

## Varenicline may raise CV events in CVD patients: FDA

JUNE 16, 2011 | Michael O'Riordan

**Rockville, MD** - The smoking-cessation drug **varenicline** (Chantix, Pfizer) may be associated with a small increased risk of cardiovascular events in patients with cardiovascular disease, according to the **Food and Drug Administration (FDA)** [1].

The new safety communication, which will be added to the warnings and precautions section of the drug's label, states that physicians need to balance the known benefits of varenicline—a drug effective in helping patients quit smoking—with the potential risks when deciding to use the drug in patients with cardiovascular disease.

In a review of a randomized, double-blind, placebo-controlled study of 700 patients treated with varenicline for smoking cessation, there was an increased risk of nonfatal MI, revascularization, angina pectoris, and peripheral vascular disease when compared with patients treated with placebo. Although the study was not designed to detect a statistical difference in the clinical end points, cardiovascular events were numerically higher among the 353 patients treated with varenicline.

The FDA states that physicians should speak with patients about seeking medical attention if they experience new or worsening symptoms of cardiovascular disease while taking varenicline.

In July 2009, the FDA required a **new boxed warning for varenicline**, stating that the drug has been associated with serious mental-health events. Reported symptoms include changes in behavior, hostility, agitation, depressed mood, suicide ideation, and attempted suicide.

Varenicline, an oral nicotine-receptor blocker, was **approved by the FDA** in May 2006 under the agency's priority-review program.

1. Food and Drug Administration. FDA drug safety communication: Chantix (varenicline) may increase the risk of certain cardiovascular adverse events in patients with cardiovascular disease. June 16, 2011. Available [here](#).

## FDA: Use of pioglitazone over one year may increase risk of bladder cancer

JUNE 15, 2011 | Shelley Wood

**Silver Spring, MD** - The **FDA** has issued an update to its ongoing **safety review of pioglitazone** (Actos, Takeda), informing physicians and the public that use of the drug for more than 12 months is linked to an increased risk of bladder cancer [1].

The news comes within days of French regulators announcing that they are suspending sales of the drug; German regulators also announced last week that pioglitazone should not be started in new patients.

In the FDA's announcement today, the agency stated that information on the drug's label, as well as the patient medication guide, will be revised to include this new information.

Specifically, says the FDA, physicians should:

- Not use pioglitazone in patients with active bladder cancer.
- Use pioglitazone with caution in patients who have a prior history of bladder cancer, adding "the benefits of blood sugar control with pioglitazone should be weighed against the unknown risks for cancer recurrence."
- Tell patients to report any signs or symptoms of "blood in the urine, urinary urgency, pain on urination, or back or abdominal pain, as these may be due to bladder cancer."
- Urge patients to read the pioglitazone medication guide.
- Report adverse events involving pioglitazone medicines to the FDA **MedWatch program**.

As previously reported by **heartwire**, the FDA has been **reviewing the safety** of pioglitazone since September 2010, citing preliminary epidemiological evidence that suggests that the diabetes medication may be linked to a higher risk of bladder cancer. Just last week, an FDA spokesperson predicted that the agency's review would "be complete within the next couple of months." Of note, the FDA announcement today refers to the review as "ongoing."

The FDA's announcement today includes an update on the data used to make the recommendations and notes that the FDA was "aware" of the French analysis that led to the action taken in that country.

The FDA review is based on an ongoing 10-year observational cohort study as well as a nested, case-control study of the long-term risk of bladder cancer in over 193 000 patients with diabetes who are members of the Kaiser Permanente Northern California (KPNC) health plan. The FDA today specified that compared with never being exposed to pioglitazone, a duration of pioglitazone therapy longer than 12 months was associated with a 40% increase in risk in the KPNC analysis and that after more than 24 months of pioglitazone use that increased risk remained, although the statistical significance of the finding was weaker. "Based on these data, FDA calculated that duration of therapy longer than 12 months was associated with 27.5 excess cases of bladder cancer per 100 000 person-years follow-up, compared with never use of pioglitazone," today's notice reads.

Additional details on the FDA's data review are included in the announcement.

According to the FDA, approximately 2.3 million patients filled a prescription for a pioglitazone-containing product from outpatient retail pharmacies in the US from January 2010 through October 2010.

1. Food and Drug Administration. FDA drug safety communication: Update to ongoing safety review of Actos (pioglitazone) and increased risk of bladder cancer. June 15, 2011. Available [here](#).

## Bariatric surgery does not improve survival

JUNE 13, 2011 | Lisa Nainggolan

**Seattle, WA** - A new study in **Veterans Affairs** (VA) patients has found no survival benefit associated with bariatric surgery among older, severely obese people when compared with usual care, at least out to seven years [1]. **Dr Matthew L Maciejewski** (Durham VA Medical Centers, Durham, NC) presented the findings here yesterday at the **AcademyHealth Annual Research Meeting**, and they were published simultaneously in the *Journal of the American Medical Association*.

Maciejewski told **heartwire** that doctors "should counsel their patients that there are numerous significant benefits to bariatric surgery—including the fact that it's the most effective weight-loss treatment, and it improves the control of chronic conditions and quality of life—but there doesn't appear to be a survival benefit at nearly seven years." It is possible that there will be a survival benefit longer term, he says, and his group is continuing to follow these patients and add in others who have had surgery more recently.

“There are numerous significant benefits to bariatric surgery . . . but there doesn't appear to be a survival benefit at nearly seven years.

The new findings contrast with those of prior studies, many of which have shown survival benefits with bariatric surgery, but most of which have examined outcomes in younger, primarily white, and female populations, said Maciejewski. But obesity-related mortality is highest in men and minority patients, who have high rates of comorbid diseases, and this is the first study that has looked at long-term survival in such high-risk patients, he points out.

In addition, in this work, statistical analyses were employed, which "represent an advance over prior work. The VA has really rich data sets, and we had body-mass-index [BMI] information on all patients, including the nonsurgical controls," information that provides for more robust results, Maciejewski explains.

### **Adjustment for confounding an important aspect of the study**

Maciejewski et al conducted a retrospective, cohort study of bariatric-surgery programs in VA medical centers, including 850 veterans who underwent Roux-en-Y gastric bypass from January 2000 to December 2006. The population was 74% male, the mean age was 49.5 years, and the mean BMI was 47.4. Race/ethnicity was 78% white, 16% nonwhite, and the remainder "unknown." Mortality for these patients was compared with that of 41 244 nonsurgical controls (mean age 54.7 years, mean BMI 42, 74% male, and 77% white) from the same 12 Veteran Integrated Services Networks.

In unadjusted analyses, bariatric surgery was significantly associated with reduced mortality (hazard ratio 0.64), but in an analysis of 1694 propensity-matched patients, bariatric surgery was no longer significantly associated with reduced mortality in both unadjusted (hazard ratio 0.83) and time-adjusted (HR 0.94) Cox regressions.

Previous studies have mostly identified control patients via the use of a diagnosis code of morbid obesity, says Maciejewski, which "means they were probably not random samples of all patients eligible for surgery, and they were probably a sicker group [than those who underwent bypass], which might overstate the benefits of surgery."

"Our results highlight the importance of statistical adjustment and careful selection of surgical and nonsurgical cohorts, particularly during evaluation of bariatric surgery according to administrative data," he and his colleagues note. The survival benefits between the bariatric surgery and control groups were modest in most previous studies and so may have been attenuated if adjustment for confounders had been possible, they explain.

### **Important to continue to track the patients**

Maciejewski says it will be important to continue to track this cohort to see whether any survival advantages for surgery emerge in the longer term.

The fact that no survival advantage has been seen so far is perhaps "not surprising," say he and his colleagues. In the only other trial to have compared bariatric surgery with "high-quality clinical data," the **Swedish Obese Subjects (SOS)** study, the survival benefit was not observed until a median of 13 years of follow-up.

It will also be necessary to incorporate other patients who have undergone more contemporary laparoscopic gastric banding or gastric-sleeve resections—procedures that are being performed more and more in the VA system. "It will be important to update the results to account for those procedures," Maciejewski observes.

But, in the meantime, even though bariatric surgery is not associated with reduced mortality, many patients may still choose to undergo such procedures, "given the strong evidence for significant reductions in body weight and comorbidities and improved quality of life," the researchers conclude.

1. Maciejewski ML, Livingston EH, Smith VA, et al. Survival among high-risk patients after bariatric surgery. *JAMA* 2011; 305:2419-2426.

## High olive-oil consumption linked to lower stroke risk

JUNE 17, 2011 | Megan Brooks

Adapted from **Medscape Medical News**—a professional news service of WebMD

**Bordeaux, France** - A diet rich in olive oil may reduce the risk of stroke in older adults, new research suggests [1].

In roughly 7600 elderly adults, higher olive-oil consumption at baseline was associated with a lower incidence of stroke over roughly the next five years, after researchers controlled for numerous confounding factors, including lifestyle and nutritional factors, stroke risk factors, and blood lipids.

**Dr Cecilia Samieri** (University of Bordeaux, France) and colleagues report their findings online June 15, 2011 in *Neurology*.

"The high prevalence of stroke in older subjects emphasizes the need for primary and secondary prevention in this age group," they conclude. "Showing a strong association between intensive olive-oil use and lower stroke incidence, our study suggests a novel approach of dietary recommendations to prevent stroke occurrence in elderly populations."

But the authors of a commentary caution against jumping to any conclusions, noting that the putative health benefits of olive oil and a Mediterranean-style diet are complex.

### The Three-City Study

Samieri and colleagues examined the association between olive-oil intake and stroke incidence in 7625 people aged 65 and older from Bordeaux, Dijon, and Montpellier, France. They are enrolled in the ongoing, population-based French **Three-City Study**, which is looking at vascular risk factors for dementia.

At baseline, 1738 (22.8%) subjects reported no olive-oil use, 3052 (40.0%) reported moderate olive-oil use, and 2835 (37.2%) reported intensive olive-oil use.

The authors note that moderate and intensive olive-oil users (relative to nonusers) were younger than nonusers and had lower values or frequencies for several stroke risk factors, weighed less, and had lower triglycerides and a lower total/HDL cholesterol ratio. They were also more apt to be regular exercisers and ate fish, fruits, and vegetables and omega-3 rich oils more often than nonusers.

Over a median of 5.25 years, 148 incident strokes were recorded (115 ischemic, 28 hemorrhagic, five undetermined).

After adjusting for sociodemographic and dietary variables, physical activity, body-mass index, and risk factors for stroke, the researchers observed a lower incidence of stroke with higher olive-oil use (p for trend=0.02). Compared with those who did not use olive oil, those with intensive use had a 41% lower risk of stroke. No other dietary variable was significantly associated with stroke incidence.

### Multivariate association between olive-oil use and six-year incident stroke

Olive-oil use	Hazard ratio (95% CI)*	p
None	Ref	—
Moderate (with cooking or dressing)	0.80 (0.53-1.20)	.28
Intensive (both cooking and dressing)	0.59 (0.37-0.94)	.03

\*Fully-adjusted model

The researchers also examined the association between plasma oleic acid and stroke incidence in a subgroup of 1245 subjects. In this group, there were 27 incident strokes during a median follow-up of five years, including 20 ischemic and seven hemorrhagic strokes.

After adjustment for a wide variety of potentially confounding factors, compared with those in the first tertile of plasma oleic acid, those in the third tertile had a 73% reduction in stroke risk (HR 0.27, 95% CI 0.08-0.90,  $p=0.03$ ).

However, in the fully-adjusted model utilizing "component analysis" of total saturated fatty acids, total omega-3 fatty acids, and other dietary factors, the intensity of the association between plasma oleic acid and stroke was reduced (HR 0.25, 95% CI 0.08-0.86;  $p=0.03$ ).

One limitation of the study, Samieri and colleagues say, is not being able to distinguish between the different types of oil olive consumed. They also say the validity of plasma oleic acid as an indirect marker of olive-oil consumption remains to be evaluated.

### Olive oil pertinent to neurologic disease, too?


In their commentary, **Dr Nikolaos Scarmeas** (Columbia University Medical Center, New York, NY) and **Dr Luc Dauchet** (Institut Pasteur de Lille, France) make the point that exploration of the relation of the Mediterranean-type diet with neurologic diseases has started "only very recently and has suggested potentially beneficial associations for Alzheimer's disease, mild cognitive impairment, cognitive decline, essential tremor, Parkinson disease, and stroke."

While the current study suggests a protective effect of olive oil in stroke, the authors caution against drawing any firm conclusions from this study until the observations "withstand the trial of randomized intervention."

They point out that covariate adjustment "can never be complete." In addition, other potentially beneficial effects of olive oil, not considered in the analyses, may be mediating the association.

They also note that olive oil is not consumed in isolation, but with a whole host of potentially healthy foods. "To add further to the complexity, the potentially beneficial biological elements of olive oil are not clear."

1. Samieri C, Féart C, Proust-Lima C, et al. Olive oil consumption, plasma oleic acid, and stroke incidence. *Neurology* 2011; DOI:10.1212/WNL.0b013e318220abeb. Available at:

<http://www.theheart.org/viewDocument.do?document=http%3A%2F%2Fwww.neurology.org> 

## Prolonged TV watching ups risk of diabetes, CV disease, and death

JUNE 14, 2011 | Sue Hughes

**Boston, MA** - Confirmation that sitting in front of the television for prolonged lengths of time has long-term adverse effects has come from a new review of studies showing a direct relation between the amount of television viewing and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality.

The review, published in the June 15, 2011 issue of the *Journal of the American Medical Association*, showed that for every two hours of television watched daily, the risk of diabetes increased by 20%, the risk of cardiovascular disease increased by 15%, and the risk of all-cause mortality increased by 13%.

Coauthor of the study, **Dr Frank Hu** (Harvard School of Public Health, Boston, MA), commented to **heartwire**: "TV watching is worse than other sedentary activities in that it is particularly passive. It has a lower energy expenditure compared with driving, reading, working at a computer, etc."

### Associated with junk food

He also maintains that watching television is associated with unhealthy eating behavior. "People tend to eat when they are watching television, and they also tend to eat junk food and sugary beverages rather than healthier food. This might be related to the large amount of commercials for junk food, which increase the appetite, or it may just be due to boredom. Junk food is more readily available and therefore suitable for eating in front of the television. Perhaps if people were not watching television, they would be more inclined to make themselves a proper healthier meal."

Hu notes that the culture of television watching is a direct result of the technological revolution. "With the availability of satellite television, with hundreds of channels, we are watching more and more TV, and with a remote control we don't even have to get up from the sofa to change channels."

He added: "I'm not advocating a ban on television. But our behavior has become excessive. The average American watches five hours of TV every day. That is too much. And people get into a vicious circle. They watch a lot of TV, so start to put on weight, and that makes it more difficult to exercise, so they watch more TV. . . . I think we need to be telling people that they can cut their risks of diabetes and heart disease by reducing their time watching TV."

### Exercise while watching TV

"Public-health messages recommend an increase in physical activity, but they don't actually stipulate less television watching. That is something that is not too difficult to change. We should also be suggesting that people do some exercise while watching television. We could develop technology to enable people to expend more energy when watching TV, like using a treadmill or other exercise equipment."

In the paper, Hu and his coauthor, **Anders Grøntved** (University of Southern Denmark, Odense), report that television watching is the most commonly reported daily activity apart from working and sleeping in

many populations around the world, with an average of 40% of daily free time occupied by TV viewing within several European countries and 50% in Australia.

They performed a meta-analysis of eight prospective cohort studies looking at the association between TV viewing and risk of type 2 diabetes, fatal or nonfatal cardiovascular disease, and all-cause mortality. Results showed pooled relative risks per two hours of TV viewing per day of 1.20 for type 2 diabetes, 1.15 for fatal or nonfatal cardiovascular disease, and 1.13 for all-cause mortality.

The estimated absolute risk differences per every two hours of TV viewing per day were 176 cases of type 2 diabetes, 38 cases of fatal cardiovascular disease, and 104 deaths from any cause per 100 000 individuals per year.

- 1- Grøntved A and Hu F B. Television viewing and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality. A meta-analysis. *JAMA* 2011; 305:2448-55