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VIEWPOINT

Re-evaluating the mythical divide between traditional and novel cardiovascular risk factors in rheumatoid arthritis

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ABSTRACT

Cardiovascular (CV) risk factors for rheumatoid arthritis (RA) are conventionally classified as 'traditional' and 'novel'. We argue that this classification is obsolete and potentially counterproductive. Further, we discuss problems with the common practice of adjusting for traditional CV risk factors in statistical analyses. These analyses do not target well-defined effects of RA on CV risk. Ultimately, we propose a future direction for cardiorheumatology research that prioritises optimising current treatments and identifying novel therapeutic targets over further categorisation of well-known risk factors.

INTRODUCTION

It has often been said that the way to live a long life is to acquire rheumatism. This is the beginning of a 1953 paper by Cobb *et al*, the first to report increased mortality in patients with rheumatoid arthritis (RA).[1] Later, numerous articles have described an increased prevalence of comorbidities in patients with RA.[2] The increased risk of cardiovascular (CV) disease is particularly well documented.[3] There is consensus that the high CV risk in patients with RA is a result of a high prevalence of 'traditional' CV risk factors and the presence of systemic inflammation, a so-called 'novel' CV risk factor.[3] Atherosclerotic CV disease is now considered to be an inflammatory disease and RA has become a model disease for studying the effect of systemic inflammation on atherogenesis.[4]

CV risk factors are often categorised as either 'traditional' or 'novel' in cardiorheumatology. We argue that this categorisation is obsolete and unconstructive; it does not help us improve the understanding of CV disease in patients with RA. We also illustrate why the widespread adjustments for traditional CV risk factors in statistical analyses for CV risk in RA are problematic. By examining the feedback between RA-associated inflammation and CV risk, we contend that a more rigorous approach is essential for accurate understanding of CV risk in RA. Lastly, we point to alternative directions in cardiorheumatology research.

'TRADITIONAL' AND 'NOVEL' CV RISK FACTORS

No consensus exists on the definition of a 'traditional CV risk factor'. Initially, the term alluded to the earliest established CV risk factors, but now it usually refers to major CV risk factors.[5 6] Dyslipidaemia, family history of CV disease, hypertension, age, cigarette smoking, diabetes mellitus, obesity and physical inactivity are frequently mentioned as 'traditional CV risk factors'.[6] On the other hand, left ventricular hypertrophy, which was described as a CV risk factor in the Framingham article that popularised the term 'risk factor', is hardly mentioned today.[7] In the specific context of RA, the term 'traditional CV risk factors' is used to describe variables that are not measures of systemic inflammation.[8]

The term 'novel CV risk factors' represents an ambiguous collection of variables.[9] Often these risk factors are recent discoveries that are difficult to measure, and the evidence for an association with the outcome is less established.[9] The novel CV risk factors are rarely included in CV risk prediction models, and, thus, are often regarded as less important in current clinical practice compared with traditional risk factors. However, this characterisation is seemingly contradicted by the fact that one of the most widely considered 'novel CV risk factors' is inflammation. In particular, the association between inflammation and CV disease risk has been known for decades

and is based on solid scientific evidence. Inflammation can also be easily measured and it has been successfully added to CV risk prediction models.[10–13]

Our considerations illustrate that the supposed distinction between 'traditional' and 'novel' CV risk factors is fragile. Furthermore, this distinction is not grounded on any biological or pathophysiological basis and does not help to create explanatory models for CV disease in RA.

More broadly, the use of the term 'risk factor', regardless of the categorisation into traditional and novel, is itself ambiguous. Investigators in different domains allude to different definitions.[14] The interpretation of 'risk factor' also depends on whether a study concerns diagnosis, prognosis, treatment effects or aetiology. In RA research, our impression is that 'risk factors' predominantly allude to aetiological factors.

CHALLENGING THE PRACTICE OF ADJUSTING FOR 'TRADITIONAL' CV RISK FACTORS

Researchers in the field of cardio-rheumatology often state that patients with RA have an elevated risk of CV disease due to inflammation and high prevalences of 'traditional' CV risk factors.[3 15–21] But when we consider the variables that are most commonly described to be traditional CV risk factors, this statement becomes a tautology: It is the inflammatory process itself, which is a defining feature of RA, that leads to elevation of these 'traditional' CV risk factors in these individuals.

More specifically, inflammation affects the risk of CV events through different mechanisms. Figure 1 provides a simplified illustration of the mediators involved in development of atherosclerotic CV disease in RA. Inflammation causes alterations in lipid composition and function, arterial stiffening and endothelial dysfunction, ultimately leading to elevated blood pressure levels. Increased blood pressure leads to further increments in arterial stiffness and endothelial dysfunction in a vicious cycle. Additionally, inflammation can cause insulin resistance and the development of diabetes mellitus, which also affects arterial stiffness and endothelial dysfunction. Moreover, pain, joint damage and sarcopenia due to RA will often reduce physical fitness, skew the lean-to-fat mass ratio resulting in increased risk of diabetes, worse lipid profiles, endothelial dysfunction, etc.[4 10 19] Smoking, recognised as a risk factor for RA development, also increases the risk of CV.[19] Many other mediators are also plausible, including thrombocyte function and atherosclerotic plaque characteristics.[19] In other words, the high incidence of traditional CV risk factors cannot be regarded as separate, or 'independent' from the mechanism underlying RA. In contrast, many of the CV risk factors can be consequences of the inflammatory state that defines RA.

Nevertheless, many researchers, including the first author of this viewpoint, have tried to untangle this complex interplay in observational studies to isolate a 'pure' effect of RA on CV risk by adjusting statistical analyses for traditional CV risk factors.[15 22–29] Such endeavours are causal inference tasks: The question concerns how RA affects, that is, causes, CV disease. The growing literature on causal inference methods has shown that

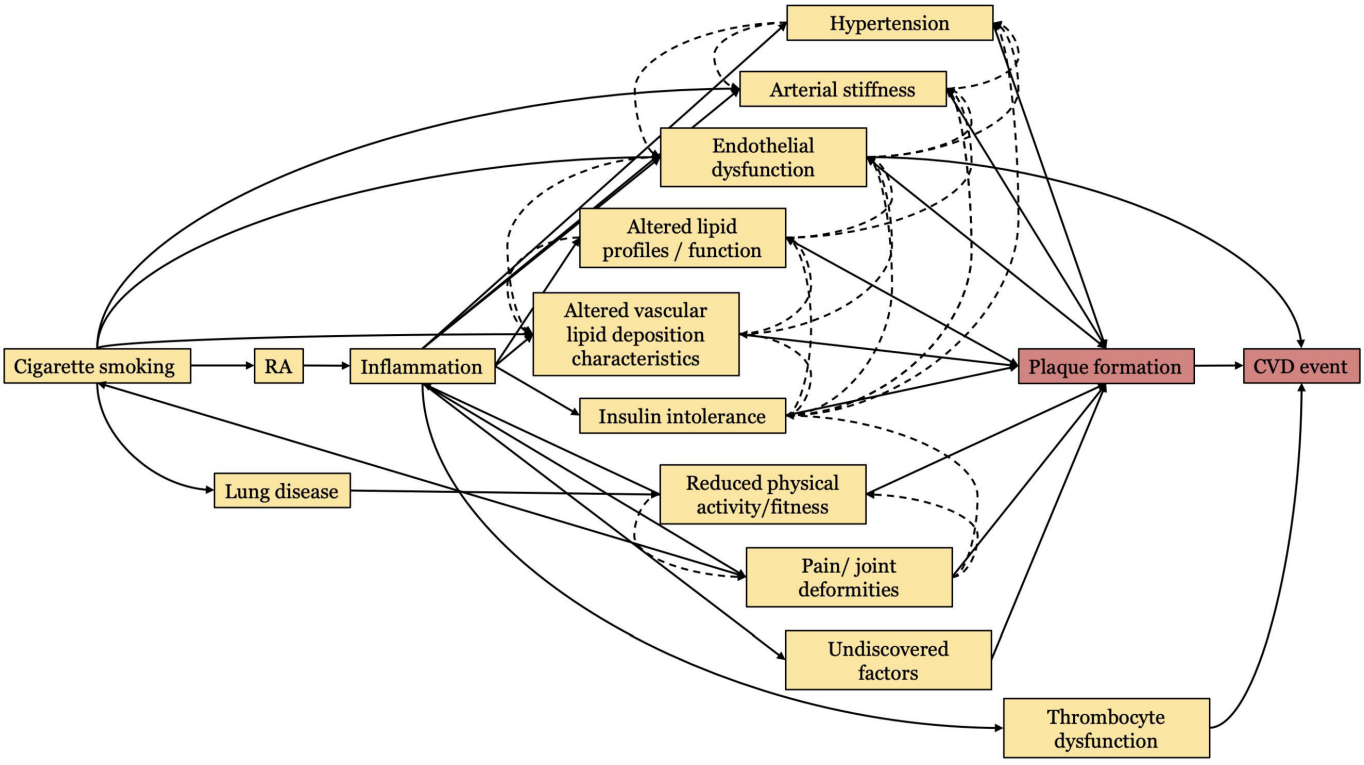

Figure 1 Illustration of mediators in the pathogenesis of cardiovascular disease (CVD) in patients with rheumatoid arthritis (RA).

answering such causal questions requires great care.[30 31] In particular, classical statistical adjustments are inadequate and do not give output that answer the practical questions of interest.[31–33]

On the other hand, a first step towards an appropriate analysis is to explicitly describe a clear research (or policy) question and then consider the assumptions needed to unbiasedly identify the answer to this question, often illustrated by a causal directed acyclic graph (DAG).[34 35] While figure 1 provides a simple illustration of the mechanisms underlying CV disease in RA, a plausible causal DAG would need to be much more involved. In particular, a causal DAG would need to include information on the temporal sequences of the variables and their common causes. When doing a rigorous causal analysis of observational data, these variables must be included in the model. For example, we need to measure an individual's 'traditional risk factors' before and after the onset of RA. Here the time ordering is crucial to discover whether the risk factors occurred as consequence of RA. However, an obvious complication is that the onset of RA is usually unknown. For example, there can be a long latent time between RA onset and diagnosis that is important for CV risk.

In summary, when performing observational studies of CV risk factors in RA, researchers should refrain from simply adjusting for variables that are consequences of the disease, as the statistical output will not reflect the effect of RA on the risk of CV disease.

A CONSTRUCTIVE SOLUTION: WHAT IS THE GOAL OF RESEARCH ON CV RISK FACTORS IN PATIENTS WITH RA?

Our criticism of the contemporary use of 'risk factors' does not imply that aetiological research is redundant. In our view, knowledge of aetiology and disease mechanisms is crucial when developing future therapies. However, in the case of RA, neither 'traditional' CV risk factors or inflammation are novel treatment targets. Thus, if the ultimate goal is to reduce CV risk in patients with RA, then it is insufficient to create categories of well-known CV risk factors. We need carefully conducted analyses that explicitly assess the causal effects of intervenable variables in patients with RA, and these analyses need to be done at different disease stages. Ideally, the analyses would be done on data from tailored randomised controlled trials (RCTs), but conducting RCTs that answer relevant questions about inflammation and CV disease is not always feasible. In particular, we are often interested in outcomes that occur over long periods of time, which would require the duration of the RCT to be decades. Many questions also concern effects of treatment strategies that are sustained over time, which might be infeasible to enforce in practice, for example, due to ethical constraints. Relatedly, realistic treatment strategies will often be updated sequentially, for example, after certain clinical events occur, but sequential RCTs require large sample sizes and detailed follow-up. Such trials are usually infeasible to run. This underscores the need for innovative research methodologies, which also can be applied to observational data. One option is to emulate a target trial from observational data; that is, we design the analysis of the observational data to target the effect we would study in an ideal—but practically and/or ethically infeasible—RCT. Such an emulation forces the investigator to be explicitly articulate and motivate, their research question and transparently express their assumptions.

A POTENTIAL FUTURE DIRECTION

The increased CV risk in patients with RA compared with the general population is well established. However, there is no consensus on the magnitude of this risk, as different studies have reported considerably different estimates.[36] One likely reason is that different RA cohorts have different degrees of cumulative inflammation. Relatedly, the similarities in CV risk in patients with RA and diabetes are often mentioned. However, this purported similarity has an ambiguous interpretation because the CV risk depends heavily on the treatment received in either patient group.[28 37–39] Further studies that merely compare CV risk between patients with RA and a different group of people, while adjusting for traditional CV risk factors and relying on single time point measurements of inflammation, are unlikely to advance our understanding of aetiology and disease progression.

A possible direction could be to investigate the risk of CV disease in patients with RA who received an early diagnosis, attained disease remission quickly and remained without signs of disease activity. This would require better information on cumulative disease activity than what is currently available. The atherogenic process is protracted and often develops over many years or even decades. Consequently, a snapshot measure of inflammation will rarely capture the chronicity and cumulative burden of inflammation that is likely more relevant for CV disease risk. The A TransAtlantic Cardiovascular risk Consortium for Rheumatoid Arthritis (ATACC-RA) consortium developed a CV risk calculator that is illustrative in this context[40]: While multiple single-point measurements of RA disease activity initially emerged as 'significant predictors' of CV disease in their analyses, only Disease Activity Score-28 and Health Assessment Questionnaire were significant in more comprehensive multivariable models. Indeed, the risk calculators did not outperform existing general population CV risk calculators. One of the postulated reasons for this failure is the reliance on cross-sectional measures of inflammation rather than longitudinal data.

Accurate longitudinal measurements of disease activity would be ideal for understanding effects of RA on CV risk.[29 41–43] Because collecting longitudinal data is often impractical in both research and clinical practice, finding biomarkers that quantify the cumulative burden

of inflammation would be valuable. An obvious analogy is the use of haemoglobin A1C to quantify the average glucose level over a period of 2–3 months.

One strategy to explore the mechanism of CV disease in patient with RA is to consider patients with RA with little or no cumulative inflammatory burden. If these individuals have a high risk of CV disease, it would be tempting to conclude that non-inflammatory factors can (partly) explain the elevated CV risk in patients with RA. However, the definition of 'high risk of CV disease' is unclear. Furthermore, a comparison between such patients with RA and the general (healthy) population would not necessarily give a valid causal estimate of the 'effect' of RA on CV disease. In particular, patients with RA might be different from the (matched) general population in many ways, which could affect the risk of CV disease.

Moreover, advances in imaging techniques can improve the assessment of inflammation in RA. Specifically, new methods such as non-calcified coronary artery plaque detection via CT angiography and arterial fluorodeoxyglucose (FDG) uptake using Positron emission tomography–computed tomography (PET-CT) have shown promising results.[44–46] These techniques allow for a more precise observation of inflammation at the plaque site and may provide an opportunity for designing RCT that specifically targets subgroups of patients with RA, as demonstrated recently.[45]

CONCLUSIONS

In their seminal 1953 paper describing the increased mortality in patients with RA, Cobb *et al* only considered age and sex when comparing the mortality risk in patients with RA to the general population.[1] Seventy years after these pioneering, although rudimentary, results were published, we propose a renewed appreciation for causes of CV disease in RA. We should move away from simple classifications of risk factors. Furthermore, the practice of separating inflammation and traditional CV risk factors, for example, in statistical models, is unproductive. As we strive to improve CV outcomes in patients with RA, we should focus on strategies to optimise the use current treatments and to identifying potential novel therapies. To this end, measures of cumulative inflammatory burden, or detailed longitudinal data, would be important. Studying CV outcomes in patients with low cumulative RA disease activity could also be useful.

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