Do Statins Harm the Liver?

In 2008, I started a series about the safety of statin therapy that I wrote for my Cholesterol Management 101 Blog on WebMD. One of the topics I discussed with respect to this class of drugs was on the potential effects on the liver. As I stated in that paper, all the information was current and evidence based at that time. It was provided by the National Lipid Association Statin Safety Task Force, which was an independent body of experts whose sole task was to answer certain question using all available resources and literature available. Their conclusions were published in the American Journal of Cardiology. Since that time, the GREASE Study-liver function test data was published in The Lancet in November 2010 and further confirms that the myth of statin induced liver toxicity is just that-a myth.

When The National Lipid Association Statin Safety Task Force originally wrote their report, each panel of experts wrote about a different area of the body in which any of these medications had been shown to effect in some way. We began our discussion at that time on the liver and statin interactions. The word liver and hepatic can be interchanged so do not be confused with the wording. I will first repeat what I originally wrote on my blog and then add to this article based on the newest data just published.

Concerned patients always ask me if a statin will damage their liver? I will try to answer this question in a concise form. I always respond that statins are one of the safest medicines and are also are one of the most studied medications. In 2005, 30 million people in the US were taking statins All medicines have both a generic and a brand name but I am sure most people only know the brand names so I will list them for you. The statins include Lipitor, Zocor (simvistatin), Vytorin, Mevacor, Crestor, Pravachol, Lescol, and the newest statin called Livalo. I would like to work backwards and give the final conclusion of the Report of the Expert Liver Panel of The Statin Safety Task Force and then detail how they came to this conclusion…."Outside of measuring liver biochemistries for the purpose of periodically updating a patient's medical history, we can find no scientific or medical basis for monitoring aminotransferase levels during long-term statin therapy as a measure to enhance patient safety. We acknowledge that the Panel's recommendations are at odds with current prescribing information for marketed statins: however, we are optimistic that the regulatory agencies and pharmaceutical industry will update their recommendations to be consistent with evidence-based data cited in this article." What does this mean? Well, it simply means that all the liver function tests, which are commonly known as AST and ALT levels, that one's physician routinely draws to check for liver problems are unnecessary according to the all available data with the exception of updating labs during an annual physical exam or if the physician having some concrete reason to do so. The evidence based data shows that routinely drawing these labs do not make statins any safer. In fact available data The available data does not support doing so in the "asymptomatic" patient on a statin. Why do they say this? The reason the Panel says this is that believe it or not "Very rare case reports of liver failure have occurred in patients receiving statin therapy." Because the association between statin therapy and liver failure is so rare there is absolutely no way one can say with confidence that the liver failure was due to statin use. It is possible that

this could be an "idiosyncratic reaction" to the statins….this means that a person could have an unexpected reaction or a type of allergy to the medicine and that is the reason for the liver failure. I like to think of it as the problem is with the way the patient's body responds to the drug rather than the class of drugs causing the problem. The Liver Panel could find "no direct evidence of death due to liver failure caused by statin therapy." This does not mean that statins will not elevate the liver enzymes because this is a known side effect. Generally a physician does nothing unless the level is >3 times the upper limit of normal but this does not mean that liver damage is occurring. This has been shown to happen<1% of the time across the dose range for marketed statins. I personally asked a friend of mine who is a liver doctor at the largest hospital in the Western US his opinion on liver problems and statins. He said that he rarely performs liver biopsies any more when patients are on statins and have elevated liver enzymes because he has yet to see a case on statin induced liver failure. There was always another explanation as to the cause of the liver failure. My own feeling is that too many physicians stop this medication unnecessarily and forget the benefits of statins in reducing cardiovascular morbidity and mortality by at least 40% because they think a small rise in the liver function tests means that there is damage ongoing to the liver. Statins can be used safely in patients with chronic liver disease and well treated cirrhosis but the physician may need to follow the patient a little more closely than would occur in a normal healthy patient on a statin. I hope this explains the true story between statins and any possible interaction with the liver.

Well now we have The GREASE STUDY by Athyros et al. An online commentary published with the study is titled**, "Liver tests are irrelevant when prescribing statins"** written by Bader who is a world famous liver doctor. I will include most of the body of his Lancet commentary in this text.

"Statins increase alanine aminotransferase (ALT) concentrations(one of the enzymes from the liver) in 10% of recipients, and this increase can exceed more than three times the upper limit of normal in 1% of patients. Despite a lack of evidence that statins cause liver disease, many physicians are reluctant to start statins in patients with an out-of-range ALT value. Most patients with high ALT will have fatty liver or non-alcoholic steatohepatitis (NASH), because 20% or more of patients in developed countries have these conditions (i.e., a fifth of people in developed countries have fatty liver or NASH, and on occasion many, but not all, have abnormal ALTs)
In **The Lancet**, Vasilios Athyros and colleagues[1] present a post-hoc analysis from a randomized trial of the efficacy and safety of a statin in patients with baseline increases of ALT that were less than three times the upper limit of normal. All of these patients were thought to have fatty liver or NASH. In patients with fatty liver or NASH, serious increases of ALT occurred no more often than in a similar group who were not given statins. Moreover, ALT improved or normalized in patients who were given statins, whereas in the group not given statins, liver tests continued to worsen. Most importantly, patients who started the trial with elevated liver-function tests derived the greatest cardiovascular benefit of any group—a favorable effect, which was substantially greater for these patients than for patients who started statins with in-range liver-function tests. Although most patients took atorvastatin, there is no reason to believe that other statins would behave differently.
The accompanying study[1] is excellent and groundbreaking. The uniform improvement in liver-function tests for patients who started with abnormal liver function matches findings for our patients with hepatitis C who were given statins. This study is the first to show an additional benefit of reducing cardiovascular events in patients with abnormal liver-function tests. No studies

show how many patients are denied statins because of pre-existing changes in liver-function tests, or how many patients have statins discontinued when ALT increases. 10–30% of patients who need statins might fall into these categories, and would therefore be denied a statin; if so, this large group represents a substantial source of cardiovascular disease, which is not being prevented. Further harm ensues from the cost of monitoring with liver-function tests. One estimate has conservatively placed the cost of monitoring statins with liver-function tests at US$10 billion per year.[4]

Statin-induced hepatotoxicity is a myth. Large trials of statins have shown no difference in the frequency or degree of ALT increases between treatment and placebo groups. Out-of-range values, which do occur with statin use, eventually return to normal even if the same statin is continued. The occurrence of acute liver failure thought to be caused by statins is well below what is now understood as the background rate of idiopathic acute liver failure in the general population. No consistent liver- biopsy picture from possible statin-related drug injury has emerged, and there are no reports of chronic carriers of drug-induced liver damage from statins. Thus, an increased ALT in this situation is not a disease. Despite the absence of liver injury from statins, a US survey showed that 50% of academic physicians would be reluctant to give a statin to a patient who presents with an ALT of more than 1·5 times the upper limit of normal. More than 40% would deny a statin to patients with chronic hepatitis C, another 2% of the general population.[5]

Most physicians believe that statins cause liver disease because of the language of package inserts. Drug companies should be encouraged to request the deletion of this point from the insert. The US Food and Drug Administration, which sets the pace for much of the world, cannot unilaterally remove this language, but can only grant such a change in response to a submitted label modification.[4]

Athyros and colleagues' findings need prospective confirmation and extension to include patients whose baseline ALT values are more than three times the upper limit of normal. However, I am confident that continued benefit of statin use for increased ALT, even in the presence of liver disease, would be shown. For too long, a raised ALT after starting a statin has been erroneously thought to represent liver disease. For too long, patients with liver disease have been denied statins for their hypercholesterolemia".

Well what does this mean? In a nutshell it means that for too long many people have been denied life saving statins. There is solid evidence that they markedly decrease cardiovascular morbidity and mortality. I was actually stunned when I looked at the package inserts for all the statins that are sold yet the recommendations for liver testing were all different yet the class of drugs effect on the liver is the same.