in the United States experience IPV. Victims of IPV are at increased risk for sexually transmitted infections, chronic pain, depression, and substance abuse (10). However, in 2004 the U.S. Preventive Services Task Force (USPSTF) indicated that there was a lack of clear evidence to recommend for or against IPV screening (11).

Findings: The investigators randomly assigned 2708 primary care patients to 1 of 3 study groups: computerized

screening for IPV and receipt of an IPV resource list (intervention group); receipt of an IPV resource list only; and receipt of a general resource list only (control group). Women in the intervention group who screened positive viewed a video advising them to seek help. Effect on quality of life, days lost from work, use of health or partner violence services, and incidence and recurrence of IPV was assessed at 1-year follow-up. Approximately 14% of women had experienced IPV. Mean quality-of-life scores ranged from 44 to 52 and did not differ significantly among the groups (physical composite score, 46.8 [$P = 0.21$]; mental composite score, 48.0 [$P = 0.51$]). Women in each group reported few days lost from work or household activities and were equally likely to have emergency department or ambulatory care visits (mean number of visits, 0.3 [CI, 0 to 0.3] and 5.7 [CI, 4.1 to 7.2], respectively). Among those who reported IPV, the intervention did not result in significant differences in resource use ($P = 0.21$) or IPV recurrence rates ($P = 0.12$).

Cautions: Women who were lost to follow-up (12%) differed significantly from those who were retained. The generalizability of findings may be limited by the urban setting.

Implications: A computerized screening tool and provision of an IPV resource list did not improve quality of life or reduce days lost from work or household activities, health care use, or IPV recurrence among screened women in outpatient primary care settings. The brevity of this intervention (a 1-time occurrence) and its lack of personalization (video and print literature rather than face-to-face counseling) may have limited its efficacy.

HPV Testing Is Useful for Routine Cervical Cancer Screening

Rijkaart DC, Berkhof J, Rozendaal L, et al. Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomised controlled trial. Lancet Oncol. 2012;13:78-88. [PMID: 22177579]

Background: Routine screening has dramatically reduced cervical cancer mortality. The Papanicolaou (Pap) smear is a common method for screening, although liquid-based cytology for primary cervical cancer screening is widespread and has the potential advantage of including HPV testing. Human papillomavirus testing is recommended for the triage of abnormal Pap smears, but its role in routine screening has been controversial.

Findings: The POBASCAM (Population Based Screening Study Amsterdam) was a population-based, randomized, controlled trial. Women aged 30 to 60 years were enrolled as part of a nationwide screening program. Screening was done every 5 years. Women were randomly assigned to either HPV or cytology cotesting (intervention group) versus cytology alone. At the second testing, HPV DNA and cytology cotesting were done in both groups. The primary outcome was CIN grade 3 or worse, a clinically significant cervical cancer precursor. All analyses used an intention-to-screen approach. A total of 22 400 participants were randomly assigned to the intervention group and 22 518 were randomly assigned to the control group. Of these, 19 999 and 20 106, respectively, were eligible for analysis at the first screen; 19 579 and 19 731, respectively, were eligible for analysis at the second screen (5 years later); and 16 750 and 16 743, respectively, attended the second screen. At baseline, more cases of CIN grade 2 or worse were detected in the intervention group (RR, 1.25 [CI, 1.05 to 1.50]). At the second screen, CIN grade 3 or worse was less common in the intervention group (RR, 0.73 [CI, 0.55 to 0.96]). Cervical cancer was also less common in the intervention group (4 in 19 579 vs. 14 in 19 731; RR, 0.29 [CI, 0.10 to 0.87]). Cumulative detection of CIN grade 3 or worse and CIN grade 2 or worse did not differ significantly between study groups or for subgroups including women invited for the first time and differing age groups. A major component of the effect was detection of high-grade cervical lesions caused by HPV-16.

Cautions: The study was not large enough to provide information about the effect of early detection of non–HPV-16 types on the development of CIN abnormalities.

Implications: Using HPV DNA testing for cervical cancer screening leads to earlier detection of clinically relevant CIN grade 2 or worse that, when treated, leads to improved protection against CIN grade 3 or worse and cervical cancer. The results of this study provide evidence for the 2012 recommendations of the USPSTF (12) and the joint guidelines of the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology (13), which support inclusion of HPV testing into routine cervical cancer screening among women aged 30 to 65 years (**Table**).

Mortality Reduction From Breast Cancer Is Smaller Than Previously Believed

Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. N Engl J Med. 2012;367:1998-2005. [PMID: 23171096]

Background: Screening should lead to diagnosis of earlier-stage cancer, and early treatment should lead to more benefit than treatment given at the time of clinical presentation. Effective screening programs should lead to a reduction in diagnosis of late-stage cancer.

Findings: Data from the SEER (Surveillance, Epidemiology and End Results) registry between 1976 and 2008 were used to evaluate trends in the incidence of early-stage breast cancer (ductal carcinoma in situ and localized disease) and late-stage breast cancer (regional and distant disease) among women aged 40 years or older. Data from the National Health Interview Survey were used to calculate the proportion of women having screening mammography. All estimates were adjusted for the transient increase associated with hormone therapy use from 1990 to 2005.

Screening mammography was associated with a doubling of the annual number of cases of early-stage breast cancer (from 112 to 234 cases per 100 000 women). The rate of presentation with late-stage breast cancer decreased by 8% (from 102 to 94 cases per 100 000 women). Assuming a constant underlying disease burden, 8 of the additional 122 cancer cases detected would be expected to progress to advanced disease. Overdiagnosis is defined as tumors detected by screening that would never have led to clinical symptoms. After adjustment for trends in breast cancer incidence, authors estimated that in 2008 more than 70 000 women were overdiagnosed with breast cancer (31% of all diagnosed cases).

Cautions: Results are based on estimates of baseline incidence, which may not be entirely accurate, and the investigators' ability to remove the effect of hormone therapy, which may not be entirely precise.

Implications: Screening mammography has led to a substantial increase in diagnosis of early-stage breast cancer, with only a small reduction in diagnosis of late-stage breast cancer. Reduction of mortality from screening seems to be smaller and the risk for overdiagnosis greater than previously believed.

Osteoporosis and Bone Health

Few Women With Normal BMD Will Develop Osteoporosis at 15-Year Follow-up

Gourlay ML, Fine JP, Preisser JS, et al; Study of Osteoporotic Fractures Research Group. Bone-density testing interval and transition to osteoporosis in older women. N Engl J Med. 2012;366:225-33. [PMID: 22256806]

Background: The USPSTF recommends screening for osteoporosis in all women aged 65 years or older and screening younger women whose fracture risk is equal to or greater than that of a 65-year-old white woman who has no additional risk factors. However, they state that "evidence is lacking about optimal intervals for repeated screening" (14). A minimum of 2 years may be needed to reliably measure a change in BMD, and longer intervals may be needed to improve fracture risk prediction.

Findings: Community-dwelling women ($n = 4597$) from the SOF (Study of Osteoporotic Fractures) who were aged 65 years or older received BMD tests at baseline and at 2, 6, 10, and 16 years. The main outcome was the estimated interval for 10% of persons to transition from normal BMD or osteopenia to osteoporosis before a hip or clinical vertebral fracture or treatment of osteoporosis. Within each T-score range, a percentage of women developed osteoporosis over 15 years. Among women with normal BMD at baseline, 0.8% developed osteoporosis; among those with mild osteopenia (T-score, −1.01 to −1.49), 4.6% developed osteoporosis; among those with moderate osteopenia (T-score, −1.50 to −1.99), 20.9% developed osteoporosis; and among those with advanced osteopenia (T-score, −2.00 to −2.49) at baseline, 62.3% developed osteoporosis at 15-year follow-up. Competing risks analyses were used to calculate the adjusted interval between baseline testing and development of osteoporosis in 10% of study participants. For women with normal BMD at baseline, it was 16.8 years; 17.3 years for those with mild osteopenia; 4.7 years for those with moderate osteopenia; and 1.1 years for those with advanced osteopenia.

Cautions: Approximately 49% of the original SOF participants could not be included in the analysis because they had osteoporosis at baseline, had a history of hip or clinical vertebral fracture, or received osteoporosis treatment. Most SOF participants were white.

Implications: Few women with normal BMD at baseline will develop osteoporosis with a screening interval of 15 years. Among women with moderate osteopenia, few will develop osteoporosis with a rescreening interval of 5 years. Rescreening recommendations will probably be based on the likelihood of osteoporosis progression according to initial BMD.

Dietary Calcium May Be Safer Than Supplemental Calcium

Li K, Kaaks R, Linseisen J, et al. Associations of dietary calcium intake and calcium supplementation with MI and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg). Heart. 2012;98:920-5. [PMID: 22626900]

Background: Calcium supplements are widely recommended for bone health, but recent meta-analyses have suggested an increase in cardiovascular events with supplemental calcium (15–17). The role of dietary calcium has been less clear.

Findings: This prospective cohort study included 23 980 residents of Heidelberg, Germany, aged 35 to 64 years who were recruited between 1994 and 1998 and did not have a history of MI, stroke, or transient ischemic attack or outlier values for dietary calcium intake at baseline. After an average follow-up of 11 years, 354 MIs, 260 strokes, and 267 cardiovascular disease deaths occurred. Persons with calcium intake in the third quartile had a decreased risk for MI compared with the first quartile (HR, 0.69 [CI, 0.50 to 0.95] for dietary calcium and 0.68 [CI, 0.50 to 0.93] for dairy calcium), but the overall trend was not significant. In subgroup analysis by sex, the effect of dietary calcium was significant in women (HR, 0.80 [CI, 0.50 to 0.94]) but not in men (HR, 0.80 [CI, 0.56 to 1.14]). Calcium supplement users had an increased risk for MI compared with nonusers (HR, 1.87 [CI, 1.17 to 2.96]). For those who took only calcium supplements, the HR was 2.39 [CI, 1.12 to 5.12]). There was no association between calcium supplements and other cardiovascular outcomes.

Cautions: Dietary intake was measured only once at baseline, and thus, variations in calcium intake over time could not be evaluated.
Implications: Increasing dietary calcium may not lead to cardiovascular benefits, although calcium supplements may be associated with an increased risk for MI.

PPIs Are Associated With Hip Fracture

Khalili H, Huang ES, Jacobson BC, et al. Use of proton pump inhibitors and risk of hip fracture in relation to dietary and lifestyle factors: a prospective cohort study. BMJ. 2012;344:e372. [PMID: 22294756]

Background: Proton-pump inhibitors are some of the most commonly prescribed drugs worldwide and have been available over the counter in the United States since 2003 (18). Previous studies have suggested an association between PPI use and hip fracture, although these studies have had limitations, including being retrospective, the inability to control for confounders, and the inability to validate the dose and duration of PPI use (19–26). The U.S. Food and Drug Administration issued a warning about the potential association in May 2010 but acknowledged that more data were needed (27).
Findings: The Nurses' Health Study prospective cohort includes 79 899 postmenopausal women who complete a questionnaire every 2 years. Data are collected on H_2-blocker use, PPI use, exercise, smoking, body mass index, alcohol intake, menopause and hormone therapy, calcium and vitamin D intake, diagnosis of osteoporosis, and use of osteoporosis medications. Use of PPIs increased from 6.75% of women in this cohort in 2000 to 18.95% in 2008. The absolute risk for hip fracture, adjusted for multiple confounders, was 2.02 per 1000 person-years in users versus 1.51 per 1000 person-years in nonusers (HR, 1.36 [CI, 1.13 to 1.63]). Risk increased with duration of use and varied based on smoking history (HR, 1.51 [CI, 1.20 to 1.91] in smokers and 1.06 [CI, 0.77 to 1.46] among those who have never smoked). The estimates were not affected by the reason for PPI use. In addition, the authors conducted a meta-analysis that incorporated all 7 studies included in the U.S. Food and Drug Administration report and an additional 4 studies. A total of 1 562 862 persons were included in the 11 studies. The pooled odds ratio of hip fracture associated with PPI use was 1.28 (CI, 1.19 to 1.37).
Cautions: Type and dose of PPI were not available. Hip fracture was self-reported, but a validation study showed that self-report was extremely accurate in this cohort of nurses.
Implications: Regular use of PPIs is associated with an increased risk for hip fracture in postmenopausal women. Clinicians should periodically evaluate the need for long-term PPI use, especially in current and former smokers.

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