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LAF and the Inflammation Connection

By Hans R. Larsen MSc ChE

From Lone Atrial Fibrillation: Toward a Cure – Volume II (2005)

Statin drugs may help prevent atrial fibrillation
HONG KONG, CHINA. Statin drugs such as simvastatin (Zocor) and atorvastatin (Lipitor) are widely used to reduce cholesterol levels. There is also evidence that they are useful in reducing systemic inflammation. Medical researchers at the University of Hong Kong now report that statins may also be effective in preventing the recurrence of atrial fibrillation. Their study involved 62 patients with lone persistent AF who had undergone successful electrical cardioversion between July 1998 and December 1999. The average age of the patients was 61 years, 74% were men and 16% (10 patients) were taking statin drugs to control their cholesterol levels.

After two years of follow-up the rate of recurrence of afib was 40% in the statin group and 84% in the control group for a relative risk reduction of 69%. The researchers believe that the anti-inflammatory properties of statins are involved in the observed risk reduction, but also point out that, "statins may also exhibit direct antiarrhythmic effects by modulating the fatty acid composition and physiochemical properties of cell membranes, with resultant alleviations in transmembrane ion channel properties".

A similar study carried out by American researchers supports the idea that statins may help prevent AF. This study involved 449 patients with coronary artery disease, but no AF at baseline. During a 5-year follow-up period 52 patients (12%) developed AF. The researchers noted that statin therapy was associated with a 50-60% lower risk of developing AF and conclude that statin therapy in patients with chronic, stable coronary artery disease appear to be protective against AF. They point out that the mechanism underlying the protective effect is unknown, but appears to be independent of the reduction in cholesterol levels.
Siu, Chung-Wah, et al. Prevention of atrial fibrillation recurrence by statin therapy in patients with lone atrial fibrillation after successful cardioversion. American Journal of Cardiology, Vol. 92, December 1, 2003, pp. 1343-45
Young-Xu, Y, et al. Usefulness of statin drugs in protecting against atrial fibrillation in patients with coronary artery disease. American Journal of Cardiology, Vol. 92, December 15, 2003, pp. 1379-83

Editor's comment: This is a very interesting finding and confirms that reducing inflammation and modifying cell membranes may be important aspects of afib prevention. Statin drugs, unfortunately, have several undesirable potential side effects including memory loss and muscle disease. These drugs also severely deplete coenzyme Q10 levels. If inflammation reduction and

membrane modification are indeed the "name of the game" then it is quite possible that high doses of fish oils (5 grams/day) may have similar effects.

Atrial fibrillation and statin drugs

OSLO, NORWAY. Statin drugs such as atorvastatin (Lipitor), lovastatin (Mevacor), pravastatin (Pravachol), and simvastatin (Zocor) are primarily used to reduce cholesterol levels, but have also been found to reduce oxidative stress and inflammation. American researchers found that they help to prevent the development of atrial fibrillation (AF) in patients with coronary artery disease and Japanese researchers recently reported that statin drugs might also be helpful in preventing the recurrence of AF after cardioversion in patients with persistent lone atrial fibrillation. The Japanese study, however, was small (10 patients on statin drugs) and not controlled or randomized.

Now Norwegian researchers report the results of a randomized clinical trial aimed at determining the effects of pravastatin on AF recurrence in 114 patients who were scheduled to undergo electrical cardioversion for AF. The patients were randomized to receive a placebo or 40 mg of pravastatin once daily for 3 weeks prior and 6 weeks after the attempted cardioversion. During this time they also received warfarin to a standard INR of 2.0-3.5. Twelve patients (6 in each group) converted spontaneously prior to cardioversion leaving 102 patients to be converted. The conversion was successful in 80 patients (78%). Six weeks after conversion 35% of patients in the pravastatin group had experienced a recurrence of AF as compared to 33% in the control group. Overall, 50% of the 114 patients were in AF 6 weeks after the attempted cardioversion either because the conversion was unsuccessful or because AF had recurred after a successful conversion. The researchers conclude that statin drugs are unlikely to have a clinically relevant effect on the rate of recurrence of AF after electrical conversion.

Tveit, A, et al. Analysis of pravastatin to prevent recurrence of atrial fibrillation after electrical cardioversion. American Journal of Cardiology, Vol. 93, March 15, 2004, pp. 780-82

Editor's comment: The Norwegian study was significantly larger and better controlled than the Japanese one. Thus it is likely that the Japanese findings were coincidental and that the effect of statin drugs in preventing AF recurrence is not significant.

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From Lone Atrial Fibrillation: Toward a Cure Volume IV (2007)

Inflammation and atrial fibrillation

IRMINGHAM, UNITED KINGDOM. British researchers present a thorough review of the current knowledge regarding an association between systemic inflammation and atrial fibrillation. Please note that the review does not distinguish between lone AF and atrial fibrillation with underlying heart disease. Thus the conclusions presented may or may not apply to lone afib.

The researchers point out that it is generally accepted that afib results in both electrical and structural remodeling of the atria. The main features of the electrical remodeling are shortening of the atrial refractory period (the rest period following a contraction of the heart muscle. The cell [myocyte] does not respond to stimulation during this period), prolongation of atrial conductivity, and the loss of rate adaptation. Another feature of the electrical remodeling is the accumulation of calcium within atrial myocytes leading to a further shortening of the atrial refractory period. The main features of the mechanical remodeling are enlargement of the left atrium and increasing atrial fibrosis (deposition of connective tissue between individual myocytes). These electrical and structural changes increase the likelihood of further afib episodes (afib begets afib).

There is now also increasing evidence that atrial fibrillation is linked to a systemic inflammation. Atrial biopsies have demonstrated the presence of inflamed tissue in both lone and non-lone afibbers. Measurements of blood levels of the inflammatory marker C-reactive protein (hs-CRP) have shown that levels tend to be higher among people with afib than among normal controls. There is also evidence that levels are higher among persistent afibbers than among paroxysmal afibbers, and finally, studies have shown that high hs-CRP levels are associated with an increased risk of developing new onset AF.

Several drugs and supplements have anti-inflammatory properties and have been found to reduce the risk of developing afib and/or reduce the number of episodes. Four studies have shown that statin drugs may have a role in the prevention of afib in humans, and animal studies have shown that statins may also reduce the frequency of episodes. Methyl prednisolone, a steroid anti-inflammatory drug, has been found to reduce recurrence of afib episodes when taken together with propafenone. There is evidence that both ACE inhibitors and angiotensin-receptor blockers (ARBs) have significant anti-inflammatory properties and may help prevent both the development and recurrence of AF – at least in patients with hypertension or heart disease. Fish oils also have significant anti-inflammatory properties and may be beneficial in preventing ventricular arrhythmias and AF occurring after bypass surgery. However, there is no convincing evidence that fish oils help prevent lone AF. Vitamin C has also been found to reduce the incidence of post-surgery afib and may help reduce the risk of early recurrence after cardioversion.
The researchers conclude that there is ample evidence of a link between inflammation and afib, and that anti-inflammatory drugs or supplements may play a role in preventing atrial fibrillation and its recurrence.
Boos, CJ, et al. Is atrial fibrillation an inflammatory disorder? European Heart Journal, *Vol. 27, 2006, pp. 136-149*

Editor's comment: As is, unfortunately, often the case in articles dealing with AF, no attempt was made here to distinguish between lone afib and afib with underlying heart disease. This is perhaps understandable since lone afibbers are a distinct minority (perhaps 20% of all afibbers). Nevertheless, recent work by Patrick Chambers, MD (*The AFIB Report*, February 2006) points to the very real possibility that lone AF may be a condition distinctly different from AF related to heart disease. Thus, the findings of the review may be only partly applicable to lone atrial fibrillation.

Inflammation and atrial fibrillation
THRACE, GREECE. The association between systemic inflammation and lone atrial fibrillation (LAF) has fascinated researchers ever since 1997 when Dr. Andrea Frustaci and colleagues at the Catholic University of Rome discovered that lone afibbers tend to show evidence of current or past inflammation in their heart tissue. Later research confirmed an association between elevated levels of high-sensitivity C-reative protein (hs-CRP), a marker of systemic inflammation, and the presence of LAF. Paroxysmal afibbers were found to have higher hs-CRP levels than controls, and persistent and permanent afibbers were found to have higher levels than paroxysmal afibbers.

Researchers at the University of Thrace now report that hs-CRP levels measured during a first LAF episode are significantly higher than those of controls and that a higher CRP level during the first episode predicts the risk of recurrence. Their study included 125 patients with a first, documented paroxysmal episode of LAF who had blood samples drawn for hs-CRP analysis while in afib. Their CRP values were compared to those of matched controls who had never been diagnosed with AF. The average (median) value for the afibbers was 0.23 mg/dL (2.3 mg/L), while the median for controls was 0.087 mg/dL (0.9 mg/L). Sixty per cent of the 125 afibbers whose first episode was documented had recurrences during a mean follow-up of 2 years.

Patients with CRP levels in the top quartile (0.23 mg/dL) were 15% more likely to have a recurrence than were patients in the bottom quartile (median of 0.1 mg/dL).

The researchers also observed that the hs-CRP levels of afibbers were significantly lower (median of 0.14 mg/dL) during sinus rhythm than during an episode (median of 0.28 mg/dL). The researchers conclude that hs-CRP may be a marker for inflammatory states that may promote the initiation of lone atrial fibrillation.
Hatzinikolaou-Kotsakou, E, et al. Relation of C-reactive protein to the first onset and the recurrence rate in lone atrial fibrillation. American Journal of Cardiology, *Vol. 97, 2006, pp. 659-61*

Editor's comment: There seems to be little doubt that inflammation and LAF are somehow connected. What is much less clear is the mechanism by which they are linked. The University of Thrace researchers and, as far as I know, all other researchers (myself included) who have given the matter some thought believe that inflammation is a causative factor in the initiation and recurrence of afib. The possibility that the association may be the opposite of what seems intuitively right, in other words, that fibrillation may result in inflammation has not been given much credence. However, this may now change with the discovery by Martin Rotter and colleagues in Bordeaux who recently reported that hs-CRP levels decrease markedly after a successful pulmonary vein isolation procedure. They concluded that restoration of sinus rhythm results in a significant decrease in inflammation. Which interpretation is correct? More research is required to determine this, but it is certainly not beyond the realm of possibilities that atrial fibrillation may result in inflammation rather than inflammation causing afib.

Statin drug may help prevent AF

MYTILINI, GREECE. There is considerable evidence that a systemic inflammation may be involved in atrial fibrillation. There is also evidence that high blood levels of the inflammation marker C-reactive protein (CRP) are associated with an increased risk of developing afib and experiencing recurring episodes. C-reactive protein levels can be effectively reduced with statin drugs (and many natural compounds), and there is some indication that doing so may reduce the risk of recurrent afib episodes after a successful cardioversion. Now Greek researchers report that the cholesterol-lowering drug atorvastatin (Lipitor) is effective in reducing the number of episodes in paroxysmal afibbers. Their study involved 80 patients who had documented asymptomatic afib episodes on a 48-hour Holter monitoring prior to beginning treatment. The patients (55 men and 25 women) were between the ages of 29 and 85 years (median 52 years). Their baseline CRP level ranged from 0.8 to 13 mg/L (0.08 – 1.3 mg/dL) with a median of 5.9 mg/L (0.6 mg/dL). NOTE: The normal range is considered to be 0 – 5 mg/L. Half the patients were assigned to receive a placebo, while the other half received 20 mg/day of atorvastatin (increased to a maximum of 40 mg/day if a 20% reduction of CRP was not achieved by 6 weeks) for the duration of the 4-6 month study period. Holter monitors were used at the beginning and end of the study to ascertain the number and duration of episodes experienced over a 48-hour period.

The researchers, not too surprisingly, found that members of the atorvastatin group experienced a significant drop in total and low-density cholesterol. They also observed that average CRP levels in the atorvastatin group dropped from 5.8 mg/L to 2.8 mg/L over the study period. The average number of afib episodes (all asymptomatic) decreased from 9 in the baseline 48-hour monitoring to 0 in the end-of-study monitoring in the atorvastatin group, while it declined from 13 to 12 in the placebo group. The researchers conclude that atorvastatin may be useful in reducing CRP levels and the frequency of afib episodes in afibbers with the paroxysmal variety.
Dernellis, J and M. Panaretou. Effect of C-reactive protein reduction on paroxysmal atrial fibrillation. American Heart Journal, *Vol. 150, November 2005, pp. 1064-69*

Editor's comment: Although intriguing, I am not certain just how much hope these findings hold for the average paroxysmal afibber. The group involved in the study was somewhat unusual in that its members had mild or no symptoms during daily life and did not report any symptoms during the two monitoring sessions. They also tended to have elevated CRP levels, which does not seem to be common among the lone afibbers I have surveyed (my own level during my worst period of afib was less than 0.3 mg/L). So would atorvastatin or CRP-lowering as such help an afibber with highly symptomatic episodes? I don't know, but I am somewhat skeptical that the claims made by the Greek researchers would apply to the majority of afibbers. However, having a high CRP level is detrimental in many ways so reducing it can certainly do no harm. Successful reduction can be achieved by supplementing with beta-sitosterol, Moducare, Zyflamend or boswellia. Statin drugs will also do the trick, but should always be taken accompanied by at least 100 mg/day of coenzyme Q10.

Successful ablation reduces inflammation

BORDEAUX, FRANCE. Several studies have shown that afibbers with persistent or permanent afib tend to have higher C-reactive protein (CRP) levels than do paroxysmal afibbers and those in sinus rhythm. What is not known is whether restoring sinus rhythm through radiofrequency ablation will reduce CRP levels to normal. Martin Rotter, MD and colleagues at the Hopital Cardiologique du Haut-Leveque have now answered this question.

Their clinical trial included 50 patients aged 43 to 63 years (49 male and 1 female). Five of the patients had long-lasting persistent afib (episode duration of 3-10 months), while the remaining 45 were in permanent afib. The patients all underwent a single pulmonary vein isolation (PVI) procedure with additional lesion lines as required to restore sinus rhythm. The patients were examined 1 and 3 months after their ablation and remained on their pre-ablation medications throughout the trial period. At 3 months, 66% (33 patients) were still in sinus rhythm, while 12 had paroxysmal afib, and 5 had atrial tachycardia. While the CRP levels among the successful and unsuccessful ablatees were similar prior to the ablation (2.82 mg/L or 0.28 mg/dL vs 2.46 mg/L or 0.25 mg/dL), there was a significant decline in the level among patients still in sinus rhythm at the 3-month checkup. Among these patients the CRP level had declined from 2.82 mg/L to 1.37 mg/L. In comparison, the average CRP level in the unsuccessful group did not change significantly (2.46 mg/L vs 2.58 mg/L).

The researchers also noted a significant decrease in left atrial size (parasternal diameter) from 45.8 mm to 42.6 mm in the successfully treated group. No such change was observed in the unsuccessful group (45.2 mm vs 45.4 mm). The study clearly demonstrates that it is not radiofrequency ablation as such that reduces atrial size and inflammation, but rather the restoration of sinus rhythm. The Bordeaux researchers conclude that restoration of sinus rhythm by a PVI results in reverse remodeling of the left atrium and a significant decrease in inflammation.

Rotter, M, et al. Decline in C-reactive protein after successful ablation of long-lasting persistent atrial fibrillation. Journal of the American College of Cardiology, *Vol. 47, No. 6, March 21, 2006, pp. 1231-33 (letter to the editor)*

Editor's comment: It is also evident from the results of this trial that being out of sinus rhythm causes inflammation (high CRP levels) rather than the other way around. This would explain why CRP levels increase from paroxysmal to persistent to permanent afib.

Lone atrial fibrillation and C-reactive protein

BOSTON, MASSACHUSETTS. There is considerable evidence of an association between inflammation and atrial fibrillation. Biopsies have found inflammatory infiltrates in patients with AF and several studies have found that AF patients tend to have higher blood levels of inflammatory markers such as C-reactive protein (CRP), prothrombin fragments and interleukin-6.

Unfortunately, most studies involving atrial fibrillation do not distinguish between AF with and without underlying cardiovascular disease, so it is not at all clear whether the inflammation connection applies to lone atrial fibrillation, that is, AF without underlying heart disease.

A group of researchers at the Massachusetts General Hospital recently released the results of a study designed to determine if systemic inflammation (as measured by CRP level) is associated with AF *per se*, or rather with an underlying cardiovascular disease. The study involved 121 lone afibbers (no history of coronary artery disease, rheumatic heart disease, cardiomyopathy, significant valvular disease, hyperthyroidism, or hypertension), 52 patients with none of the above conditions except hypertension, and 75 healthy controls without heart disease, hypertension and AF. The mean age of the lone afibbers at enrolment was 54.3 years and the mean age at diagnosis was 44.8 years. The mean age of the AF + hypertension participants at enrolment was 60.2 years and the mean age at diagnosis was 50.6 years. Most study participants (83%) were men, and most lone afibbers (91.7%) and AF + hypertension patients (84.6%) had paroxysmal afib. Just over 56% of the lone afibbers had experienced more than 100 episodes. It is interesting that 34% of the lone afibbers and 37% of the AF + hypertension patients had a first-degree relative with AF.

All study participants underwent a detailed medical examination and had an electrocardiogram and an echocardiogram at enrolment. They also provided a blood sample for CRP analysis. The researchers observed no statistically significant difference in CRP levels between lone afibbers and controls (1.34 vs 1.21 mg/L); however, they did note a significant difference between AF + hypertension patients and controls (1.90 vs 1.21 mg/L), but suggest that this is primarily due to a greater proportion of overweight and obese individuals in the hypertensive group. They found no difference in CRP levels between the 20% of afibbers taking statin drugs and those not taking them. They also found no significant difference in CRP level among lone afibbers who were in sinus rhythm at time of blood sampling versus those in afib (1.37 vs 1.38 mg/L).

Finally, they observed no significant difference in CRP values between paroxysmal and permanent afibbers. They did, however, observe a strong correlation between a high body mass index and an elevated CRP level. The researchers conclude that atrial fibrillation on its own (without underlying heart disease, hypertension or obesity) is not associated with evidence of systemic inflammation.
Ellinor, PT, et al. C-reactive protein in lone atrial fibrillation. American Journal of Cardiology, *Vol. 97, May 1, 2006, pp. 1346-50*

Editor's comment: This study confirms my own intuitive feeling that systemic inflammation (high CRP levels) may not be as important in true lone atrial fibrillation as previously thought. It also strongly underlines the importance of not automatically assuming that data obtained from studies of AF patients in general are necessarily applicable to lone afibbers. The study is also of considerable interest in that it confirms many of the values obtained in our early LAF surveys. For example, the percentage of women in the sample of lone afibbers was 17% vs 21% in our database of 625 lone afibbers. The average age at diagnosis was 45 years vs 47 years in our database; the average blood pressure was 122/75 vs 124/76 in our LAF Survey V. This is a comforting confirmation that our surveys do indeed reflect the general population of lone afibbers.

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