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Clinical Oncology [ALERT]

A monthly update of developments in cancer treatment and research

## ABSTRACT & COMMENTARY

# Chemotherapy Prior to Chemoradiotherapy for Neoadjuvant Rectal Cancer Treatment

*By William B. Ershler, MD*

SYNOPSIS: In a series of consecutive patients with locally advanced rectal cancer, a novel treatment regimen was studied that involved "induction chemotherapy" followed by chemoradiotherapy prior to total mesorectal excision. The investigators found a high local control rate and promising disease-free and overall survival outcomes.

SOURCE: Schou JV, et al. Induction chemotherapy with capecitabine and oxaliplatin followed by chemoradiotherapy before total mesorectal excision in patients with locally advanced rectal cancer. *Ann Oncol* 2012;23:2627–2633.

Approximately 50% of patients with rectal cancer present with locally advanced disease, and for these patients the current standard of care includes preoperative chemoradiotherapy (CRT) followed by total mesorectal excision (TME).[1,2] The addition of preoperative CRT has resulted in improved rates of local control but not disease-free survival (DFS) or overall survival (OS).[3,4] CRT as it is currently configured has limited effect on the rates of distant recurrence. Thus, an effort to eliminate distant metastatic disease as a component of the initial treatment plan would seem worthwhile.

To this end, Schou and colleagues from Herlev Hospital in Copenhagen developed a modified CRT program that included initial capecitabine/oxaliplatin (CAPEOX) chemotherapy followed by CRT all prior to TME.

A total of 84 consecutively admitted patients with T4 tumors, T3N+ tumors, or T3 tumors involving or with a distance ≤ 1 mm to the mesorectal fascia were included. Initial chemotherapy was with capecitabine at 2000 mg/m$^2$ administered in divided doses twice a day for 14 days followed by 7 days of rest. Oxaliplatin was given every 3 weeks at a dose of 130 mg/m$^2$ for two cycles. Radiation therapy (RT) was given with 54 Gy in 27 fractions (five fractions/week). Capecitabine (1650 mg/m$^2$ in divided doses) was continued through the radiation therapy and administered on the days of RT.

Of 84 consecutively admitted patients starting induction CAPEOX, 77 patients underwent surgery. R0 resection was achieved in 94% and T downstaging in 69%. In the intention-to-treat group, pathological complete response was seen in 23%. Five-year DFS and OS were 63% (95% confidence

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interval [CI], 52.2%-73.7%) and 67% (95% CI, 56.1%-77.3%), respectively.

As expected, nodal status assessed from the TME specimen proved to be an important predictor of both DFS and OS. Twenty-one patients (28%) had malignant lymph nodes in the resected specimen. For patients without malignant lymph nodes, the 5-year OS was 85% (95% CI, 75.3%-94.9%) compared with 44% (95% CI, 20.7%-66.7%) in patients with malignant lymph nodes and a hazard ratio of 4.5 (95% CI, 1.8-11.1) was seen. The 5-year DFS was 86% (95% CI, 75.9%-95.1%) for patients without malignant lymph nodes compared with 29% (95% CI, 8.8%-48.4%) in patients with malignant lymph nodes and the hazard ratio was 7.5 (95% CI, 3.1-18).

Grade 3/4 toxicity was seen in 18%, and four deaths occurred within 2 months of therapy. Of the four deaths, one had colitis, leading to sepsis. The second developed acute renal dysfunction, bilateral bronchopneumonia, and several minor pulmonary embolisms as determined by autopsy. The third died of ileus and the autopsy report also showed signs of heart failure. The fourth patient died of unknown cause after two series of CAPEOX. Two incidents of cerebral vascular accident were observed, one after a single cycle of CAPEOX and the second halfway through CRT, respectively. One patient had a resectable tumor after finishing both induction chemotherapy and chemoradiation but was considered unfit for surgery. Morbidity within 30 days of surgery was fistula formation (n = 3), anastomotic leak (n = 3), pelvic abscess (n = 2), and local infection (n = 7).

## COMMENTARY

Presurgery RT and CRT have proven effective in reducing local recurrence.[3] In a recent pooled analysis of 2795 patients receiving either RT or CRT prior to TME, it was noted that for those receiving CRT there was an apparent benefit in terms of distant metastases and overall survival.[5] Yet, distant recurrence in liver, lung, or in other organs remains a fairly common occurrence even in those receiving CRT. The currently reported approach in which an initial chemotherapy "induction" was given prior to CRT was founded on the rationale that more intensive early chemotherapy might successfully eliminate existing microscopic metastases and result in fewer late recurrences. The results were encouraging, particularly because no distant recurrences were identified after 36 months (through 56 months of follow-up).

Nonetheless, there are some precautionary concerns. Although consecutive patients were treated according to protocol, this was a single-institution, retrospective analysis and such treatment outcomes may not be generalized. Furthermore and importantly, there was significant toxicity during the chemotherapy induction precluding the application of CRT/TME in a few patients. Thus, the observed excellent local control rate and promising DFS and OS data need to be confirmed by prospective, randomized clinical trial before "induction chemotherapy" becomes a community standard. ■

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# ABSTRACT & COMMENTARY

## Cognitive Function in Breast Cancer Survivors

*By William B. Ershler, MD*

SYNOPSIS: There has long been an appreciation of the risk of cognitive decline associated with chemotherapy but questions remain about the magnitude and duration of the observed deficits.

In this meta-analysis of studies that included neuropsychological assessments at a minimum of 6 months after completion of breast cancer chemotherapy, definite but small deficits were found for both verbal and visuospatial capabilities. In this analysis, age and educational status were not found to be moderators of acquired deficits.

SOURCE: Jim HSL, et al. Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. *J Clin Oncol* 2012;30:3578-3587.

Whereas there has been substantial research on the cognitive effects of chemotherapy, including prior meta-analyses,[1-4] the issue remains unclear whether such treatment produces long-term deficits, and if so, how much. It remains well-established that moderate-to-severe cognitive impairment occurs in a substantial percent of chemotherapy-treated breast cancer patients (between 15% and 75%[5,6]). Yet, evidence is mixed regarding long-term cognitive deficits in patients treated with chemotherapy. Furthermore, some data now suggest that cognitive deficits may develop after the completion of treatment.[7]

Previous meta-analyses, the latest of which was published in 2006, were not focused specifically on the post-chemotherapy period, and since these publications there have been several reports providing additional information. Thus, Jim and colleagues performed the current meta-analysis, the goal of which was to assess cognitive functioning in breast cancer survivors who were treated with chemotherapy a minimum of 6 months prior to analysis.

The investigators, by searching PubMed and other major databases, found 2751 abstracts, and from these they found 17 studies that met stringent criteria for inclusion in this analysis. The 17 studies included 807 patients previously treated with standard-dose chemotherapy for breast cancer and on whom cognitive studies were performed 6 months or more after completion of chemotherapy. Neuropsychological tests were categorized according to eight cognitive domains: attention, executive functioning, information processing, motor speed, verbal ability, verbal memory, visual memory, and visuospatial ability.

Deficits in cognitive functioning were observed in patients treated with chemotherapy relative to controls or prechemotherapy baseline in the domains of verbal ability ($g = -0.19$; $P < 0.01$) and visuospatial ability ($g = -0.27$; $P < 0.01$). Patients treated with chemotherapy performed worse than non-cancer controls in verbal ability and worse than patients treated without chemotherapy in visuospatial ability (both $P < 0.01$). Age, education, time since treatment, and endocrine therapy did not moderate observed cognitive deficits in verbal ability or visuospatial ability (all $P \geq 0.51$).

## COMMENTARY

Results indicate that, on average, observed cognitive deficits in patients with breast cancer previously treated with chemotherapy are small in magnitude and limited to the domains of verbal ability and visuospatial ability. That the magnitude of observed deficits is small is reassuring, particularly when considering some of the fairly dramatic changes that have been reported for breast cancer patients actively receiving therapy. However, persistence of deficits 6 months and beyond raises concerns that such deficits might be long lasting, if not permanent.

One unexpected finding was that age and education status were not shown to moderate the effects of chemotherapy-induced cognitive change. However, the strength of this and other conclusions based on meta-analysis is only as robust as the studies examined in the analysis, and the authors acknowledged that there might not have been sufficient numbers of older or less-educated patients to demonstrate significant associations. In contrast, in one recent report,[8] age and "cognitive reserve" (an attribute comprised of such factors as education, employment, and cognitive stimulation) were shown to be important factors predicting chemotherapy-associated decline. Thus, older patients with low levels of pretreatment cognitive reserve were found to be most vulnerable to post-treatment cognitive decline.

Another concern is that this, as with many of the reports of chemotherapy-associated brain deficits, focused on breast cancer patients only. Such patients often receive additional and somewhat complex treatment regimens that include surgery, radiation, and hormonal treatments, all of which may confound interpretation of observed findings. Thus, it would be premature to generalize these findings to chemotherapy treatment in general. Further, most of the primary studies on this topic exclude patients who might be at highest risk for cognitive decline, such as those with significant comorbidities, depression, or neurologic disorders. Thus, as highlighted by the accompanying editorial,[9] the findings from this meta-analysis might significantly under represent the magnitude of the cognitive impact of cancer treatments. ■


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## ILLUSTRATIVE CASE SERIES

# Aspirin and Cancer Prevention

***By Jerome W. Yates, MD***

*Hematology/Immunology Unit, National Institute on Aging, National Institutes of Health*

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

A 62-year-old Caucasian woman returns to her primary care physician for a follow-up visit after routine colonoscopy and is accompanied by her 63-year-old husband. The gastroenterologist had resected three adenomatous polyps and suggested a repeat colonoscopy in 1 year. She is presently taking no daily medicines and is in good health, and her physician suggested that she might consider taking aspirin (either 325 mg or if that dose caused gastrointestinal symptoms an 81 mg enteric-coated tablet, daily). He had explained that there was now evidence that such treatment is associated with diminished polyp development and colon cancer, as well as reduced cardiovascular disease in individuals taking daily prophylactic aspirin.

Her husband then inquired whether he should be taking aspirin for the same reasons, but particularly to prevent prostate cancer. He is concerned because his younger brother (age 62) just died from metastatic prostate cancer, and although there was no definitive diagnosis his 84-year-old father may have had prostate cancer.

Their physician said that daily aspirin was the most cost-effective way of preventing some cardiovascular disease and selected cancers, and he would suggest they both consider this approach while being cognizant of potential "bleeding problems" and the need for routine follow-up because both had risk factors for cancer deserving professional attention.

## Discussion

Hippocrates (460 B.C-377 B.C.) left records that a powder from the leaves and bark of willow trees could be used to treat pain and fever, and 19th century scientists found the active ingredient to be salicin. Subsequent extractions of salicin yielded salicylic acid, which caused gastritis when ingested and required buffering to become acetyl salicyclic acid (aspirin). Beyond pain relief and its antipyretic properties, aspirin has been found to decrease platelet adhesion and thereby diminish platelet clumping and clot formation. Preclinical studies have shown that aspirin inhibits cyclooxygenase (particularly COX-2 isoform), an enzyme found to be overexpressed in some cancer cells. Whereas the mechanisms by which COX-2 influences cancer development and growth is incompletely understood, there is evidence that it plays a role in carcinogenesis, cancer growth, apoptosis, and blood vessel formation.[1] In a recent meta-analysis of 139 observational studies,[2] the investigators conclude that published observational studies when taken in aggregate demonstrate a beneficial role of aspirin on colorectal and other digestive tract cancers and modest risk reductions for breast and prostate cancer. However, the authors point out the significant heterogeneity across studies and that dose-risk and duration-risk relationships still remain unclear.

This patient presented above had three adenomatous polyps and had no history of taking aspirin regularly in the past. In an earlier meta-analysis of randomized trials examining aspirin as a chemopreventive agent for patients with colorectal adenomas, the data would seem to support the recommendation by her physician.[3] Inasmuch as adenomatous polyps are considered premalignant, aspirin treatment in this situation may, indeed, be preventing occult colorectal cancer at its earliest stage of development. Along with the follow-up colonoscopy, the

suggestion for aspirin chemoprevention for this patient is reasonable if well tolerated.

The situation for her husband presents a different set of questions:
1. Is this a case of familial prostate cancer?
2. Are there clinical differences besides risk for sporadic and familial prostate cancer?
3. Do aspirin or other anticoagulants play a role in prostate cancer prevention and/or its clinical course?

In the case of the patient's husband, there is an increased probability that there may be a familial risk because of the relatively young age of his brother who had prostate cancer to which his death was attributed. The presence of a suggestive clinical diagnosis of prostate cancer in the elderly father, who was a nursing home resident, should serve as an indication closer follow-up of the patient's husband. Fatal familial prostate cancers may represent a subgroup, because some familial prostate cancer patients demonstrate good survival following diagnosis.[4] The largest cohort studies suggest a statistically significant risk reduction for incident prostate cancers among aspirin users.[2] Daily aspirin reduces the risk for developing metastases and dying from prostate cancer based on information extracted from randomized controlled trials.[5] With demonstrable efficacy in the presence of overt disease, it is an unproven but logical extrapolation to expect benefit in limiting incident prostate cancers or the rate of progression of covert disease.

In summary, both wife and husband may benefit from daily aspirin exposure in the attempt to prevent cancer and cardiovascular disease. There are risks of chronic aspirin treatment and these should be considered when treating otherwise healthy individuals. ■


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## ABSTRACT & COMMENTARY

# The Changing Paradigm of Vulva Cancer Management


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

*Professor, University of Texas; M.D. Anderson Cancer Center, Houston*

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



SYNOPSIS: **Among women with early-stage squamous cell carcinoma of the vulva, sentinel node biopsy is a reasonable alternative to inguinal femoral lymphadenectomy. Histological ultrastaging is an important adjuvant to sentinel node assessment for metastatic disease.**


SOURCE: Levenback CF, et al. Lymphatic mapping and sentinel lymph node biopsy in women with squamous cell carcinoma of the vulva: A Gynecologic Oncology Group study. *J Clin Oncol* 2012;Jul 2 [Epub ahead of print].


This article originally appeared in the October 2012 issue of *OB/GYN Clinical Alert*.


Sentinel lymph node biopsy is an assessment tool for early metastatic nodal spread used in management of many solid tumors. To evaluate its safety as a replacement for inguinal femoral lymphadenectomy (IFN), a multi-institutional clinical trial was conducted proscribing sentinel lymph node (SLN) biopsy ahead of full IFN in women with early-stage vulvar cancer. Eligible patients were to have invasive (≥ 1 mm) squamous cell carcinoma of the vulva between 2 and 6 cm in size and clinically non-suspicious groin nodes. Sentinel lymph node localization was performed using dye and radionuclide with optional lymphoscintigraphy. Identified SLNs were prepared using step sectioning and stained for cytokeratin using immunohistochemistry (IHC). In all, 452 patients underwent the procedure with SLNs being identified in 418 (92%). Nodal metastases were identified by routine pathological assessment in 102 and by IHC in 30 additional patients (node metastasis rate 29%). Among those where a SLN was identified, the false-negative rate (SLN histologically negative, but metastatic nodal disease positive on IFN) was 8% (11/132). The false-negative predictive value, a metric that also includes the majority population of true-negative assessments (1-negative-predictive value) was 3.7%. In women with primary tumors < 4 cm in size, the false-negative rate was 2%. The authors conclude that the procedure may be safely substituted for IFN in selected women with early-stage vulvar cancer.

## COMMENTARY

Primary carcinoma of the vulva is a rare but debilitating disease of primarily elderly women. In the last 100 years, surgical excision following the Halsteadian approach for breast cancer led to disease cures, but with great morbidity and disfiguration. Significant milestones in contemporary management came with documentation of: 1) the safety of separating the primary radical excision of the vulva from the IFN (the "triple incision" technique),[1] 2) the recognition that lateralized primary tumors were rarely associated with bilateral groin metastases,[2] and 3) primary vulvar excision didn't require complete vulvectomy. Further advances came with introduction of radiation (and chemoradiation) both as adjuvant and neoadjuvant therapy.[3] Indeed, these modifications improved survival, reduced morbidity, and provided, in many cases, functionality to the vulva. SLN biopsy is the next great iteration in this continuum. The importance of the procedure is underscored by the observation that most women with early-stage disease will not have nodal spread and gain nothing other than morbidity, such as lymphedema, from IFN. The obvious concern in adopting a "minimalization" alternative to full IFN is missing prevalent disease without therapy,[4] particularly since recurrent groin disease is particularly difficult to manage and is often a fatal event.

SLN biopsy is not new to management of vulvar cancer; early descriptions appeared in the early 1990s.[5] However, large-scale validation took the international community to assemble the collective experience of two organizations to highlight the safety of this approach. I have previously highlighted one of these, the GROINS-V study, which reported about 4 years ago.[6] The latest, from the Gynecologic Oncology Group, largely recapitulates that experience, particularly when similar cohorts are examined. The primary difference between the studies, though, is the level of experience of the contributing members. The majority of contributors to the latter study were novices with the technique and did not have to undergo a competency evaluation prior to participating in the trial. This may have led to the higher than initially expected false-negative rate, but it provides external validity for the procedure in this rare disease. Under the identified constraints (tumors less than 4 cm, squamous histology, and clinically negative groins), SLN appears to be safely substituted for IFN. Current investigation is prospectively assessing the merit of SLN-only groin dissection (node negative and node positive) for survival and morbidity, including quality of life. ■


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# Birth After 30 Lowers Endometrial Cancer Risk


***By Rebecca Bowers***

*Consulting Editor, Contraceptive Technology Update*


**Ms. Bowers reports no financial relationships relevant to this field of study.**


This article originally appeared in the November 2012 issue of *Contraceptive Technology Update*.


Women who last give birth at age 40 or older have a 44% decreased risk of endometrial cancer when compared to women who have their last birth under the age of 25, according to results of a new international study.[1] Study findings indicate the risk begins to decrease after age 30 by about 13 percentage points for each five-year delay in last births.

Cancer of the endometrium is the most common gynecologic malignancy in the U.S. and accounts for 6% of all cancers in women.[2] In 2012, the American Cancer Society estimates there will be 47,130 new cases of uterus cancer (endometrial cancer and uterine sarcomas), with 8010 deaths attributed to the two cancers.[2] Symptoms can include abnormal vaginal bleeding, spotting or other discharge (particularly after menopause), pelvic pain or mass, and weight loss (usually seen in later stages of the disease.)[3] Risk of disease increases with age. More than half of all endometrial cancers are diagnosed in women ages 50-69.[3]

What are possible causes for endometrial cancer? Exposure of the endometrium to estrogen that is "unopposed" by progesterone is a common cause. Since pregnancy results in large changes in exogenous estrogen and progesterone levels, data indicates that pregnancy influences the incidence of endometrial cancer.[1]

What prompted the international research team to look at the impact of later childbirth on the incidence of endometrial cancer? Researchers analyzed impact of age at last birth, because data indicates parity and number of children are important factors influencing woman's risk of developing endometrial cancer, says V. Wendy Setiawan, PhD, lead investigator and assistant professor in the Department of Preventive Medicine at the University of Southern California Keck School of Medicine in Los Angeles.

However, whether timing of birth and age of giving birth are also associated with risk is unclear, says Setiawan. This question led the researchers to look at age at birth in relation to endometrial cancer risk. The current analysis focused on age at last birth because previous studies indicate that women who gave birth to their last child after 30 or 35 have lower risk of endometrial cancer compared to women who had their last birth at a younger age.[4-5]

To perform the analysis, the research team pooled individual-level data from four cohort and 13 case-control studies in the Epidemiology of Endometrial Cancer Consortium, a National Cancer Institute-supported consortium dedicated to studying the etiology of endometrial cancer through collaboration. A total of 8671 cases of endometrial cancer and 16,562 controls were included in the analysis.

After adjusting for known risk factors, data indicate that endometrial cancer risk declined with increasing age at last birth (*P* [trend] < 0.0001). The pooled odds ratio per 5-year increase in age at last birth was 0.87 (95% confidence interval [CI], 0.85-0.90). Women who last gave birth at age 40 or older had a 44% decreased risk compared with women who had their last birth under age 25 (95% CI, 47-66). The protective association was similar across the different age-at-diagnosis groups and for the two major tumor histologic subtypes (type I and type II), the researchers report. No effect modification was observed by body mass index, parity, or exogenous hormone use, they state.[1]

The current study, which is the largest to date to examine the issue, confirms the finding that late age at last birth is independently associated with a reduced risk of endometrial cancer, says Setiawan. Data also demonstrate that the protective association persisted for decades, she notes.

## Talk with Patients

Researchers point to several potential biologic mechanisms that might explain why age at last birth might protect against endometrial cancer. They

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include:

- women who are capable of becoming pregnant at an older age might possess a "healthy" endometrium or experience fewer anovulatory cycles;
- prolonged exposure to progesterone during pregnancy might be more protective at older ages, when endometrial cancer development normally occurs;
- shedding of premalignant and malignant cells from the mucosal lining of the uterine cavity, which are more likely to exist with advancing age, might occur during childbirth.[1]

Woman who choose to space their births might obtain additional protection against endometrial cancer with the use of combined oral contraceptives (COCs). According to *Contraceptive Technology*, women who use COCs for at least a decade reduce their risk of developing endometrial cancer by 80% compared to nonusers.[6,7] This protection against cancer endures for up to 20 years following pill discontinuation.[8]

For women who have endometrial hyperplasia, a precursor to endometrial carcinoma, *Contraceptive Technology* authors advise use of COCs as a treatment to reverse the condition.[7] ■

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## CME Questions

**1. Two cycles of capecitabine/oxaliplatin prior to chemoradiotherapy (CRT) and total mesorectal excision for locally advanced rectal cancer was demonstrated to be:**

a. effective in achieving local control without added toxicity when compared to CRT alone.
b. achieving comparable excellent local control as CRT and definitively less metastatic late recurrence when compared to CRT alone.
c. achieving comparable excellent local control as CRT and data indicating the possibility of less metastatic late recurrence when compared to CRT alone.
d. effective in reducing the rates of late recurrence but at the cost of less satisfactory local control.

**2. The current meta-analysis of cognitive decline associated with breast cancer chemotherapy was remarkable in that it demonstrated which of the following?**

a. Moderate-to-severe decline in eight domains of cognitive functioning
b. Definite but small in magnitude decline in eight domains of cognitive functioning apparent at a minimum of 6 months after chemotherapy
c. Definite but small in magnitude decline in two domains of cognitive functioning (verbal and visuospatial ability) apparent at a minimum of 6 months after chemotherapy
d. Dramatic decline in two domains of cognitive functioning (verbal and visuospatial ability) apparent at a minimum of 6 months after chemotherapy

**3. In the recent meta-analysis by Bosetti and colleagues, data for cancer prevention by regular aspirin use was most favorable for which tumor type?**

a. Breast cancer
b. Prostate cancer
c. Colorectal cancer
d. Lymphoma

**4. The false-negative predictive value was used as the primary validation metric in the Levenback et al study because it:**

a. is a substitute for specificity in node-negative patients.
b. represents the rate of node-positive patient in whom the SLN was negative.
c. predicts the false-negative rate.
d. considers both correctly determined node-positive and node-negative patients.

## [IN FUTURE ISSUES]

Cetuximab for Patients with Urothelial Tract Carcinoma

Clinical Briefs in Primary Care™

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By Louis Kuritzky, MD

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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## Secondary Prevention of Lacunar Stroke

**Source:** SPS3 Investigators. *N Engl J Med* 2012;367:817-825.

LACUNAR STROKES (L-CVA) ARE SMALL subcortical brain infarctions that may comprise as many as 25% of ischemic strokes. Aspirin (ASA) monotherapy is already established as appropriate treatment for secondary prevention of ischemic stroke, as is clopidogrel (CLOP) monotherapy. In the CAPRIE trial, CLOP provided a *marginal* advantage over ASA for major adverse cardiovascular events (absolute risk reduction = 0.5%) in the overall study population, leading some to advocate clopidogrel routinely over ASA. It is often underrecognized that in the CAPRIE trial, study subjects who enrolled specifically because of previous stroke did *not* experience any statistically significant stroke reduction with CLOP compared to ASA; the outcomes were the same.

The Secondary Prevention of Small Subcortical Strokes (SPS3) trial is the first published trial to compare the efficacy of ASA monotherapy vs ASA + CLOP in reference to L-CVA. The study population included more than 30% Hispanics, concordant with the observation that L-CVA is more common in Hispanics.

At the conclusion of the trial (3.4 years mean), ASA + CLOP was *not* more effective than ASA alone in preventing L-CVA. Among the study population (n = 3020 adults with prior L-CVA), most new strokes were L-CVA (71%).

Unfortunately, as has been seen in other studies of combined ASA + CLOP, bleeding risk was significantly increased compared to ASA alone, as was all-cause mortality. Two prior trials in vasculopathic populations (MATCH, CHARISMA) have arrived at similar conclusions: For persons with stable non-acute vascular disease, ASA + CLOP is not more beneficial than ASA alone, but incurs greater bleeding risk. ■

## Quality-of-life Effects of PSA Screening

**Source:** Heijnsdijk EA, et al. *N Engl J Med* 2012;367:595-605.

THE EUROPEAN RANDOMIZED STUDY OF Screening for Prostate Cancer (ERSPC) is a clinical trial in which adult men (n = 162,243) were randomized to prostate-specific antigen (PSA) screening or no screening. While this trial did find a statistically significant reduction in prostate cancer deaths, overall mortality was not affected, supporting the current recommendations by the United States Preventive Services Task Force (USPSTF) that PSA screening be abandoned. Although the USPSTF decision was based on the "hard" data about mortality, there is likely also substantial quality-of-life (QOL) burden engendered from PSA screening, since many — indeed, the vast majority of — men diagnosed with prostate cancer through PSA screening will die with, not from, their prostate cancer. Additionally, adverse effects of intervention for (the mostly) early prostate cancer detected through screening are not uncommon, and include erectile dysfunction and incontinence. Finally, even in men who elect not to have a surgical intervention in response to prostate cancer detected as a result of PSA screening, it would take little imagination to envision substantial ongoing concerns/anxieties referable to that diagnosis.

Heijnsdijk et al report that per 1000 men screened by PSA, nine fewer prostate-cancer related deaths would occur and 73 life-years would be gained. After adjustment for overdiagnosis and overtreatment of prostate cancer subsequent to PSA screening, these benefits were reduced by almost one-fourth. In an era when PSA screening is no longer supported because of an insufficiently favorable risk:benefit ratio, recognition of the negative QOL impact of PSA screening may help clinicians (and their patients) better come to terms with the now well-recognized limitations of PSA screening. ■

## PSA Elevations After Prostate Cancer Radiotherapy

**Source:** Crook JM, et al. *N Engl J Med* 2012;367:895-903.

SINCE PROSTATE CANCER (PCA) IS OFTEN ANdrogen-dependent, PCA recurrences after radiotherapy are often treated with androgen deprivation by means of regimens consisting of continuous luteinizing hormone-releasing hormone agonists (LHRHa) combined with antiandrogens. Unfortunately, such treatment is associated with hot flashes, decreased libido, urinary symptoms, and fatigue. Might intermittent androgen deprivation be equally effective, but less problematic as far as adverse effects?

Crook et al randomized patients who had undergone radiation treatment for PCA but had a post-treatment PSA > 3.0 ng/dL to continuous or intermittent androgen deprivation.

For overall mortality, intermittent androgen deprivation was non-inferior to continuous treatment. The time to development of castration-resistant disease (the stage at which androgen deprivation no longer represses disease progression) was significantly longer for intermittent treatment. Similarly, the adverse effects of hot flashes, libido, and urinary symptoms were all significantly fewer in the intermittent treatment group. In addition to necessitating a substantially reduced amount of medication (and of course, expense), intermittent androgen deprivation regimens are non-inferior for overall mortality, and are associated with superior quality of life. ■

## Attenuated CV Benefits of Clopidogrel in Diabetes

**Source:** Andersson C, et al. *JAMA* 2012; 308:882-889.

There is no controversy over whether antiplatelet therapy (e.g., aspirin, clopidogrel, prasugrel) reduces cardiovascular (CV) events when used for secondary prevention (i.e., post-acute coronary syndrome, post-myocardial infarction [MI], post-stroke). It is equally apparent that risk reduction through antiplatelet therapy is not equal among all risk groups. For instance, although aspirin (ASA) consistently shows CV risk reduction in mixed populations post-MI, two clinical trials of ASA comprised solely of diabetics failed to show benefit. Diabetics are known to have greater platelet reactivity, and their platelets are relatively resistant to antiplatelet effects as measured by medication-induced platelet aggregation inhibition testing.

Comparative benefits of clopidogrel in diabetics vs non-diabetics have not been described well enough. To assess whether diabetics fare as well with clopidogrel post-MI as non-diabetics, Andersson et al reviewed data from the Danish nationwide administrative registries of patients discharged from the hospital post-MI (n = 58,851), of which 12% had diabetes.

One-year follow-up compared outcomes among all persons treated with clopidogrel. Although all groups did have CV risk reduction from clopidogrel treatment, there was a significant difference between diabetics and non-diabetics, favoring non-diabetics. For instance, the hazard ratio (HR) for all-cause mortality was more than twice as favorable for non-diabetics (HR = 0.75, a 25% reduction) than diabetics (HR = 0.89, an 11% reduction).

The obstacle of clopidogrel-resistant platelets can be overcome by dose intensification (i.e., more clopidogrel), combination therapy (i.e., clopidogrel + ASA), or consideration of another P2y12 agent (i.e., prasugrel). Unfortunately, however, each of these methods has been associated with an increased risk for bleeding. Optimization of antiplatelet therapy in diabetics remains somewhat elusive. ■

## Is A1c Always the Best Game in Town to Monitor Type 2 Diabetes?

**Source:** Wright LAC, Hirsch IB. *Diabetes Spectrum* 2012;25:141-148.

Even as time-honored a metric as A1c has limitations. There are, for instance, situations in which A1c can markedly mis-estimate actual sustained glucose concentrations. Since A1c measurement requires hemoglobin to be exposed to excess glucose for the entire life of a red cell (90-120 days), anything that shortens red cell life (e.g., thalassemia, Hgb C, HbS, hemolysis) will *underestimate* actual sustained glucose levels (since red cells don't live long enough to become fully glycosylated). Hemoglobin F, which is persistent in a small percentage of adults, glycosylates so rapidly that even very modest elevations of glucose can induce marked elevations of A1c (A1c 12%-17% or greater), grossly *overestimating* sustained glucose levels.

Fructosamine is a composite measure of relatively short-lived serum proteins that have become converted into irreversible ketoamines, of which glycated albumin is the primary component (approximately 90%). Since this process occurs over a few weeks, red cell life span — shortened or not — has no impact. Similarly, however, the measurement of fructosamine only provides an observation window of the sustained glucose levels in the preceding 2-3 weeks. Any condition that alters serum protein turnover (eg, thyroid dysfunction, hypopoproteinemia, nephrotic syndrome) can invalidate fructosamine measurement.

Glycated albumin, the primary protein constituent of fructosamine, has been compared with A1c and fructosamine in patients with advanced chronic kidney disease, and found to be the most accurate marker in this population, although it is subject to the same perturbations as fructosamine mentioned above.

One other serum marker not used commonly in the United States, but widely used in Japan, is 1,5 anhydroglucitol (1,5-AG), which reflects sustained glucose over a 2-14 day period. Normally, 1,5-AG is reabsorbed by renal tubules; when plasma and urine glucose are high, they compete with 1,5-AG for reabsorption, resulting in loss of 1,5-AG in the urine, with a corresponding diminution in plasma 1,5-AG. This metric has been found to be particularly useful in measurement of postprandial glucose excesses.

For the time being, A1c will remain the metric of choice for most patients. When A1c and individual glucose measurements are discordant, consideration of another metric is appropriate. ■

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# Do Benzodiazepines Cause Dementia in the Elderly?

***In this issue:*** Dementia and benzodiazepines; effectiveness of omega-3 fatty acid and *Ginkgo biloba* supplements; and FDA actions.

## Benzodiazepines and dementia

Can benzodiazepines increase the risk for dementia? Researchers in France studied 1063 men and women with an average age of 78 who were free of dementia and did not start taking benzodiazepines until they had been followed for at least 3 years. During a 15-year follow-up, 253 cases of dementia were confirmed. New use of benzodiazepines occurred in 9% of the study population and was associated with an increased risk of dementia (32% benzodiazepine group vs 23%, adjusted hazard ratio 1.60, 95% confidence interval [CI] 1.08-2.38). After correcting for the existence of depressive symptoms as well as age and diabetes, the hazard ratio was unchanged. A secondary analysis looking at participants who started benzodiazepines at different times during follow-up also showed an elevated risk of dementia. Results of the complementary, nested, case-control study showed that ever use of benzodiazepines was associated with an approximate 50% increased risk of dementia compared with never users. The authors conclude that in this prospective, population-based study new use of benzodiazepines was associated with a significantly increased risk of dementia. They further conclude that "indiscriminate widespread use should be cautioned against" (*BMJ* 2012;345:e6231). The obvious criticism of the study was the presence of confounders — whether use of benzodiazepines was a marker for early onset dementia rather than a cause. While the authors feel the study was carefully controlled, selection bias cannot be completely ruled out. They further state that the research should be done on younger patients to see if starting benzodiazepines at ages younger than 65 may have deleterious effects. They also recommend that "physicians and regulatory agencies should consider the increasing evidence of potential adverse effects of this drug class for the general population." ■

## Popular supplements' use questioned

Two popular supplements — omega-3 fatty acids and *Ginkgo biloba* — may be of limited value, according to two recent studies. Omega-3 fatty acids are thought to have a number of benefits, including lowering triglyceride levels, preventing arrhythmias, decreasing platelet aggregation, and lowering blood pressure. But the fish oil supplement's ability to prevent major cardiovascular events has been debated in the literature. Twenty studies of nearly 67,000 patients were included in a meta-analysis looking at the effect of omega-3 on all-cause mortality, cardiac death, sudden death, myocardial infarction, and stroke. After correcting for dose and comorbidities, there was no difference in the absolute or relative risk of any of the outcomes associated with omega-3 supplementation. The authors concluded that marine-derived omega-3 polyunsaturated fatty

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acid supplementation was not associated with a lower risk of all-cause mortality, cardiac death, sudden death, myocardial infarction, or stroke (*JAMA* 2012;308:1024-1033).

*Ginkgo biloba* for the prevention of Alzheimer's disease (AD) was studied in a randomized, parallel group, double-blind, placebo-controlled trial of adults age 70 years or older who spontaneously reported memory complaints to their primary care physician in France. Patients were randomized to a twice per day 120 mg standardized *Ginkgo biloba* extract or matching placebo and followed for 5 years. The primary outcome was conversion to probable AD. More than 2800 patients were enrolled with about 1400 patients in each group. By 5 years, 61 participants in the ginkgo group were diagnosed with AD vs 73 in the placebo group (hazard ratio 0.84, 95% CI 0.60-1.18; $P = 0.306$). Adverse events were the same between both groups and mortality was roughly the same as well. Sixty-five participants in the ginkgo group had a stroke compared to 60 in the placebo group ($P = 0.57$). The authors conclude that long-term use of standardized *Ginkgo biloba* extract did not reduce the risk of progression to AD compared to placebo (*Lancet Neurology* 2012;11:851-859). ■

## FDA actions

The FDA has approved teriflunomide for the treatment of relapsing forms of multiple sclerosis (MS). The approval was based on a 2-year study in which the drug reduced relapses by nearly a third compared to placebo — results that are about the same as other MS drugs and no better than Merck's popular injectable interferon beta 1a (Rebif). Side effects include diarrhea, abnormal liver function tests, nausea, and hair loss. It should not be used during pregnancy. Teriflunomide has the advantage of being a once-daily oral medication, the second oral MS medication after Novartis' fingolimod (Gilenya). Teriflunomide will be marketed by Sanofi Aventis as Aubagio. A third oral MS medication, Biogen Idec's BG-12, was recently found to reduce MS relapses by about 50% (*N Engl J Med* 2012;367:1087-1097; 1098-1107). BG-12 is not yet approved by the FDA, but a decision is expected before the end of the year.

The FDA has delayed the approval of apixaban (Eliquis) once again. Pfizer and Bristol-Myers Squibb's novel oral anticoagulant (NOAC) was expected to be approved last spring after publication of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, which showed that the drug was effective in preventing strokes in patients with non-valvular atrial fibrillation — data that suggested that the drug was perhaps even more effective than the two other NOACs, dabigatran (Pradaxa) and rivaroxaban (Xarelto). In June, the FDA told the manufacturers they needed "additional information on data management and verification from the ARISTOTLE trial." Now, the agency says that the review date will be March 17, 2013. No reason was given by the FDA for the delay.

About 25% of Internet consumers have purchased prescription medications online, while at the same time, the prevalence of fraudulent Internet pharmacies has grown. The FDA has now launched a national campaign to raise public awareness called BeSafeRx – Know Your Online Pharmacy, a resource that provides patients and caregivers with a better understanding of who they are buying from, and makes sure the medication they buy matches what their doctor prescribed. The FDA recommends that patients only buy medications from online pharmacies that require a prescription, are located in the United States, have a licensed pharmacist available for consultation, and are licensed by the patient's state board of pharmacy. More information can be found at www.FDA.gov/BeSafeRx.

The FDA has approved enzalutamide to treat men with late-stage, castration-resistant prostate cancer under the agency's priority review program. The drug was approved based on a study of nearly 2000 men with metastatic prostate cancer who had been previously treated with docetaxel. Men treated with enzalutamide lived an average of 18.4 months vs 13.6 months for men treated with placebo. Enzalutamide is co-marketed by Astellas and Medivation as Xtandi.

The FDA has also approved a new agent for the treatment of advanced colorectal cancer. Regorafenib is a multi-kinase inhibitor that was also approved under the FDA's priority review program. In a study of 760 patients with previously treated metastatic colorectal cancer, regorafenib extended survival about 45 days to 6.4 months from 5 months for placebo as well as progression-free survival of 2 months vs 1.7 months for placebo. Regorafenib is marketed by Bayer as Stivarga. ■