March 3, 2012 BD Response to FDA statement regarding Statins

The Food and Drug Administration announced on Tuesday (February 28, 2012) the changes to the safety information on the labels of statins regarding memory loss, diabetes risk and liver function testing.

FDA Warning regarding Statin Therapy and Memory Loss: The statin labels will also now reflect reports of certain cognitive effects such as memory loss and confusion experienced by some patients taking the drugs, the agency said. It said those reports generally have not been serious and the symptoms were reversed by stopping use of the statin. The memory loss issue was more anecdotal from adverse event reporting and not from formal studies, the FDA said, adding that there was no proof that the problem was caused by statins but that it wanted people to be aware of the possibility.

Side effects of any medication, including statin therapy, must be analyzed with each patient during each visit. The recent statement by the FDA allows us to investigate the data associated with statin therapy, memory loss, diabetes risk and liver function evaluation.

Bale/Doneen Response regarding Statin Therapy and Memory Loss:

C. Cramer, PhD, Ed. al., Neurology 7.2008;71:344-350

1,674 patients, greater than 60 years old, Mexican American decent, 27% on statin therapy, followed for 5 years. 130/1674 patients developed dementia. For those taking statins, there was a statistically significant 48% reduced risk of developing dementia (95% CI 0.34-0.80). This study was adjusted for education, smoking, presence of at least one Apo E 4 allele and history of stroke or diabetes.

Arvanitakis Z, Schneider JA, Wilson RS, et al. Neurology 1/18/2008:

Religious Orders Study – an ongoing, prospective clinical-pathologic study of dementia. 119 statin users (67 lipophilic) and 215 non statin users, median age 75 years old, free of dementia. They were followed average of 12 years. 16 developed alzheimer's disease. After adjusting for age, gender and education, baseline statin use at any time during the trial was NOT associated with Alzheimer's risk. Statin type also did not influence cognition. 47 people had brain autopsy at the time of their death. No influence found on the classic Alzheimer's pathology or cerebral infarction was observed.

BMC Med 7/19/2007; Simvastatin linked to reduced incidence of dementia, Parkinson's disease.

Population-based database contains diagnostic, medication, and demographic information on 4.5 million subjects, 94.4% were male. 835,049 of subjects were taking a statin. (727,128 simvastatin, 53,869 atorvastatin, 54,052 lovastatin). Incidence of dementia and Parkinsons disease were reduced by greater than 50% for those that had continuously used a statin for at least seven months. Results were statistically significant for simvastatin but not for others due to sample size discrepancies. The mechanism of action for this reduction of alzheimers and parkinsons with statin therapy was speculated to be a result of the inflammatory benefits and increase in neural growth factors in the brain.

Robert C. Green, Sally E. McNagny, ParimalaJayakumar, L. Adrienne Cupples, Kelly Benke, Lindsay Farrer, for the MIRAGE Study Group Boston, MA. Statin Use Is Associated with Reduced Risk of Alzheimer's Disease.
Family-based, case-control study of 2581 subjects enrolled at 15 research centers from 1996-2001, including 614 African American subjects. Subjects included 912 persons with probable or definite AD by research criteria, and 1669 of their non-demented relatives. The association between statin use and risk of AD was evaluated. Adjustments for age, sex, ethnicity, education, history of heart disease, stroke, diabetes and APOE genotype were made.
Statin use was associated with a 79% reduced risk of AD (adjusted OR = 0.21, 95% (CI) 0.14 to 0.33). Non-statin cholesterol lowering medications were not significantly associated with reduced risk of AD (adjusted OR = 0.73, 95% CI 0.30 to 1.8). APOE genotype did not alter the association between risk of AD and statin use. The protective effect of natural statins was not significantly different from that of synthetic statins.
Diabetes: The FDA recently reported a concern with statin therapy and diabetes risk by siting the 2008 Crestor study of nearly 18,000 patients. A separate study published in the Lancet medical journal in 2010 found that statins can raise the risk of diabetes by 9 percent.

Bale/Doneen Response:

Sattar N., ProfPhD, et. al. *Lancet*. 3/2010 Vol. 375, Issue 9716:735-742

Meta analysis of statin trials analyzed for new incident diabetes. The trials analyzed included Atorvastatin (ASCOT-LLA), Simvastatin (HPS, 4S), Rosuvastatin (**Jupiter**, Corona, GISSI-HF), Pravastatin (WOSCOPS, LIPID, **PROSPER**, MEGA, ALLHAT-LLT, GISSI PREVENTZIONE) and Lovastatin (AFCAPS/TexCaps).

Eleven of the thirteen trials showed no significant association between statin use and new onset diabetes. The two trials that showed a significant relationship between new incident diabetes were Jupiter (1.26 [1.04-1.81]) and Prosper (1.32 [1.03-1.69]). In order to better understand this association, we must analyze the patient demographics and the entry criteria of each trial.

Prosper included men and women aged 70-82 years with a history of risk factors for vascular disease to pravastatin 40mg/day or placebo followed for 3.2 years. . Primary endpoint was a composite of coronary death, non-fatal myocardial infarction, and fatal or non-fatal stroke. As we know, insulin resistance is the most common root cause of vascular disease and affects approximately 72% of all individuals with atherosclerosis. This elderly, at-risk population was at high risk to develop diabetes regardless of statin therapy.

Jupiter randomly assigned men and women with LDL levels <130mg/dL and hsCRP levels $\geq$2.0mg/L. Participants were assigned rosuvastatin 20mg daily or placebo. Combined primary end point of MI, CVA, arterial revascularization, hospitalization for unstable angina or death from CV causes. The trial was stopped after a median follow-up of 1.9 years due to the dramatic drop in the primary end point in treatment vs placebo group. Additionally, hsCRP was reduced by 37%. We must recognize that insulin resistant individuals usually have normal LDL levels and elevated vascular inflammation. The Jupiter population, although not formally analyzed for insulin resistance during the selection process, certainly mimic the demographics that we recognize for insulin resistance. Therefore, it makes plausible discussion that these Jupiter patients were on a path towards diabetes regardless of rosuvastatin usage.

As we move forward into some recent analysis (Preiss, D. et al. JAMA 2011;305:2556-2564). It remains a bit unclear whether statin therapy is associated with a tendency for an increase in diabetes or whether these individuals are simply at a higher risk for diabetes because of an underlying (and often undiagnosed) insulin resistant condition. Baseline data from trials comparing intensive-dose to moderate-dose statin therapy showed fasting plasma glucose levels at or near levels of glucose impairment prior to entering the statin trial, indicating that the patients were already on their way to a diabetic diagnosis. PROVE-IT TIMI 22 – baseline glucose of 101, TNT – baseline FPG 97, IDEAL baseline FPG 99. A to Z and SEARCH did not have FBS reported. Understanding the pathology of insulin resistance allows us to find surprise in the fact that only one of these five trials were significant for new onset diabetes while at least 70% of the participants in these trials were insulin resistant at baseline.

Finally, and most recently, Archives of Internal Medicine published the following manuscript: <u>Statins Associated with New Onset Diabetes in Post-Menopausal Women</u>**(Culver, A.L. et al. Arch Intern Med 1/2012)**. 153,840 women were included in the analysis. Out of the 10,834 women treated with statin therapy for three years, 9.93% (n=1076) self- reported diabetes while the 143,006 not selected for statin therapy, only 6.41% (n=9166) self-reported diabetes after three years. The conclusion was then drawn that "statin therapy is associated with new onset diabetes in post-menopausal women". However, to appropriately draw this dramatic conclusion, the demographics of the two groups upon entry would have to be similar. Albeit troubling, the following demographic differences had p values of <0.001. The group of menopausal women that were included in the statin arm were statistically older, had higher BMI's and had a higher percentage of caloric intake from carbohydrates. Alcohol intake and exercise intake were lower in the statin group. The percentage of statin users were higher for Asian and Pacific Islanders. Additionally, more of the statin users had been smokers and had a higher family history of diabetes. All of these demographic differences placed these women at statistically higher risk for diabetes regardless of statin therapy. If the researchers wish to draw this conclusion, it would be necessary to divide the 10,834 women who had been selected for statin therapy and give half of the group a statin and half placebo for three years and compared new onset (or self-reported) diabetes. **Liver Function:**The FDA also stated that one safety warning long associated with the class of medicines will be reversed. Patients taking statins will no longer need periodic monitoring of liver enzymes, since cases of serious liver injury are rare and unpredictable in individual patients.

Bale/Doneen Response: We feel this recommendation is flawed for several reasons, including liver toxicity with mono-statin therapy, combination lipid therapy liver toxicity issues and also the value of monitoring liver function for improvement in NASH with statin therapy.

Journal of American College of Cardiology. 7/31/2007; 50:409-420: 23 randomized, controlled trials assessing statin therapy including high dose trials (PROVE-IT, TNT and IDEAL demonstrated that higher dose of statin can cause an increased risk of liver toxicity.

On another front, monitoring liver function in statin treated individuals has been shown to mark an improvement in patient's NASH (non-alcoholic steadohepatitis). As reported by Athyros, V. et al., Lancet 2010;376:1916-1922, "Statins can reduce CV Morbidity and Improve liver function in patients with abnormal liver tests potentially secondary to NASH".

Lastly, many statins go through CYT P450 3A4 pathway that interacts with many medications. Patients being treated for atherosclerosis and dyslipidemia are often on multiple medications, making it necessary to check hepatic function regularly.

Bottom line: There is a plethora of published evidence which would refute the recent FDA statement on statins.

Bale/Doneen Method – Amy Doneen and Bradley Bale