HEALTH AND STRESS

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STRESS FROM CRP vs. LDL AND INFLAMMATION

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As emphasized in recent Newsletters, there is increasing evidence that cholesterol and fatty foods do not cause heart attacks or coronary atherosclerosis. Similarly, although statins may benefit patients who have had a myocardial infarction, this is not due to any lipid lowering effects, nor do statins prevent coronary events in healthy people.

Also Included In This Issue

Statins have now also been promoted to treat or prevent Alzheimer's, colon cancer, osteoporosis, kidney damage in diabetics, macular degeneration, autoimmune diseases like rheumatoid arthritis, inflammatory bowel disease, as well as to decrease rejection rates in organ transplants. There is no evidence of elevated LDL in these disorders, nor any reason to suspect that long term statin therapy would be either beneficial or safe.

Statins have been the best selling and most profitable prescription drugs ever since they became available. But fierce competition has now forced pharmaceutical companies to find ways to prove that their product is superior or safer. That's difficult to do, since all statins lower LDL and pose similar health hazards depending on the dose, which depends entirely on an arbitrarily determined level of LDL according to current guidelines.

Faced with the fact that lowering lipids does not explain how statins work, other "pleiotropic" effects, like reducing inflammation and/or clot formation have been proposed. These would be more plausible justifications for their use, especially for the unrelated disorders noted above. As a result, some authorities believe that the treatment of coronary heart disease should now focus on reducing inflammation rather than cholesterol and/or LDL. This is particularly important with respect to primary prevention in healthy people who have been increasingly labeled as being at "increased risk" to promote sales. The latest risk factor is a high CRP (C-reactive protein), which is being touted as the most accurate method to measure the severity of inflammation thought to contribute to heart disease, despite the fact that CRP can be elevated for many other reasons. It is not clear whether some statins have advantages over others with respect to their ability to lower CRP or if this necessarily means they would be more effective in preventing or treating heart disease. Several studies over the past five years have been designed to find answers to these and related questions.

Is Crestor More Effective Than Other Statins In Reducing Inflammation?

Crestor seems to have gotten the jump on other statins because of the JUPITER study. (**J**ustification for the **U**se of statins in **P**rimary prevention: an **I**ntervention **T**rial **E**valuating **R**osuvastatin). Some appreciation of the wide media attention this attracted is illustrated by the following press headlines.

Fox News-Cholesterol Drug Causes Risk of Heart Attack to Plummet

"People with low cholesterol and no big risk for heart disease had dramatically lower rates of heart attacks, death and stroke if they took the cholesterol pill Crestor, a large study found."

A ***New York Times*** first page headline and prominent lead story proclaimed

Cholesterol-Fighting Drugs Show Wider Benefit

"A large new study suggests that millions more people could benefit from taking the cholesterol-lowering drugs known as statins**, even if they have low cholesterol**, because the drugs can significantly lower their risk of heart attacks, strokes and death."

The ***Wall Street Journal*** also noted the financial implications

Cholesterol Drug Cuts Heart Risk in Healthy Patients

"AstraZeneca's cholesterol drug Crestor sharply lowered risk of heart attacks among apparently healthy patients in a major study that challenges longstanding heart-disease prevention strategies**. The findings could substantially broaden the market for statins, the world's best-selling class of medicines."**

All this excitement was generated by the JUPITER study, which reported that

men and women with normal LDL but elevated CRP levels who took 20 mg. of rosuvastatin (Crestor) daily, reduced their risk of coronary events and deaths by 44% more than controls who received a placebo. LDL plunged 50% to an average of 55mg/dL, the lowest levels ever reported in a major statin study. CRP fell 37% but there was no correlation between this and the degree of LDL lowering. Crestor reduced the risk of a first heart attack or stroke and the need for procedures to clear or bypass clogged arteries by 46% to 54%, and deaths from any cause by 20 percent. This was groundbreaking because it appeared to **demonstrate for the first time that a statin could prevent coronary events and premature deaths in healthy people.** In addition, **these benefits were not due to lowering LDL**, a significant blow to the lipid hypothesis.

However, the cholesterol crusaders ignored this as they also jumped on the Crestor bandwagon, including Dr. Steven Nissen, head of cardiology at Cleveland Clinic, and a consultant to the FDA. Nissen has a reputation as a whistleblower, since he was largely responsible for the withdrawal of Vioxx, as well as black box warnings for the diabetes drug Avandia because of their adverse cardiac side effects. He also urged stiffer warnings for Vytorin, which contains a statin (Zocor) and Zetia, another drug that lowers cholesterol by inhibiting its absorption. Zetia lowers cholesterol by 15% to 20%, and although there was no evidence it reduced plaque formation, it was thought that combining it with Zocor would reduce cholesterol and plaque formation more than Zocor alone. But in the ENHANCE study of over 700 patients with very high cholesterol due to a genetic trait, plaque grew twice as fast in the combination Vytorin group compared to those who took only Zocor. This was hard to explain, especially since both LDL and CRP fell much more in those taking the two drugs. Nissen described the Vytorin results as "shocking", and said "This is as bad a result for the drug as anybody could have feared. Millions of patients may be taking a drug that has no benefits for them, raising their risk of heart attacks and exposing them to potential side effects." Contrast this diatribe with his following laudatory quotes about JUPITER in the media:

Bloomberg News - "This may be the **most important trial we've seen in a decade**," and that the study findings are an "**out-of-the-park home run**."

LA Times - "It's a **blockbuster**. It's absolutely paradigm shifting."

CNN - "This is a huge reduction, **unprecedented reduction in risk** occurring very quickly."

Forbes - "It's potentially a **game-changer**."

Time - "This is unprecedented...**I have never seen a result of this magnitude reduction in risk**. The results were significant enough to stop the study 3 years early."

The Washington Post - "It's **a breakthrough study**," and "This changes medical practice in a major way. People are going to flock to their doctors to get their CRP measured and if it's elevated, they will say, 'Here, this drug you can take.' We'll save many lives and a lot of money."

USA Today - "This is going to have **huge repercussions**. It means that men over 50 and women over 60 are going to get their CRP checked, and if they're high, they're going to get 20 milligrams of rosuvastatin...We know that we can **reduce their risk of heart attack and stroke and angioplasty by nearly 50%.** We've never seen this magnitude of risk reduction in a statin trial."

Low LDL And High HDL But More Deaths From Heart Disease?

Nissen was not involved in the JUPITER study, so these accolades are all the more surprising, since he had always emphasized that lowering LDL "bad" cholesterol should be the "cornerstone" of statin therapy, and the lower the better. There was no explanation as to why patients taking Vytorin had **more atherosclerotic plaque despite having much lower LDL as well as CRP** than the Zocor controls. It had been observed that people with very high "good" HDL cholesterol had low rates of coronary disease. The Framingham study showed that for a given level of LDL, risk of heart disease increased 10-fold as the HDL level varied from high to low. Even when LDL was very low, risk increased if HDL was not high enough. Nissen had previously attempted to demonstrate that torcetrapib, a drug that raises HDL, would improve the ability of Pfizer's Lipitor to reduce atherosclerosis as measured by the IVUS (intravenous ultrasound) procedure he had pioneered. However, his two-year study of 15,000 high risk patients was terminated abruptly and unexpectedly after a little more than a year because **of 82 deaths in the combination torcetrapib/Lipitor group, compared to only 51 in those taking Lipitor alone.** There were also higher rates of hypertension, heart failure, angina and revascularization procedures in the combination group, **despite the fact that they had increased their HDL by close to 60% and reduced LDL 13% over baseline values.**

This was a huge blow to Pfizer and its stock plunged. Nissen was also disappointed, but pointed out that there was 50 percent less plaque in the combination group, at least as measured by his IVUs intravenous ultrasound technique. He had used this previously in the Crestor ASTEROID study (**A** **S**tudy **T**o Evaluate The **E**ffect Of **R**osuvastatin **O**n **I**ntravascular Ultrasound **D**erived Coronary Atheroma Burden). The recommended starting dose of Crestor is 10 mg., or 20 mg. in patients resistant to other statins. A 20-mg.

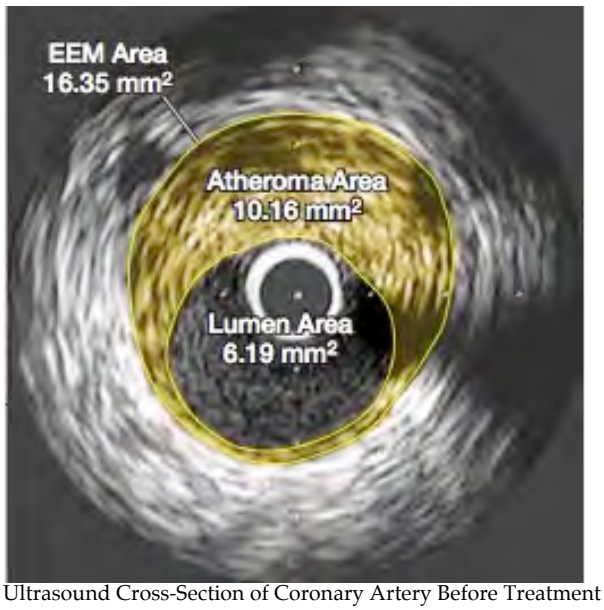
dose was used in JUPITER, but the ASTEROID patients received 40 mg. of Crestor daily in an effort to obtain maximal LDL and plaque reduction as rapidly as possible. An 80 mg. Crestor tablet had been rejected by the FDA because of serious side effects, so there were some safety concerns about the 40 mg. dose. In March 2004, only eight months after its release, the Public Citizen consumer advocacy group asked the FDA to ban Crestor. Three cases of kidney failure associated with severe rhabdomyolysis had already occurred in the U.S., resulting in one death, and seven cases of rhabdomyolysis and nine of kidney failure had been reported in Canada and the U.K. This was ominous, since it is well established that the vast majority of adverse drug reactions are never reported. Baycol, an early statin, was approved by the FDA in 1997. By the time it was banned in 2001, 1,899 cases of rhabdomyolysis had been reported. Numerous cases and deaths could have been prevented, since a significant number of these occurred long after unequivocal evidence that it should have been withdrawn.

In June 2004, the FDA issued a Public Health Advisory notifying healthcare professionals of a revised package insert for the 22 member states of the European Union in response to adverse event reports in patients receiving Crestor. It highlighted certain populations that might be at increased risk for serious muscle disease, especially at the highest approved dose of 40 mg. In May of 2005, a study published in the American Heart Association's journal, *Circulation*, revealed that kidney failure and muscle weakness were two to eight times more frequent among Crestor users than those taking other cholesterol lowering drugs such as Lipitor and Zocor. The kidney problems were due to blockage of its tiny tubules by the breakdown fragments of muscle cells. AstraZeneca sent a letter to all British physicians urging them to start with a 10 mg. dose, but despite repeated requests for a ban, or at least a black box warning, the only change in the U.S. was an additional alert that Asian patients might be more likely to suffer side effects.

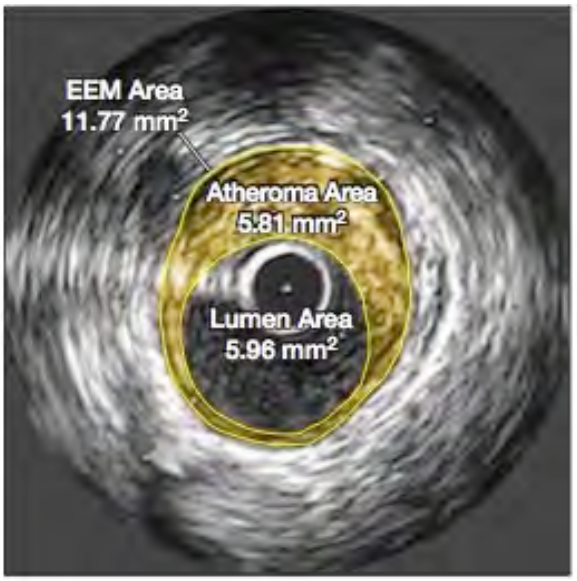
However, there were apparently no such problems in the ASTEROID study. In patients who took 40 mg. Crestor daily, the mean baseline LDL of 130.4 dropped to 60.8, an impressive 53.2% reduction. In addition, mean baseline HDL of 43 increased to 49, an unprecedented 14.7% increase. But the real triumph was a 6.8% to 9.1% reduction in plaque based on Nissen's ultrasound measurements. The results, which were published in the March 14, 2006 issue of *JAMA*, led to lavish media headlines, including this Reuters press release "A Drug is Found to Reduce Plaque in Arteries". It stated **"a statin drug [Crestor] has been shown for the first time to reverse the buildup of plaque in coronary arteries"** and that "the changes in cholesterol levels seen were the largest ever seen in a major trial of statin drugs". Nissen described the results as "shockingly positive", adding, "Previous similar studies with statins have shown slowing of coronary

disease, but not regression. This regimen significantly lowered bad cholesterol, and surprisingly, markedly increased good cholesterol levels. . . . We conclude that very low LDL levels (below current guidelines), when accompanied by raised HDL, can regress, or partially reverse, the plaque buildup in the coronary arteries."

Pfizer immediately countered with a statement indicating that the REVERSAL study had previously demonstrated that its top-selling Lipitor showed a 5.9% reduction in only 18 months and was extremely well tolerated. Others pointed out that plaque regression had also been demonstrated with Zocor, which was now available as generic simvastatin at a fraction of the Crestor $3.50 per tablet price. There were also concerns that only 500 patients had been studied at one center and that there was no placebo or another statin control group that could be used for comparison, especially with respect to plaque reduction. In addition, there were claims that Nissen's intravenous ultrasound results had been misrepresented. The article indicated that examination of coronary arteries before and after taking Crestor 40 mg./day for 2 years, showed that **plaque "volume" was reduced by 40%** in the most diseased arterial segment in 349 patients. Actual images of a coronary artery before and after Crestor therapy in what was described as a representative case are reproduced below.



Ultrasound Cross-Section of Coronary Artery Before Treatment



Ultrasound Cross-Section of Coronary Artery After Treatment

In actuality, it was the cross-sectional areas of atheroma that were compared before and after treatment, since it was assumed that these measurements were directly proportional to their respective volumes and that that the area of the lumen would increase proportionally. What was not discussed in either the press releases or the article was that **the lumen area actually decreased by 4 percent.** As can be seen, these images also showed that the arterial wall had thickened. This might not be beneficial

since a smaller lumen and a stiffer arterial wall would both tend to increase blood pressure, an effect that was also not addressed in the published report. The Results section of the Abstract section of the article stated, "adverse events were infrequent and similar to other statin trials" and the Comments section conclusion indicated, "This very intensive statin regimen was well tolerated." However, the total dropout rate appears to have been 25%, and no details were provided to explain this. In addition, this trial may have been too short for Crestor side effects reported in other studies to have surfaced, raising questions about long-term safety with this maximum permissible daily dose. It is easy to understand Nissen's enthusiasm for the JUPITER results, since it provided further support for his ASTEROID study that suggested the superiority of Crestor over other statins not only for reducing inflammation, but also preventing heart disease in healthy people.

Why Many Feel JUPITER Should Be Brought Back Down To Earth

However, a closer analysis suggests that some of the JUPITER conclusions may have been manufactured. The study involved men over 50 and women over 60 with no history of heart disease but who had an elevated CRP and normal cholesterol. Its purpose was to demonstrate that those receiving 20 mg. of Crestor daily would have fewer coronary events due to a lowering of CRP, compared to controls taking a placebo. Since the authors claimed that the study demonstrated this, the obvious inference would be that anyone with an elevated CRP should be treated with Crestor even if there were no other risk factors for heart disease. In that regard, while the participants were described as "apparently healthy" without any other risk factors, they were older (median age 66), overweight (median BMI 28.3 or 165 lbs for the average 5' 4" woman or 192 lbs for the average 5' 9" male), had elevated blood pressures, higher blood sugars and glycosylated hemoglobins consistent with undiagnosed diabetes. Any of these would put them at increased risk, so that the results might not necessarily apply to those without these potential health hazards. Specifically excluded from the study were women taking hormone replacement therapy, anyone with hypertension, thyroid or autoimmune disease, history of alcoholism or drug abuse, or evidence of liver or kidney abnormality, since earlier studies demonstrated that Crestor could be dangerous for them. The Crestor group had 54 more cases of diabetes that were not considered significant, even though this 25% increase was more than the difference in heart attacks or strokes between the two groups.

JUPITER was scheduled to run until 520 confirmed primary "end points" had been reached. These "end points" were fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, stent insertion, hospitalization for unstable angina, or confirmed death due to cardiovascular disease. However, the way end point statistics were collected, one person might be recorded as

having several, even though they had only one incident or hospitalization. There was so much overlap that it is very hard to know exactly what was being reported. It was anticipated that the study might last five years, but it was stopped after 23 months at which time only 393 end points had been reported. Although an "unequivocal reduction in cardiovascular mortality" was publicly announced as the major reason, the data did not support this. The only justification for termination was that the placebo group had experienced 109 more of these confusing end points and it was felt that continuing the study would subject them to increased harm. This was exaggerated in reports claiming that **Crestor reduced by almost 50% the risk for a major first cardiovascular event.** But this was relative risk. As can be seen below, **the actual risk reduction (AR) was less than 1%.**

Rate of primary endpoint: Crestor 1.6%; placebo 2.8% → **AR, 1.2%.**

Rate of fatal or nonfatal MI: Crestor 0.35%; placebo 0.76% → **AR 0.41%.**

Rate of fatal or nonfatal stroke: Crestor 0.37%; placebo 0.72% → **AR 0.35%**

It would appear from the above that the Crestor group indeed had slightly less than half as many heart attacks. But **those taking Crestor also had 150% more fatal heart attacks.** The data were presented in a manner that obscured this, since it was reported as follows:

Any myocardial infarction: Crestor **31,** Placebo **68**

Nonfatal myocardial infarction: Crestor **22,** Placebo **62**

To find the number of fatal heart attacks, subtract "Nonfatal myocardial infarction" from "Any myocardial infarction". This reveals **9 deaths in those receiving Crestor (29%), compared to 6 in the placebo group (9%).** Stroke is similarly presented to show a 50% reduction from Crestor:

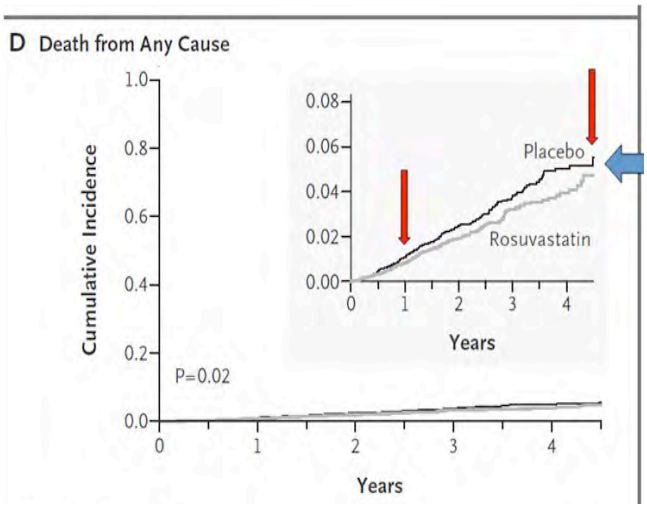
Any stroke: Crestor **33,** Placebo **58**

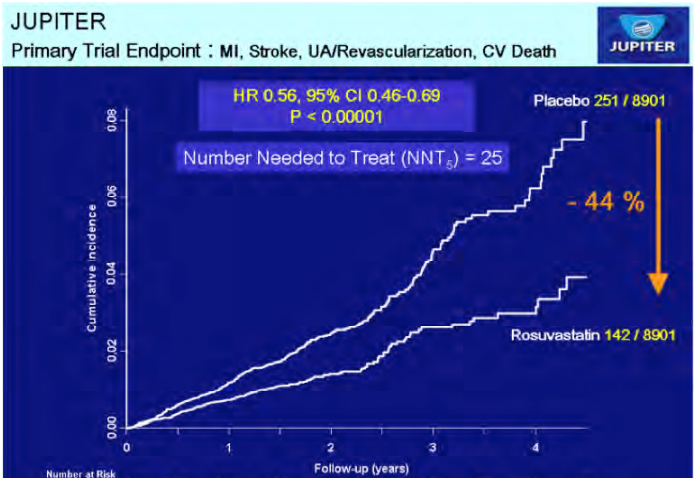
Nonfatal stroke: Crestor **30,** Placebo **64**

This translates into 3 fatal strokes in the Crestor group and 6 fatal strokes in those taking a placebo. Cardiovascular mortality (fatal myocardial infarction + fatal stroke) is therefore identical in the two groups (12 against 12). Why didn't the authors mention this?

There were also concerns about conflicts of interest and the role of the sponsor. The lead author is a co-holder of the patent for the hsCRP test that was used, and has become the standard (at $50.00/test). Nine of the 14 authors had significant financial ties to AstraZeneca, whose investigators also collected, controlled and managed the raw data and monitored the collection sites. It is well established from other drug company sponsored studies that bias can creep in, such as the preponderance in the placebo group of patients with a family history of heart disease or metabolic syndrome, both of which significantly increase risk. At the time the study was terminated, one out of four were not taking their study pills, and we

don't know why, or how many of the deaths came from this group. The fact is that of the almost 18,000 subjects there was a difference of less than 50 deaths between the two groups during the study, and the gap seemed to be closing. Some feel this may explain why JUPITER was terminated prematurely, since a longer period of observation might have shown no difference or even more deaths in the Crestor group, as illustrated below.





In the any (all) cause mortality graph to the left, the bottom two curves for Crestor and placebo are almost identical, which happens when very small numbers are involved. On the two divergent curves at the top, the authors had to use **a different scale** to make it appear that there was a major difference. The primary trial endpoint graph to the right was manipulated by utilizing the same tactic. As previously noted, the end point tabulation was confusing since a patient could have more than one and some, such as death, were more important than being hospitalized for angina. The patient population was also unusual, since it would be difficult to assemble almost 18,000 people with both an LDL under 130 and an elevated CRP and no history of heart disease, especially if you exclude people with any history of an inflammatory disorder, as the researchers did. It is thus not surprising that 1,315 sites in 26 different countries were required. This averages out to 13 subjects per center, which is quite small and raises other questions.

AstraZeneca is said to have spent $1 billion in promoting Crestor in the first year it became available, and quickly gained the nickname "superstatin" or "gorilla statin". Nobody knows how much it has spent since then on its GALAXY program that involves 70,000 patients from over 55 countries. In addition to those previously noted, there are COMET, MERCURY I, MERCURY II, PULSAR, POLARIS, STELLAR and METEOR. Like ASTEROID and JUPITER, these are all acronyms based on the first letter of the official title of each study, an ingenious feat in itself. However, it certainly paid off for JUPITER, since earlier this year, the FDA approved Crestor "to reduce the risk of

stroke, myocardial infarction and arterial revascularization procedures in individuals without clinically evident coronary heart disease but with an increased risk of cardiovascular disease (based on age (men ≥50 and women ≥60), high-sensitivity C-reactive protein (hsCRP) ≥ 2 mg/L, and the presence of at least one additional risk factor, such as hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease." Until some other statin can make this claim, this could prove to be a billion dollar bonanza for AstraZeneca.

The ancient Greeks named their planets after deities that had human attributes. Mars was the god of war or death, Venus was the goddess of love, Mercury was the god of knowledge and communication, and Jupiter was the supreme god and god of the sky and storms. The biggest storm in the solar system is allegedly the red spot on Jupiter, but the trial that bears its name is stirring up a tempest back on earth. There have been numerous other criticisms with multiple rebuttals and denials. There is so much controversy that a recent issue of *Archives of Internal Medicine*, a respected AMA journal, devoted four articles and an editorial to various aspects of the ongoing dispute. These arguments suggest that Erasmus may have been correct 500 years ago, when he described Jupiter as follows,

> Jupiter, not wanting man's life to be wholly gloomy and grim, **has bestowed far more passion than reason /you could reckon the ratio as twenty-four to one.**

Moreover, he confined reason to a cramped corner of the head and left all the rest of the body to the passions. Most objections center around the implication, if not the conclusion, that an elevated CRP alone is a risk factor for heart disease that should be treated with Crestor, and that the results in this select group of patients apply to other age groups and should be considered for primary prevention in healthy people (at a cost of $1,300.00/year). Treating someone who has had a heart attack for five or ten years because they are at significantly increased risk for a recurrent coronary event makes sense. But prescribing statins for several decades to someone in their thirties or forties because of an elevated CRP is difficult to justify in view of lack of evidence about either long term efficacy or adverse side effects. Nor is it known whether other statins that are less expensive or safer may be just as effective in reducing the inflammatory process that is presumed to cause coronary atherosclerosis.

What Is "Inflammation" And How Does It Cause Heart Disease?

The notion that "inflammation" might be the cause of atherosclerosis is hardly new, and until the advent of the cholesterol theory, was apparently the prevailing view. The celebrated pathologist Rudolph Virchow, who first noted the presence of cholesterol in atheroma in 1856, described

atherosclerosis as ***endarteritis*** *deformans.* The suffix "itis" emphasized that it resulted from an inflammatory process that injured the inner lining of the arteries, and that the cholesterol deposits started to appear subsequently. Virchow was very specific about this when he wrote

> We cannot help regarding the process as one which has arisen out of irritation of the parts stimulating them to new, formative actions; so far therefore it comes under our **ideas of inflammation**, or at least of those processes which are extremely **nearly allied to inflammation**.....We can distinguish a **stage of irritation preceding the fatty metamorphosis,** comparable to the stage of swelling, cloudiness, and enlargement which we see in other inflamed parts. I have therefore felt no hesitation in **siding with the old view** in this matter, and in admitting an inflammation of the inner arterial coat to be the starting point of the so-called atheromatous degeneration.

Notice the highlighted words that he used to describe this process as "coming under our ideas of" and "nearly allied to" inflammation. That was because 2,000 years earlier, Celsus had defined inflammation as heat, pain, redness and swelling (*calor, dolor, rubor,* and *tumor*), to which Virchow had added disturbance of function (*functio laesa*). All of these were signs and symptoms that could be seen or felt. In contrast, this process was asymptomatic and could only be verified by microscopic examination. Swelling, and perhaps "cloudiness were the only changes reminiscent of inflammation, which is why Virchow avoided using this word.

So precisely what do we mean when we refer to reducing inflammation to treat or prevent heart disease? What components of inflammation are we specifically referring to? Is there a more meaningful term or phrase to describe this chronic low grade and smoldering progressive pathologic process? Hans Selye, who was interested in studying the effect of stress and steroids on inflammation, devised a unique granuloma pouch technique that provided a standardized way to measure both the gross and microscopic responses to an inflammatory stimulus. Glucocorticoids like cortisol had an inhibitory effect while others increased the response, and the same was true for different pituitary hormones. Selye also wrote several books detailing the effects of stress on the cardiovascular system that described inflammatory-like pathologic changes prior to a myocardial infarction. Being a purist, he referred to these as prophlogistic, (from *phlogosis* the Greek word for inflammation) which may be more accurate and preferable.

As the Nobel Laureate Richard Feynman emphasized, "I learned a long time ago the **difference between knowing something and the name of something**." If reducing inflammation prevents coronary heart disease, then why was the powerful anti-inflammatory drug Vioxx recalled because of increased heart attacks, strokes and sudden death? Perhaps there are different types of prophlogistic activities with different causes and markers that are

more accurate than CRP. In some chronic stress-related inflammatory conditions such as care giving for Alzheimer patients, there is no change in CRP, in contrast to a rise in interleukins (IL-6, IL-1) that can persist for years after the stressor has disappeared. In other situations, homocysteine, various cytokines or acute phase reactants may provide more information than CRP.

Coronary heart disease is a multifactorial disorder that can have many causes, some of which, like stress, homocysteine, infections, and free radical damage may be interrelated. Numerous contributing factors that influence susceptibility range from family history, age, gender, diabetes, hypertension and smoking, to sex hormones, obesity, physical activity, and alcohol consumption. It would be naive to believe that CRP levels reflect an accurate assessment of all the varied prophlogistic activities of these diverse agencies that we clump together as inflammation — or to assume that lowering CRP will safely and effectively reduce coronary mortality in healthy people that may not be at increased risk. Association never proves causation. Treating an elevated CRP would simply repeat the same mistake that is still being made with LDL. However, as Albert Einstein noted, **"We live in a world where it is easier to break an atom than a preconceived idea."**

As Einstein also warned, **"Not everything that can be counted, counts, and not everything that counts can be counted."** The first part of this statement applies to CRP and LDL, which are easy to measure, but may have little significance. The second part pertains to our inability to measure something that we call "inflammation", but which may include several different processes yet to be defined — so stay tuned for updates on this.

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