Cardiovascular Disease Reduction in Rheumatoid Arthritis by Statins: The Final Evidence?

The risk of cardiovascular disease (CVD) in patients with rheumatoid arthritis (RA) is considerably higher than in the general population and equals that in patients with diabetes\(^1\). The most convincing study in this respect comes from Denmark\(^2\). The study, which coupled nationwide registers to identify persons with new-onset RA, new-onset diabetes, and persons who had a first myocardial infarction (MI), comprised more than 4.3 million persons, of whom about 10,500 developed RA and 130,000 diabetes. The incidence rate ratio (IRR) of MI in RA was 1.7 (95% CI 1.5–1.9); identical to the risk in diabetes: IRR 1.7 (95% CI 1.6–1.8). Therefore, just as in diabetes, CVD risk management is also needed for RA.

CVD risk management starts with assessment of the cardiovascular risk profile (with determination of blood pressure, smoking status, and lipid profile). On the basis of these data and risk calculators such as Framingham and the Systematic Coronary Risk Evaluation, the 10-year cardiovascular risk of a particular person can be calculated. Primary prevention involving treatment with statins and/or antihypertensive agents is then only indicated when this 10-year risk is above a certain value. However, there is little evidence about the outcome of this strategy, particularly for statin treatment.

Despite the fact that the increased cardiovascular risk in RA is well known — and thus the need for CVD prevention — numerous recent reports indicate that CVD risk management is still poorly implemented. One of the reasons might be a lack of “hard” cardiovascular endpoint trials in RA, making doctors reluctant to prescribe statins.

First, interpreting lipid levels in the context of an inflammatory situation, as in RA, might be difficult because lipid levels are influenced by disease activity as well as antiinflammatory therapy. In RA, an inflammatory state leads to a decrease in total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C); but this is actually “paradoxically” associated with an increased cardiovascular risk\(^3\). Therefore, it is recommended to assess the lipid profile when disease activity is low or absent\(^4\). Further, chronic inflammation not only leads to quantitative lipid changes but also affects HDL-C structure and function, rendering HDL–C proinflammatory, thus further complicating the relationship of lipids with CVD.

Second, if hyperlipidemia is present, the complex interaction between lipids and inflammation raises the question of whether statin treatment is effective in RA, and if so, what is the proper target for lipid-lowering treatment\(^5\)?

A number of (posthoc) studies have assessed the efficacy of statins in patients with RA, and suggested that statins were not less effective in these patients than in the general population\(^6\). However, a final answer is not yet available. Ideally, large randomized, controlled trials investigating statins on CVD outcomes are needed, but these are very difficult to conduct because of the general decrease of incident cardiovascular disease, illustrated by the TRACE-RA trial that was terminated prematurely for this reason\(^7\). TRACE-RA demonstrated a 34% risk reduction for CVD in the statin group, although this did not reach statistical significance.

In this issue of the Journal, the findings of the TRACE-RA study are supported by the findings of An and colleagues\(^8\). Because it is not likely that other statin intervention trials will be conducted, this large database study is the best alternative. Naturally, database studies have inherent methodological flaws, but one of the virtues is the ability to study large cohorts of patients and controls. An, et al used a large database from the Kaiser Permanente Southern California that comprises all aspects of care among the membership of more than 4 million persons.

Two cohorts of patients with RA (n = 1522 and n = 1746) were matched with, respectively, general control persons (n = 6511) and osteoarthritis patients (n = 2544). Patients and controls also had hyperlipidemia as well as 1 statin prescription or more, and the 2 RA groups and their controls were followed up for 3.1 years and 4.0 years, respectively. As expected, the prevalence of traditional classic risk factors was higher in patients with RA. Importantly, it was convinc-
ingly demonstrated that the effect of lowering LDL-C concentrations on reduction of CV events was similar in both RA groups and in their matched controls. These data further support previous findings about the beneficial effects of statins on CV risk in RA.

Unfortunately, the authors were not able to evaluate data regarding disease activity. In RA, active inflammation decreases all lipid levels compared with individuals without RA. Because HDL-C is relatively the most suppressed, an unfavorable lipid profile results. The influence of disease activity at baseline on LDL-C levels could have had an effect on CV risk estimation and on the recommended LDL-C target. Further, inflammation could interfere with followup LDL-C measurements, rendering it unclear whether the lowered LDL-C levels during statin therapy were the result of changes in inflammatory activity. It is important to realize that a reduction in lipid levels resulting from disease activity does not indicate a decrease of CV risk. Further, mechanistic studies should address this aspect.

There is no longer doubt about the efficacy of statin therapy in RA, considering that all the (circumstantial) evidence points in the same direction as the main studies: the (posthoc) subgroup analyses of (secondary) prevention trials, the TRACE-RA trial, and the present investigation.

Actually, the CVD reduction by statins in RA could be somewhat larger than in the general population because statins also have anti-inflammatory properties that might be important in the cardiovascular context. The relationship between inflammation and lipids in RA emerges long before the onset of clinical disease. It might be that dyslipidemia induces inflammation, and statin therapy in this phase can even prevent (or delay) development of RA. A large placebo-controlled investigation in patients with seropositive arthralgia is currently under way.

In daily clinical practice, underuse of lipid-lowering/statin therapy persists. Comorbidities such as hypertension and hyperlipidemia are often undertreated in patients with a chronic disease, but specific information on undertreatment in RA is sparse. Adherence to primary prevention measures is known to be poor. Usually statins are well tolerated, but because most adverse effects of statin therapy are muscle-related, discontinuation of statins might be more common in RA. Finally, it is not always clear who is responsible for CVD risk assessment and management. Coordination between all involved (para)medics is essential, and the responsibility for CVD risk management should be defined locally. The European League Against Rheumatism task force for CVD risk management recommends that the treating rheumatologist ensure that CVD risk management is performed in patients with RA.

It is hoped that the current (reassuring) evidence for the efficacy of statin therapy leads to a better uptake. The investigation of An and colleagues also indicates 76% increased CVD risk after controlling for LDL-C. This remaining higher risk is due to the other traditional cardiovascular risk factors as well as RA itself. It is important to realize that the contribution of RA disease activity is about the same as traditional CVD risk factors. Hence, treatment with antiinflammatory drugs only is not sufficient to normalize the cardiovascular risk in RA. Both these aspects should be addressed in CVD risk prevention. Otherwise, effective CVD reduction will remain elusive!

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