

NEWS AND VIEWS

The Y Chromosome's Possible Role in Cardiovascular disease (CVD) Among Men

CVD which kills thousands each year may be passed genetically from father to son, according to a study published in February 9 issue of *The Lancet*. The study shows that the Y chromosome plays a role in the inheritance of coronary artery disease (CAD). The study, led by researchers at the University's Department of Cardiovascular Sciences and Department of Genetics, took four years to complete and was primarily funded by the British Heart Foundation besides being supported by the National Institute for Health Research, LEW Cart Charitable Fund, National Health and Medical Research Council of Australia, the European Union, and the Wellcome Trust.

The team at the University of Leicester analysed DNA from over 3,000 men from British Heart Foundation Family Heart Study (BHF-FHS) and the West of Scotland Coronary Prevention Study (WOSCOPS). The researchers found that, of nine haplogroups identified, 90 per cent of British Y chromosomes belong to one of two major groups - named haplogroup I and haplogroup R1b1b2. The risk of CAD among men who carry a Y chromosome from haplogroup I was 50 percent higher age-adjusted risk of coronary artery disease than did men with other Y chromosome lineages in BHF-FHS, and the risk was independent of traditional risk factors such as high cholesterol, high blood pressure and smoking, and socioeconomic risk factors. Analysis of macrophage transcriptome in the Cardiogenics Study revealed that 19 molecular pathways showing strong differential expression between men with haplogroup I and other lineages of the Y chromosome were interconnected by common genes related to inflammation and immunity, and that some of them have a strong relevance to atherosclerosis.

The researchers believe the increased risk is down to the haplogroup I's influence on the immune system and inflammation, that is how our bodies respond to infections. The major novelty of these findings is that the human Y chromosome appears to play a role in the cardiovascular system beyond its traditionally perceived determination of male sex.

(*The Lancet* 2012; 379(9819):915 – 922)

Amoxicillin has No Effect on Acute, Uncomplicated Bacterial Rhinosinusitis

Treatment with the antibiotic amoxicillin for patients with acute uncomplicated rhinosinusitis did not result in a significant difference in symptoms compared to patients who received placebo, according to a study in the February 15 issue of *JAMA*. Antibiotics are commonly used to treat this condition even though there is limited evidence supporting their effectiveness. The study was conducted to examine the effect of amoxicillin treatment over symptomatic treatments on disease-specific quality of life in adults with clinically diagnosed acute bacterial rhinosinusitis. It was felt that, considering the public health threat posed by increasing antibiotic resistance, a strong evidence of symptom relief was needed to justify prescribing of antibiotics for a usually self-limiting disease like common cold. The trial included 166 adults (36 % men) who were randomized to receive a 10-day course of either amoxicillin in the dose of 1,500 mg per day (n = 85) or placebo (n = 81) administered in 3 doses per day. In addition, all received a supply of symptomatic treatments (e.g., acetaminophen) for use as needed.

Some of the most common symptoms reported by participants at the beginning of the study included facial pain or pressure, postnasal discharge, and cough and runny nose. All patients received a 5 to 7 day supply of symptomatic treatments for pain, fever, cough, and nasal congestion to use as needed; 92 percent concurrently used 1 or more symptomatic treatments (94 percent for amoxicillin group vs. 90 percent for control group).

The primary outcome for the study was the improvement in disease-specific quality of life after 3 to 4 days of treatment as assessed with the Sinonasal Outcome Test-16 (minimally important difference of 0.5 units on a 0-3 scale). Secondary outcomes included the patient's assessment of change in sinus symptoms and functional status, recurrence or relapse, and satisfaction with and adverse effects of treatment. The outcomes were assessed by a telephone interview at days 3, 7, 10, and 28.

The researchers found that the average change in test scores was similar in both groups at day 3 (amoxicillin group, 0.59; control group, 0.54) and at day 10, but differed at day 7, favoring amoxicillin (average difference between groups of 0.19). There were no statistically significant differences in reported symptom improvement at day 3 (37% for amoxicillin group versus 34% for control group) or at day 10 (78% for amoxicillin group versus 80% for control group). At day 7, more participants treated with

amoxicillin reported symptom improvement (74% for amoxicillin group versus 56% for control group).

The researchers found there was also no difference by study group in terms of days missed from work or inability to perform usual activities; rates of relapse and recurrence by 28 days; additional health care use; and satisfaction with treatment. No serious adverse events occurred. The study groups did not differ in reporting adverse effects from the study medication. The study, funded by a grant from the National Institute of Allergy and Infectious Diseases, reminds us that the most of the common community-acquired infections resolve spontaneously.

(JAMA 2012;307[7]:685-692)

Hepatitis C Overtakes HIV as Cause of Death in the United States

The hepatitis C virus (HCV) has rapidly surpassed HIV as a cause of death in the U.S., according to an *Annals of Internal Medicine* study. The study, entitled "The Increasing Burden of Mortality From Viral Hepatitis in the United States Between 1999 and 2007" by Kathleen *et al* was conducted to examine mortality from HBV and HCV in comparison to HIV. CDC researchers examined nearly 22 million death records over 9 years.

The results of the study revealed that between 1999 and 2007, recorded deaths from HCV increased significantly to 15 106, whereas deaths from HIV declined to 12 734 by 2007. Factors associated with HCV-related deaths included chronic liver disease, HBV co-infection, alcohol-related conditions, minority status, and HIV co-infection. Factors that increased odds of HBV-related death included chronic liver disease, HCV co-infection, Asian or Pacific Islander descent, HIV co-infection, and alcohol-related conditions. Roughly three quarters of HCV-related deaths occurred in people between the ages of 45 and 64.

The authors conclude that by 2007, HCV has superseded HIV as a cause of death in the United States, and deaths from HCV and HBV disproportionately occurred in middle-aged persons. The authors further say that this relatively young age of people dying from HCV "portends a large and ever-increasing health care burden." The main limitation of the study is that a person other than the primary physician of the decedent frequently completed the death certificate, and HCV and HBV often were not detected and thus not reported as causes of death.

To achieve decreases in mortality similar to those seen with HIV requires new policy initiatives to detect patients with chronic hepatitis and link them to care and treatment. The experience with HIV mortality reduction suggests that a similar approach to HBV and HCV prevention might lead to similar reductions in mortality from viral hepatitis over time.

(*Ann Intern Med* 21 February 2012;156(4):271-278)

Analysis Confirms Role of Endometriosis in Heightened Risk for Ovarian Cancer

Endometriosis increases risk for invasive ovarian cancer, an analysis of several international studies confirms, but the risk does not extend to all tumor subtypes. The results appear in the *Lancet*

Oncology. Researchers pooled data from 13 case-control studies performed within the Ovarian Cancer Association Consortium. In those studies, which included some 8000 women with invasive ovarian cancer and 13,000 controls, women self-reported whether they had a history of endometriosis. Roughly 9% of women with invasive cancer reported a history of endometriosis, compared with 6% of controls. Women with a positive history were more likely to have clear-cell, endometrioid, and low-grade serous tumors, but the other two tumor subtypes (mucinous and high-grade serous) were not associated with endometriosis.

A commentator writes that because some of the tumor subtypes associated with endometriosis present at an early stage and thus could be resected, targeted screening could be considered for some women.

Journal Watch, February 22, 2012 (First Watch@jwatch.org)

FDA Advisers Recommend Approval of New Diet Pill

Experimental obesity drug Qnexa won the backing of U.S. health advisors on Wednesday, raising hopes for approval of the first prescription weight-loss pill in 13 years. Vivus Inc's Qnexa, a combination of phentermine and topiramate, was one of three promising obesity drugs rejected by the USFDA in the past two years over safety concerns. In 2010, the FDA rejected the pill's approval over concerns that it could raise the risk for heart problems and birth defects. During this week's meeting, advisers said the manufacturer should conduct a study on the potential for heart problems, while supporting the company's intent to restrict its use to nonpregnant women. The advisers were split on whether the heart study should be performed before or after the pill's approval. It is the first to come back up for review after more extensive clinical trials, as public health officials urge the FDA to consider a medical treatment for a condition that has taken epidemic proportions.

A panel of outside experts to the FDA voted 20-2 to recommend approval of Qnexa, saying they were convinced that the benefits it offers in treating obesity outweighed the potential heart risks and birth defects associated with the drug. Panelists did say Vivus should conduct a study on possible heart problems and supported the company's plan to limit its use to women who are not pregnant. During discussions, panelists seemed divided on whether the heart-focused safety study should happen before or after the drug is approved. They took no formal vote on that issue. A pre-approval study could delay the time before Qnexa is available to patients. The vote, possibly reflects the clinical community's concern about the challenge of obesity. Keeping in view that there are few treatments for obesity for those who don't respond to lifestyle treatments, "treating obesity is not risk neutral", said some advisory panel members.

Obesity, a leading cause of diabetes, heart disease and other serious health problems, has reached epidemic proportions in the United States, with about a third of the population obese and more than half overweight. The agency has experienced previous high-profile safety scares involving diet drugs. In 1997, the infamous diet drug "fen-phen" was pulled from the market after reports of fatal heart-valve problems in some users. Another diet pill, Meridia, was pulled from the U.S. market in 2010 after being linked to heart problems. The only prescription obesity drug currently approved for long-term use is Roche Holding AG's Xenical, which got the

FDA's nod in 1999. GlaxoSmithKline markets a lower-dose, over-the-counter version called Alli. But both have their side effect issues, including liver problems and uncontrolled bowel movements, and provide only modest weight loss. FDA staff reviewers said patients taking the drug had more safety problems, including memory loss and higher heart rates, than those on a placebo, and some of these problems could get worse over time. However, Vivus said the drug also reduced blood pressure, and a link between heart rates and heart health was not conclusive. Panelists called for the company to study whether a higher heart rate was tied to heart health.

Source: Journal Watch(<http://www.jwatch.org/>)

Statin Labels Updated to Include Diabetes, Memory, and Drug Interaction Risks

The FDA is making several changes to the labels of statins following a comprehensive review, the agency announced that:

Incident diabetes and increased blood glucose are possible with statin use. Several meta-analyses found an increased risk for diabetes (9%–13%) in patients taking statins.

Reversible memory loss and confusion are possible, though rare. The FDA said there is no evidence that these side effects lead to significant cognitive decline later.

Routine monitoring of the liver enzyme alanine aminotransferase is no longer required, although testing before statin initiation and as clinically indicated is still recommended. The agency has concluded that serious liver injury among patients taking statins is rare and cannot be prevented with routine monitoring.

Use of lovastatin is now contraindicated with strong CYP3A4 inhibitors — including itraconazole and erythromycin — to reduce the risk for rhabdomyolysis. Lovastatin's new label also lists dose limitations and several other drugs to avoid.

Journal Watch, February 29, 2012 (FirstWatch@jwatch.org)

Nicotine Patch No Better Than Placebo in Helping Pregnant Smokers Quit

The nicotine patch is no better than placebo in helping pregnant smokers abstain from cigarettes until delivery, according to a New

England Journal of Medicine study. Some 1000 pregnant smokers between 12 and 24 weeks' gestation were randomized to receive 8 weeks of nicotine-replacement or placebo patches. All participants also received behavioral counseling before randomization and several times during the intervention period. The primary outcome — abstinence until childbirth — did not differ significantly between the nicotine and placebo groups (9% and 8%, respectively). Adverse pregnancy and birth outcomes generally did not differ between the groups, although low adherence rates (3%–7%) limited safety assessments.

An editorialist, citing previous studies with similar outcomes, concludes: "Pending more data on the efficacy and safety of nicotine-replacement therapy during pregnancy, this therapy cannot be recommended with any clinical certainty." In an interview with Clinical Conversations, study author Dr. Tim Coleman said, "Women should really ... try very hard [to quit] with behavioral support alone."

Journal Watch, March 1, 2012 (FirstWatch@jwatch.org)

Internet-Based Therapy Effective in Treating Teens with Chronic Fatigue Syndrome

Specialized Internet-based cognitive-behavioral therapy appears to effectively treat chronic fatigue syndrome in teenagers, according to a Lancet study. Some 140 Dutch patients aged 12 to 18 years with chronic fatigue were randomized to either usual care or an Internet-based intervention consisting of a cognitive-behavioral therapy module and e-mails with a therapist. On average, teens and parents in the intervention group logged in to the module 255 times and e-mailed the therapist 90 times during 6 months of treatment. The intervention group had better results than the control group in all three primary outcomes: full school attendance (75% vs. 16%), lack of severe fatigue (85% vs. 27%), and normal physical functioning (78% vs. 20%). The improvements persisted at 12 months, and members of the control group who crossed over to the intervention group at 6 months also saw improvements by month 12.

Commentators write: "With chronic fatigue syndrome now identified as a common cause of long-term school absence, an accessible and flexible treatment for adolescents is most welcome."

Journal Watch, March 1, 2012 (FirstWatch@jwatch.org)