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CLINICAL ONCOLOGY ALERT

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INSIDE

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Hodgkin's Lymphoma and Male Fertility

ABSTRACT & COMMENTARY

By William Ershler, MD

Synopsis: *For young males cured of Hodgkin's Lymphoma, infertility is a significant issue. In a comprehensive review of patients treated on the German Hodgkin Study Group, investigators found that there were both qualitative and quantitative changes in sperm production prior to therapy, and that most drug combinations, particularly those that contained alkylating agents, caused a high rate of azoospermia. Serum FSH levels correlated with fertility status, and may be a useful surrogate for more extensive semen analysis.*

Source: Sieniawski M, et al. Assessment of male fertility in patients with Hodgkin's lymphoma treated in the German Hodgkin Study Group (GHSG) clinical trials. *Ann Oncol*. 2008;19:1795-1801.

HODGKIN'S LYMPHOMA (HL) HAS A BIMODAL INCIDENCE PEAK, but the majority of patients are young. When it occurs at younger ages, overall prognosis is good and, for many, the disease will be completely eradicated. However, the treatment required to achieve cure is associated with long-term consequences, including second malignancies, compromised cardiac and pulmonary function, and endocrine deficiencies. Although not life-threatening, infertility engenders a high psychosocial burden and diminished quality of life. A recent report revealed that 51% of men with cancer expressed their wish to preserve their capacity for procreation in the future, including 77% of men who were still childless when their cancer was diagnosed.[1]

Several factors influence fertility in men after HL treatment. Primary among these is chemotherapy, especially alkylating agents.[2] Also to be factored in, however, is the recent observation that a large portion of men with HL have low sperm counts even prior to receiving treatment.[3]

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The current study was undertaken to provide a more comprehensive evaluation of male fertility among patients treated for HL. For this, male patients treated within the German Hodgkin Study Group (GHSG) from 1988 through 2003 were examined before and, for many, at later intervals after HL treatment. Fertility status was correlated with clinical and biological features at the time of diagnosis, as well as the treatment regimen received.

Prior to HL treatment, of 202 patients (median age 26 years), only 20% had normal sperm counts, 11% had complete absence of sperm in the ejaculate (azoospermia), and 69% had either low sperm counts, altered motility, or both (dyspermia). In post-treatment analysis (n = 112), 64% of patients had complete absence of sperm in the ejaculate, 30% other dyspermia, and 6% normal sperm counts ($p < 0.001$). Azoospermia was observed in 90% of patients treated with chemotherapy alone, 67% of those treated with combined modality, and 11% of those treated with radiotherapy alone ($p < 0.001$). Azoospermia was more frequent after four cycles of cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine, and dacarbazine (COPP/ABVD) (91%), eight cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) baseline (93%), and eight cycles of BEACOPP escalated (87%), compared with two cycles of COPP/ABVD (56%; $p = 0.003$). There was a statistically significant difference in post-treatment-follicle-stimulating hormone (FSH) levels between patients with azoospermia and those with preserved spermatogenesis ($p = 0.001$).

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■ COMMENTARY

Although male infertility is an acknowledged adverse consequence of chemotherapy, the prevalence, as defined in this analysis, was quite remarkable. The current research provides a comprehensive assessment in terms of treatments received and overall effect on male fertility in a fairly large series of patients treated on specific protocols. The data confirm the association with alkylating agents and demonstrate, to some degree, a dose effect. That is, patients who received less cyclophosphamide or procarbazine were less likely to become azoospermic compared to those who received more. Similar rates of azoospermia were observed in those treated with MOPP (mechlorethamine, vincristine, procarbazine and prednisone).[4] Although there were few patients included in this series who received ABVD alone, in other series, the incidence of treatment-induced azoospermia is reportedly significantly less, to the order of 5%.[5] It is also notable that prior to therapy, only 20% of men had normal semen analyses and 11% had azoospermia. The mechanisms accounting for these findings are incompletely understood, although factors such as disease-related damage to germinal epithelium and disturbances in the hypothalamic-hypophysial axis, as well as the impact of cytokines on spermatogenesis have been proposed.[3,6,7]

It is also notable that FSH levels were elevated in the majority of patients. In contrast, LH and testosterone levels remained normal in most; findings that had been previously observed in this setting.[5,8] The pattern suggests that spermatogonia are sensitive, whereas Sertoli and Leyding cells are more resistant to the toxic effects of alkylating agents. Additionally, FSH levels appear to correlate with fertility status after treatment, and this may be of clinical value in guiding judgment, particularly for those who are disinclined to providing samples for semen analysis. ■

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Transplanting Bad-acting CLL

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *In a retrospective review of hematopoietic stem cell transplantation for pre-treated patients with chronic lymphocytic leukemia, who have 17p deletion, three-year overall and progression-free survival were 44% and 37%, respectively. This matches favorably when compared to patients with the same chromosomal abnormality treated with chemotherapy alone. Although an uncommon CLL variant, patients with 17p deletion should be considered candidates for hematopoietic stem cell transplant.*

Source: Schetelig J, et al. Allogeneic hematopoietic stem-cell transplantation for chronic lymphocytic leukemia wit 17p deletion: a retrospective European Group for Blood and Marrow Transplantation analysis. *J Clin Oncol*. 2008;26: 5094-5100.

There have been several reports demonstrating that hematopoietic stem-cell transplantation (HSCT) can provide improved remission duration and overall survival in patients with advanced chronic lymphocytic leukemia (CLL).[1-3] It would seem logical that patients with adverse prognostic indicators, such as ZAP70 or unmutated VH gene would be most likely to benefit from HSCT, but earlier reports suggest that the presence of these factors does not influence overall transplant outcome.[4,5] However, for those with 17p deletion (17p-), HSCT may offer the greatest chance for prolonged survival. The p53 tumor suppressor gene resides on the 17th chromosome, and its absence has been associated with a defect in triggering apoptosis in response to DNA damage, such as that produced by chemotherapy. Thus, CLL patients with 17p- are non-responsive to standard chemotherapy, such as with purine analogues,[6] although gratifying but temporary responses frequently result from treatment with the monoclonal antibody alemtuzumab.[7,8]

To test whether HSCT would improve outcomes after HSCT in patients with CLL and 17p- deletion, Schetelig et al performed a retrospective analysis. For this, baseline data from patients with available cytogenetic data were downloaded from the European Group for Blood and Marrow Transplantation registry. Additional information on the course of CLL and follow-up was collected by questionnaire.

A total of 44 patients with 17p- CLL received allogeneic HCST between March 1995 and July 2006 from a matched sibling (n = 24) or an alternative donor (n = 20). 17p- CLL had been diagnosed by fluorescent in situ hybridization in 82% of patients and by conventional banding in 18% of patients; the median age was 54 years. Before HCST, a median of three lines of chemotherapy had been administered. At HCST, 53% of patients were in remission. Reduced-intensity conditioning was applied in 89% of patients. Acute grade 2 to 4 graft-versus-host disease (GVHD) occurred in 43% of patients, and extensive chronic GVHD occurred in 53% of patients. At last follow-up, 19 patients were alive, with a median observation time of 39 months (range, 18 to 101 months). Three-year overall survival and progression-free survival rates were 44% and 37%, respectively. The cumulative incidence of progressive disease at four years was 34%. No late relapse occurred in nine patients, with a follow-up longer than four years.

COMMENTARY

By fluorescence in situ hybridization, chromosomal abnormalities can be detected in up 80% of CLL cases and most frequently these involve deletions of the 13th or 11th chromosome or trisomy 12. 17p deletion occurs from 3%-7%[9] and is a harbinger of a particularly

poor prognosis, with a poor response to chemotherapy, a median survival of less than two years, and virtually no progression-free survival beyond three years. Thus, this report, albeit retrospective and relatively small, offers some hope for an effective treatment approach to this selected group of CLL patients. Such patients should be considered candidates for HSCT early in their course, perhaps after initial treatment with alemtuzumab. Additional research is clearly needed to define appropriate HSCT strategies, including approaches to myeloablation and GVH prevention, while not eliminating a graft vs leukemia effect, a feature that was also of apparent importance in this series. Furthermore, there is clearly a need for new agents that are not dependent on p53 inasmuch as HSCT remains a risky procedure for the bulk of CLL patients over the age of 70 years. ■

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MGUS and Myeloma May Predispose to Venous Thromboembolism

ABSTRACT & COMMENTARY

By Andrew S. Artz, MD

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Dr. Artz reports no financial relationship relevant to this field of study.

Synopsis: *Recent studies have suggested that multiple myeloma and monoclonal gammopathy of unknown significance (MGUS) may predispose to venous thromboembolism, even in untreated patients. The authors retrospectively reviewed Veteran Affairs hospital discharge records from 1980 to 1996 for the diagnosis of MGUS or MM, as well as the subsequent development of a deep venous thrombosis (DVT) in the era before the regular use of thalidomide or lenalidomide. There was an increased adjusted risk of developing a DVT after the diagnosis of MGUS or MM of 3.3 (95% CI 2.3 - 4.7) and 9.2 (95% CI 7.9 - 10.8), respectively. Much of the excess risk occurred during the first year after diagnosis.*

Source: Kristinsson SY, et al. Deep vein thrombosis after monoclonal gammopathy of undetermined significance and multiple myeloma. *Blood*. 2008;112:3582-3586.

THE ASSOCIATION OF CANCER VENOUS THROMBOEMbolism such as deep venous thrombosis (DVT) and pulmonary embolism have been long appreciated.[1] Multiple myeloma (MM) may also predispose to thrombosis, though the risk is greatly magnified by use of immunomodulatory drugs (IMiDs) such as thalidomide or lenalidomide.[2] Monoclonal gammopathy of

unknown significance (MGUS) is a much more common plasma cell dyscrasia occurring in 1% or more of all adults and may evolve into MM.[3] MGUS can be distinguished from MM by the presence of a serum monoclonal protein concentration < 3 g/dL, fewer than 10% plasma cells in the bone marrow, and absence of lytic bone lesions, anemia, hypercalcemia, or renal insufficiency related to a plasma cell disorder. Most cases of MGUS follow a benign course and do not require intervention. Interestingly, two recent series suggested that MGUS may predispose to VTE.[4,5]

Kristinsson et al retrospectively reviewed discharge records of more than 4 million patients admitted into the United States Veterans Affairs hospitals between 1980 to 1996 (before widespread use of IMiDs). They ascertained cases of MM and MGUS from the ICD codes. They identified 2374 (0.06%) cases of MGUS and 6192 (0.15%) patients with MM. They focused on DVT rather than PE because a PE diagnosis was less specific, especially in the time prior to faster CT scans that can detect pulmonary emboli. The crude incidence of DVT was 0.9 per 1000 person years. The risk of DVT was increased 3.3 times (95% CI, 2.3-4.7) for MGUS and 9.2 times (95% CI, 7.9-10.8) for MM. The cumulative risk of developing a DVT within four years after the diagnosis for MGUS was 1.4% (95% CI, 0.8 to 2.0) and 4.2% (95% CI, 3.5 - 4.9) for MM. The adjusted relative risk for a DVT compared to the entire cohort one year after diagnosis for MGUS was 8.4 (95% CI, 5.7-12.2) and for MM was 11.6 (95% CI, 9.2-14.5), respectively. The elevated risk for DVT appeared limited to the first year after diagnosis for MM, as opposed to a more constant risk for MGUS. No difference was found between whites and blacks in the risks of DVT for MGUS or MM. MM developed in 9.5% of patients diagnosed earlier with MGUS, and only one of these had a DVT diagnosed before a diagnosis of MM occurred, indicating that evolution to MM did not appear to account for the DVT risk for MGUS.

■ COMMENTARY

Venous thromboembolic disease commonly complicates the care of cancer patients. Although the increased risks of using immunomodulatory drugs such as thalidomide and lenalidomide in MM has become well appreciated, a risk of DVT may also be present at baseline prior to treatment. Several studies have recently suggested that even in monoclonal gammopathy of unknown significance (MGUS), the risk of DVT may be elevated, suggesting a similar pathogenic mechanism for these plasma cell dyscrasias, leading to prothrombotic tendency.

In this study, Kristinsson et al sought to confirm the prior findings. They found in a large retrospective review of more than 4 million patients admitted to the Veterans Affairs hospitals that the risk of DVT was increased by three or nine times for patients having a pre-existing diagnosis of MGUS or MM, respectively. In addition, for patients with MM, the risk was mostly isolated to the first year after diagnosis, whereas for MGUS, the elevated risk for DVT persisted over time. Kristinsson et al point out that the data were derived from a period between 1980-1996 before routine use of thalidomide and lenalidomide. Also in this era, before low molecular weight heparins allowed outpatient treatment of DVT, cases almost always required an inpatient admission and, thus, discharge summaries capture most symptomatic DVTs. The data are the strongest yet to support the emerging hypothesis that both MM and MGUS predispose to DVT, rather than treatment alone.

The demographic composition of patients admitted to the VA system is skewed toward men and African-Americans compared to the general population, which limits generalizability. More important limitations relate to possible ascertainment bias that may complicate a retrospective review of hospital discharges. One can expect cases of MM and symptomatic DVT to be accurately recorded. However, for MGUS, ascertainment is much less reliable, and many, if not most, cases were either unrecognized or undocumented on the discharge diagnosis. For example, only 0.15% of patients had MGUS diagnosed, whereas one can expect around 2%-3% or more in those 50 or over. It remains quite plausible that factors leading to a diagnosis of MGUS may also be linked to DVT, thus giving the false impression that MGUS predisposes to DVT. For example, some cases of MGUS may have received treatment either because they were evolving into myeloma or practice patterns differed twenty years ago. Clearly, treatment of MGUS would increase the chance of documenting MGUS. Since the addition of chemotherapy or steroids to IMiDs increases the risks of DVT compared to IMiDs alone,[6] it seems reasonable to assume that other treatments, if used, such as steroid, might also increase the risk of DVT. Alternatively, a diagnosis of MGUS may have led to closer follow-up or evaluation by a hematologist, where a diagnosis of DVT could be more likely.

If validated, the findings could have enormous implications related to the population attributable risk of DVT considering the high prevalence of MGUS

among older adults, a population already at increased risk of DVT.[3]

Many questions remain unanswered: What are the mechanisms whereby DVT risk is increased for plasma cell dyscrasias? Does an increased risk of DVT correlate to a higher chance of pulmonary embolus? Is the relationship between MGUS or MM and DVT affected by the immunoglobulin isotype? Is DVT prophylaxis warranted?

In conclusion, MGUS and MM may have an increased risk of DVT, independent of treatment with lenalidomide or thalidomide. ■

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Percent-"Free" PSA Improves Predictive Value for Those with Low-Total PSA Levels

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *Low PSA levels do not assure the absence of prostate cancer. Among a large number of patients referred for prostate biopsy, 524 had PSA levels of < 2.5 ng/mL and, of these, 125 (23%) were found to have cancer. The ratio of "free" PSA to total PSA was shown to have high predictive value in this subset of patients.*

Source: Walz J, et al. Percent free prostate-specific antigen (PSA) is an accurate predictor of prostate cancer risk in men with serum PSA 2.5 ng/mL and lower. *Cancer*. 2008;113: 2695-2703.

It is now well understood that serum prostate-specific antigen (PSA) is not a perfect screening tool in that low levels are not indicative of absent or negligible risk. For example, the prostate cancer prevention trial (PCPT) demonstrated that 17% of patients with unremarkable digital rectal examination (DRE) and total PSA (tPSA) levels of 1.1-2.0 ng/mL, and 24% of patients with a tPSA of 2.1-3.0 ng/mL, were shown to have biopsy-proven prostate cancer.[1] In light of earlier observations that the ratio of free-to-total PSA improved predictive value for patients with higher PSA levels,[2,3] Walz et al assessed the ability of percent-free PSA to discriminate between benign and malignant prostate biopsy outcomes in men with PSA ≤ 2.5 ng/mL.

Between 1999 and 2006, 7,880 consecutive men underwent initial prostate biopsy at two major European urology referral centers (Hamburg, Germany and Milan, Italy). Of these, 543 (6.9%) had total PSA levels ≤ 2.5 ng/mL. Of these, 125 (23%) were found to have prostate cancer. Age, total PSA, percent-free PSA, and digital rectal examination findings represented predictors of prostate cancer at biopsy in logistic-regression models. The area under the receiver operating characteristics curve (AUC) quantified the discriminative ability of the predictors. The pathological characteristics of the detected cancers were assessed in individuals treated with radical prostatectomy.

Of those in whom biopsy revealed prostate cancer, 64% underwent a radical prostatectomy and, of these,16.5% were pT3 stage and 35.6% had a pathological Gleason score of 3 + 4 or higher. The most accurate predictor of prostate cancer on biopsy was percent-free PSA (0.68), as compared with age (0.50), total PSA (0.57), or rectal examination findings (0.58). Of patients with percent-free PSA below 14%, 59% had prostate cancer. For those with a percent-free PSA > 28%, prostate cancer occurrence was 9%. In multivariate models, percent-free PSA ($p < .001$) and rectal examination findings ($p = 5 .001$) were the only independent predictors of

prostate cancer. The combined AUC of all predictors (0.69) was not significantly higher than that of percentage of free PSA alone (0.68).

■ COMMENTARY

The risk of prostate cancer is clearly non-negligible in patients with PSA ≤ 2.5 ng/mL. In this study, almost 25% of such patients were found to have prostate cancer, and over one-third had locally-advanced disease. These are striking numbers with significant public health implications. On the one hand, it is important to recognize that these were patients seen at major referral centers and how well they reflect the general population is to be considered. On the other hand, in this cohort, almost 75% had normal rectal exams (in addition to their PSA level of ≤ 2.5 ng/mL). In fact, it is not at all clear what prompted referral for biopsy in the first place. Thus, it is unlikely that 25% of men with PSA levels at or below 2.5 ng/mL and normal DRE have prostate cancer; the prevalence is still likely to be higher than commonly appreciated. This raises the question of whether the prostate cancers discovered in those with low PSA levels are of clinical significance and, unfortunately, in a significant percentage, they are, as witnessed by the locally advanced stage found in over one-third who underwent surgery.

Thus, despite the limitations inherent in retrospective review (patient selection, etc.), this report is notable in that it once again indicates the prevalence of this disease (which will only increase in the next two decades with the aging demographics) and the risk of relying on a low PSA level to indicate absence of disease. Furthermore, and importantly, the data presented indicate the added predictive value of determining the percent-free PSA, as this may ultimately prove useful in developing screening strategies. ■

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CME Questions

44. The incidence of azoospermia (complete absence of spermatozoa on semen analysis) was observed in approximately what percentage of patients treated on Hodgkin's lymphoma chemotherapy protocols:

a. 10%
b. 35%
c. 55%
d. 90%

45. Which of the following CLL-associated chromosomal abnormalities is associated with the worst prognosis?

a. Deletion of 11q
b. Deletion of 13q
c. Deletion of 17p
d. Trisomy 12

46. In a retrospective review of Veterans Affairs hospital discharges, what did the authors find related to multiple myeloma (MM) and monoclonal gammopathy of unknown significance (MGUS)?

a. Patients diagnosed with MGUS or MM had an increased risk of developing a deep venous thrombosis (DVT)
b. Only patients diagnosed with MM had a heightened risk of DVT but not those diagnosed with MGUS
c. Only patients diagnosed with MGUS had a heightened risk of DVT but not those diagnosed with MM
d. All the increased risk of DVT in patients with MGUS or MM was attributable to treatment with thalidomide

47. For patients with PSA levels <2.5 ng/mL, which of the following factors offer significant independent prognostic value in multivariate analysis?

a. patient age
b. % free PSA
c. history of urinary tract symptoms (nocturia, frequency)
d. All of the above

Answers: 44. (d); 45. (c); 46. (a); 47. (b)

CME Objectives

The objectives of *Clinical Oncology Alert* are:

- to present the latest information regarding diagnosis and treatment of various types of cancer;
- to present prevalence/surveillance data and long-term follow-up results of chemotherapy/radiation regimens; and
- to describe new advances in the field of oncology.

In Future Issues:

FLOT: A Treatment Option for Gastric Cancer

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VOLUME 13, NUMBER 12 PAGES 23-24 DECEMBER 2008

Early intensive anti-diabetic treatment may improve β-cell function

Source: Chen HS, et al. Beneficial effects of insulin on glycemic control and β-cell function in newly diagnosed type 2 diabetes with severe hyperglycemia after short-term intensive insulin therapy. *Diabetes Care* 2008;31:1927-1932.

Approximately 50% of β-cell function has been lost at the time of initial diagnosis of type 2 diabetes. The UKPDS suggested that neither insulin, metformin, nor oral agents demonstrated any particular advantage as far as progressive subsequent decline in β-cell function is concerned. Whether intensive initial glucose control with insulin followed by routine diabetic control with either insulin or oral agents improves control and/or β-cell function was the subject of this publication by Chen et al.

Newly diagnosed type 2 diabetics with severe hyperglycemia (n = 74) were hospitalized and received intensive basal-prandial insulin therapy to maintain near-normal fasting, preprandial, and bedtime glucose; once good glycemic control had been attained and maintained for 10-14 days, subjects were discharged and randomized to continued maintenance of tight control with basal-prandial insulin or oral agents (metformin and/or sulfonylurea titrated to maintain FBS 90-130 mg/dL).

The insulin-maintenance group had significantly greater improvements in A1c at 6 months, although FBS levels were similar to the oral agent group. A comparison of β-cell function at 6 months indicated that patients receiving basal-prandial insulin treatment had better outcomes than those on oral agents.

Evolution of management techniques for type 2 diabetes continues to suggest an earlier and more prominent role for insulin therapy. These data suggest that how one gets to goal may be important, and that early introduction of insulin may have advantages over oral agents. ■

How long should 'clear sailing' certificate last after colonoscopy?

Source: Imperiale TF, et al. Five-year risk of colorectal neoplasia after negative screening colonoscopy. *N Engl J Med* 2008;359:1218-1224.

The 2008 guidelines from the American Cancer Society (ACS) have given the green light to support a variety of different colon cancer screening tools, though colonoscopy (COL) continues to have the greatest advocacy from health professionals. The currently recommended interval for re-examination after a negative COL is 10 years in average-risk individuals. Imperiale et al looked at the yield of COL performed 5 years after an initial negative screening COL in average-risk individuals (n = 1256).

Upon rescreening, no cancers were found. Advanced adenomas were found in 1.3%; the relative risk for a new advanced adenoma was 3-fold higher in men than in women.

These data are somewhat surprising when contrasted with a recent study of individuals undergoing two colonoscopies the same day at Indiana University, in which the adenoma miss rate of colonoscopy by experienced endoscopists was 24%! Nonetheless, in neither study does it appear that frank carcinoma was missed. Although this trial does not confirm that a 10-year interval, as recommended by current ACS guideline, is appropriate, it indicates that over a 5-year interval, no new cancers were discovered. ■

The Swedish Diabetes CVD Risk Score

Source: Cederholm J, et al. Risk prediction of cardiovascular disease in type 2 diabetes. *Diabetes Care* 2008;31:2038-2043.

Cardiovascular disease (CVD) risk prediction helps to identify persons at high risk, stratify treatment groups, and motivate healthful behaviors and modification of risk factors. Diabetic patients are at particularly high risk of CVD, yet currently available risk scoring systems have not performed particularly well.

The Swedish National Diabetes Register provided the patient population from which a new CVD risk predictor has been developed.

During a mean follow-up of 5.6 years (n = 11,646 adult diabetics), 1482 first CVD events occurred. Risk factors with strong association to CVD events were confirmed to be A1c, age at onset of diabetes, duration of diabetes, gender, BMI, smoking, SBP, use of antihypertensive medication, and use of lipid-lowering medication. When these risk factors were used in randomly selected subgroups from the population, accuracy of CVD risk prediction was excellent.

Because this risk prediction tool utilizes information that is generally readily clinically available, and is structured to inform us about predicted 5-year risk (rather than 10-year risk in several other popularly used risk scores), the Swedish Diabetes CVD Risk Score may find popular utility. ■

Ethnic disparity in colon polyps detected during routine screening

Source: Lieberman DA, et al. Prevalence of colon polyps detected by colonoscopy screening in asymptomatic black and white patients. *JAMA* 2008;300:1417-1422.

Both the incidence and rate of mortality of colon cancer (CCa) is higher in black men and women than whites; CCa also occurs at a younger age in blacks than in whites. Health care access issues, lesser adherence to screening recommendations, or less frequent screening recommendations by health care providers to some minority groups might explain some—but not all—of this disparity. Sociopolitcal and economic issues aside, there may simply be a greater incidence of CCa and precancer (i.e., polyps) in black men and women.

Lieberman et al evaluated data from sites (n = 67) routinely performing screening colonoscopy in asymptomatic individuals. During the 2004-2005 interval, 80,061 white and 5464 black persons underwent screening colonoscopy. The primary endpoint of the data analysis was the prevalence of large polyps (> 9.0 mm).

Overall, black women were 62% more likely than white women to have a large polyp discovered on screening colonoscopy; black men were 16% more likely to have a large polyp found. This information should encourage clinicians to be particularly vigilant that black men and women participate in timely screening colonoscopy. ■

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Cannabis withdrawal: Under-recognized

Source: Hasin DS, et al. Cannabis withdrawal in the United States: Results from NESARC. *Am J Psychiatry* 2008;69:1354-1363.

Opinions on the consequences of marijuana use are wide-ranging: Some experts express grave concern that it may induce COPD, increase risk of lung cancer, promote the emergence of schizophrenia, and lead to "heavy drug" use; others essentially dismiss these (potential) adversities as inadequately established to permit accusations that marijuana has any commonplace serious adverse effects. Like alcohol, where there is an established "dose-response curve," indicating that alcohol in moderation is associated with beneficial health outcomes, as opposed to excessive alcohol, which leads to numerous adverse events, there may be a particular degree of marijuana use that leads to toxicity.

There is no specific DSM-IV diagnostic code for marijuana withdrawal, perhaps reflecting the commonplace observation at the time of its publication that few reports had documented such a specific syndrome. The National Epidemiologic Survey on Alcohol and Related Conditions may change that.

During 2001-2002, live interviews were conducted with frequent cannabis users, defined as at least 3x/wk utilization (n = 2613). To make sure that discontinuation syndromes upon cessation of marijuana were not confounded by discontinuation of other substances sometimes concomitantly used (e.g, alcohol), there was a separate subgroup of "cannabis-only" users (n = 1119).

Frequent marijuana users commonly reported withdrawal symptoms in two primary patterns: a weakness-hypersomnia-psychomotor retardation constellation and an anxiety-restlessness-depression-insomnia cluster.

The incidence of withdrawal was essentially identical among cannabis-only users to that of multi-substance users. Finally, the noted withdrawal symptoms were reported to produce a significant degree of impairment. When presented with such symptoms, clinicians may need to consider marijuana withdrawal. ■

Effect of PUFAs on chronic heart failure

Source: GISSI-HF Investigators. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure. *Lancet* 2008;372:1223-1230.

The pharmacologic treatment of chronic heart failure (CHF) is already complex, often requiring an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, beta-blocker, aldosterone antagonist, nitrates, hydralazine, and diuretics. Despite risk reduction with each of these tools, residual risk remains substantial. Polyunsaturated fatty acids (PUFAs) may be another tool to reduce residual risk in CHF.

Some secondary prevention trials of myocardial infarction have indicated risk reduction with PUFAs use, primarily due to prevention of sudden death (attributed to antiarrhythmic properties of PUFAs). Whether similar benefits might be seen in patients with CHF was the subject of this clinical trial.

CHF patients (n = 6975) were enrolled in a randomized placebo-controlled trial of 1 g/d PUFAs (administered as one daily capsule containing eicosapentanoic acid and docosahexanoic acid). At 3.9 years (mean), there was a statistically significant 9% relative risk reduction of all-cause mortality in those who received PUFAs. The tolerability profile of PUFAs was similar to placebo. PUFAs therapy may provide meaningful risk reduction in patients with CHF. ■

PHARMACOLOGY WATCH

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

Are 5-α Reductase Inhibitors Associated with Hip Fractures?

In the issue: 5-α reductase inhibitors and hip fracture in men; the effects of drug-reimbursement policy on outcomes; new guidelines for type 2 diabetes; beta-blocker-associated bradycardia is linked to CVD events; FDA Updates.

DO 5-α REDUCTASE INHIBITORS AFFECT BONE DENsity in men? These drugs, which include finasteride (Proscar®) and dutasteride (Avodart®), have been used for more than a decade to treat benign prostatic hyperplasia (BPH). The drugs block the conversion of testosterone to dihydrotestosterone, the more powerful androgenic agent, which is responsible for secondary sex characteristics, but also adverse effects such as BPH, acne, and male pattern baldness. The 5-α reductase inhibitors shrink prostatic tissue and improve BPH symptoms over time and also can be associated with erectile dysfunction and gynecomastia. Recently researchers looked at the correlation between use of finasteride and bone health, which is highly dependent on steroid pathways. Researchers from Kaiser Permanente in Southern California performed a population-based case-control study of 7076 men age 45 and older with incident hip fractures over a 10-year period. Control patients were 7076 men without hip fracture. The rate of BPH was the same in both groups. There was no suggestion of a dose-response relationship between exposure to 5-α reductase inhibitors and hip fracture (P = 0.12). Interestingly, there was slightly higher rate of α-blocker use in the hip fracture group. The authors conclude that exposure to 5-α reductase inhibitors is not associated with increased risk of hip fracture; in fact, there was a trend toward a protective effect. The increased risk associated with exposure to α-blockers (which can cause orthostasis) needs further investigation (Jacobsen SA, et al. Association between 5-alpha reductase inhibition and risk of hip fracture. *JAMA* 2008;300:1660-1664).

Effect of drug-reimbursement policy on health care outcomes

Researchers recently looked at clopidogrel use and health outcomes for cardiac patients before and after a Canadian provincial government changed its prior-authorization policy for medications to a more liberal limited-use policy. Researchers looked at all patients 65 years or older with acute myocardial infarction who underwent PCI with stenting. The primary outcome was composite rate of death, recurrent acute myocardial infarction, PCI, and coronary artery bypass grafting at one year. After the change in benefits, the rate of clopidogrel use for 30 days after hospitalization increased from 35% to 88% and the mean time to first dispensing of clopidogrel decreased from 9 days to 0 days. The one-year composite cardiovascular outcome decreased from 15% in the prior-authorization

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group to 11% in the limited-use group ($P = 0.02$). The authors conclude that removal of prior-authorization leads to improvement in timely access to clopidogrel after coronary stenting and improved cardiovascular outcomes (Jackevicius CA, et al. Cardiovascular outcomes after a change in prescription policy for clopidogrel. *N Engl J Med* 2008;359:1802-1810).

Updated guidelines for type 2 diabetes

The American Diabetes Association and the European Association for the Study of Diabetes have updated their treatment guidelines and algorithms for the treatment of type 2 diabetes. Published simultaneously in *Diabetes Care* and the European journal *Diabetologia*, the guidelines update the initial August 2006 guideline and the January 2008 update to reflect safety issues surrounding the thiazolidinediones (TZDs) and also introduces new classes of medications to the algorithm. Retained as step 1 therapy are lifestyle interventions and metformin. Step 2 therapy includes insulin and sulfonylureas, while TZDs have been dropped as initial therapy. Of the two TZDs, only pioglitazone (Actos™) is recommended by the guideline. Safety concerns regarding rosiglitazone (Avandia®) have resulted in the guideline group to state: "…given that other options are now recommended, the consensus group members unanimously advised against using rosiglitazone." The GLP-1 agonist exenatide (Byetta®) is elevated to tier 2 with the guideline pointing out the advantage of weight loss associated with the drug, but also noting it is given by two injections per day, has frequent GI side effects, is very expensive, and does not have an established long-term safety history. Other drugs newly mentioned in the guideline include the α-glucosidase inhibitors (starch blockers), acarbose (Precose™) and miglitol (Glyset®); the glinides, repaglinide (Prandin®) and nateglinide (Starlix®); the amylin agonist primlintide (Symlin®); and the DPP-4 inhibitor sitagliptin (Januvia®) (Nathan DM, et al. Medical management of hyperglycemia in type 2 diabetes: A consensus algorithm of the initiation and adjustment of therapy. *Diabetes Care* 2009;32:1-11; Available at: http://care.diabetesjournals.org/misc/dv08-9025.pdf).

Beta-blockers and hypertension

Beta-blockers have come under increasing fire for treatment of hypertension. Now a new study links beta-blocker-associated bradycardia with increased risk of cardiovascular events. Researchers from Columbia University performed a meta-analysis of 9 randomized controlled trials evaluating beta-blockers for hypertension and from which heart rate data were reported. The compiled studies included more than 34,000 patients taking beta-blockers and more than 30,000 on other antihypertensive agents, as well as nearly 4000 patients receiving placebo. Lower heart rate associated with beta-blocker use was linked to a greater risk for all-cause mortality ($r = -0.51$; $P < 0.0001$) and cardiovascular mortality ($r = -0.61$; $P < 0.001$). There was also a statistically significant increase in myocardial infarction, stroke, and heart failure associated with lower heart rates. The authors conclude that in contrast to patients with myocardial infarction and heart failure, beta-blocker-associated reduction in heart rate increases the risk for cardiovascular events and death for hypertensive patients. The authors even suggest that beta-blockers may no longer be indicated for treatment of hypertension in the absence of compelling indications (Bangalore S, et al. Relation of beta-blocker-induced heart rate lowering and cardioprotection in hypertension. *J Am Coll Cardiol* 2008;52:1482-1489).

FDA Updates

The FDA has approved a new selective α-blocker for the treatment of benign prostatic hyperplasia. Silodosin is an α-1 receptor blocker with high affinity for prostate, bladder, and urethra. It will be marketed in an 8 mg dose to be given once daily; however, 4 mg should be used in men with hepatic or renal impairment. Silodosin will be marketed by Watson Pharmaceuticals as Rapaflo™.

The FDA will investigate a report for the Institute of Safe Medication Practices regarding varenicline (Chantix®), Pfizer's smoking cessation drug. For the second straight quarter, varenicline accounted for more reported serious injuries than any other prescription drug with a total of 1001 new cases reported to ISMP, including 50 deaths. The FDA has previously issued a Public Health Alert about psychiatric side effects from the drug, but the new report sites numerous cases involving vehicular or other accidents, or syncope with a high potential to cause accidents. The federal government has already taken action to ban airline pilots and military missile crews from using the drug. Sales of varenicline have dropped sharply this year as a result of these reports. ■