Guilt by Association: The Challenge of Teasing Apart the Effect of Various Risk Factors for Coronary Heart Disease in Systemic Lupus Erythematosus

Since the original description over 3 decades ago of the association between atherosclerotic coronary heart disease (CHD) and systemic lupus erythematosus (SLE) by Urowitz, *et al*[1] many advances have been made in our understanding of the role of traditional, novel, and disease-related risk factors for clinical CHD in SLE[2]. Esdaile, *et al* have shown that traditional risk factors such as hypercholesterolemia and hypertension account only partly for the increased risk of CHD in SLE, indicating that disease- and treatment-related factors may also be important[3].

In the latest installment in the field, published in this issue of *The Journal*, Haque, *et al* seek to identify and quantify the role of various risk factors for clinical CHD in SLE, using a case-control design[4]. They show that patients with clinical CHD are more likely to be male, older, and hypertensive, to have a family history of CHD, to have more "damage" on the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index, and to have been exposed to azathioprine prior to their CHD event. The "LASER" study highlights several methodological challenges in studies of cardiovascular risk factors in SLE.

The first challenge relates to study design. While prospective collection of data on risk factors and CHD outcomes is the ideal model, many studies to date, including the LASER study, have used a retrospective chart review method. Not only does this introduce a possible source of bias, particularly in relation to the temporal association between exposure and outcome, it also means that the dataset may be incomplete for certain key variables. Here the choice and definition of risk factors ("independent variables") for inclusion in the analysis are also limited to information that is routinely collected and documented in the course of clinical care. In the LASER study, a cholesterol value obtained 3–6 months following a CHD event was sought in 5 patients in whom cholesterol levels had not been collected prior to an event. While information on serology and therapy was complete, information on cholesterol and family history of CHD was missing for many patients. The LASER study evaluated the role of a range of risk factors, namely demographic variables such as age and sex, classic CHD risk factors including hypertension, hypercholesterolemia, family history of CHD, smoking, diabetes mellitus, and SLE-related variables such as organ manifestations and damage, serology, and therapy. However, some novel and emerging risk factors such as high sensitivity C-reactive protein were not included, presumably due to lack of available data.

SLE has a relatively low population prevalence of around 1:1000, and the lifetime prevalence of clinical CHD in SLE is around 10%[5]. This means that due to the low number of CHD "outcome events," studies of cardiovascular risk factors in SLE are limited in statistical power to demonstrating moderate to large effects for a small number of independent variables. A matched-control design, as used in the LASER study, enables evaluation of the independent role of certain risk factors, while keeping others, such as disease duration, consistent across cases and controls. However, with relatively small sample sizes, it may not always be possible to match for more than one or 2 variables, or to find a suitable control match for every case.

In studies of cardiovascular risk factors in SLE, the definition of independent and outcome variables is critically important. In the LASER study, hypertension, hypercholesterolemia, family history of CHD, diabetes mellitus, and smoking were defined as "present ever," from the first clinic visit to event (or "dummy date" in controls). However, there is a continuum of risk associated with variables such as blood pressure and cholesterol, which may not be identified using dichotomous definitions that use conventional cutpoints. In addition, it is increasingly recognized that such variables take a dynamic course over time in patients with SLE, fluctuating due to changes in disease activity and treatment. Therefore, single-point-in-time measurements of these variables may not enable adequate quantification of risk by failing to record cumulative exposure. Surprisingly,

in contrast to several other studies, in the LASER study, hypercholesterolemia was not found to be independently associated with CHD events. One possible explanation for this may be the categorical manner in which this risk factor was defined using a cutpoint of 5.2 mmol/l.

The accurate definition of outcomes is also fundamental to the internal validity of such risk factor studies. In the LASER study, clinical CHD events, namely myocardial infarction, angina pectoris, and sudden cardiac death, were carefully defined on the basis of clinical features and electrocardiographic and enzyme changes. In addition, the diagnosis of angina was confirmed by a cardiologist or an objective test such as a stress test or coronary angiography.

The second challenge in studies of cardiovascular risk factors in SLE relates to measuring disease activity. The role of inflammation in atherosclerosis is being increasingly recognized[6]. Indeed, chronic inflammation has been proposed as the link between SLE and CHD[7]. Ibanez, et al have shown that for every 1-unit increase in the time-adjusted mean SLE disease activity index 2000 (SLEDAI-2K) score, the hazard of a CHD event increases 1.08-fold (hazard ratio 1.08, 95% CI 1.00, 1.16, p = 0.046)[8]. Karp, et al have also shown that recent lupus disease activity measured using the SLEDAI-2K correlates with higher values of several well recognized coronary risk factors and overall 2-year CHD risk[9].

In addition to the relatively small sample size, the main weakness of the LASER study is the lack of disease activity data. This is likely due to the retrospective design of data collection. While it has been shown that the SLICC/ACR damage index may be accurately determined by retrospective chart review[10], due to its fluctuating nature, it is inherently more difficult to retrospectively capture the phenomenon of "disease activity."

The third challenge lies in evaluating the influence of therapy on cardiovascular risk. Therapy includes corticosteroid and immunosuppressive medications used to treat SLE itself, and cardiovascular drugs such as those used for the treatment of hypertension and hyperlipidemia. In the LASER study, details of immunosuppressive treatment were collected. However, there was no collection of data on cardiovascular drugs such as antiplatelets, antihypertensives, and lipid-lowering agents. Patients who had clinical CHD were more likely to have been exposed to azathioprine (adjusted odds ratio 3.2, 95% CI 1.33, 7.59) than controls. The investigators suggest the possible explanation of persistent underlying active disease, with azathioprine failing to adequately control "grumbling" disease activity. However, they also acknowledge that lack of accurate disease activity measures over time makes it impossible to draw firm conclusions from this observation.

In the LUMINA cohort, Toloza, et al also found that azathioprine use was associated with vascular events[11].

Whether the risk of ischemic events with azathioprine use is directly related to the drug itself or the underlying indications for its use needs to be elucidated.

To date, teasing apart the effect of corticosteroids from disease activity and traditional cardiac risk factors has been an arduous task, as these risk factors are intricately linked. Not only are corticosteroids used to treat active disease, they are also implicated in elevating blood pressure, blood glucose, and cholesterol level, which are all independently associated with CHD. Therefore, on the one hand, corticosteroids may protect against CHD by controlling inflammation. On the other hand, corticosteroids may contribute to cardiovascular risk independently, and through accrual of traditional risk factors. In the study by Karp, et al, even after adjustment for SLE activity and other potential confounders, a 10-mg increase in the average daily prednisone-equivalent dose in the preceding year was associated with a statistically significant increase in several atherogenic lipids and lipoproteins, systolic blood pressure, body mass index, and blood glucose level, as well as a 16% increase in the estimated 2-year CHD risk[8].

Propensity score analysis is one possible technique that may be used to adjust for "confounding by indication," where patients with more active SLE are more likely to be treated with steroids. There is currently no consensus as to the best definition of corticosteroid "exposure." In the past, this has been variously defined as "use ever" or "current use," or quantified as average daily dose or total cumulative dose. In the LASER study, corticosteroid treatment was categorized as "previous use" or "never used," and the average daily dose was calculated where available. Irrespective of the definition of exposure, corticosteroid use was not found to be significantly associated with clinical CHD.

Overall, despite some methodological weaknesses discussed above, the LASER study conveys a strong message consistent with the findings of previous studies. Specifically, clinical CHD in SLE is related to demographic, disease, and treatment-related factors. The accurate definition and quantitation of risk associated with each of these risk factors hinges on careful study design, a sizable sample of patients, and appropriate definition of independent and outcome variables. There is scope to modify many, but not all, of these risk factors. Future studies need to take the next step of determining whether therapeutic intervention aimed at treating specific risk factors reduces risk of CHD events in SLE.

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