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## **TITLE**

The role of non-invasive cardiovascular imaging in assessment of cardiovascular risk in Rheumatoid Arthritis: where we are and where we need to be

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## ABSTRACT

### OBJECTIVES:

This review assesses risk assessment of cardiovascular disease (CVD) in Rheumatoid Arthritis (RA) and how non-invasive imaging modalities may improve risk stratification in the future.

### FINDINGS:

RA is common and patients are at greater risk of CVD than the general population. Cardiovascular (CV) risk stratification is recommended in European guidelines for patients at high and very high CV risk in order to commence preventative therapy. Ideally, such assessment should be carried out immediately after diagnosis and as part of ongoing long-term patient care in order to improve patient outcomes.

The risk profile in RA is different from the general population and is not well estimated using conventional clinical CVD risk algorithms, particularly in patients estimated as intermediate CVD risk. Non-invasive imaging techniques may therefore play an important role in improving risk assessment. However, there are currently very limited prognostic data specific to RA patients to guide clinicians in risk stratification using these imaging techniques.

### CONCLUSIONS:

RA is associated with increased risk of CV mortality, mainly attributable to atherosclerotic disease, though in addition, RA is associated with many other disease processes which further contribute to increased CV mortality. There is reasonable evidence for using carotid ultrasound in patients estimated to be at intermediate risk of CV mortality using clinical CVD risk algorithms. Newer imaging techniques such as cardiovascular magnetic resonance and computed tomography offer the potential to improve risk stratification further, however, longitudinal data with hard CVD outcomes are currently lacking.

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory arthritis that affects not just the joints, but also multiple organ systems including the heart and cardiovascular (CV) system. The excess atherosclerosis associated with RA[1] has focussed efforts on the identification of patients at risk of cardiovascular disease (CVD) in order to be able to deliver preventative and risk reduction management strategies. This review examines the evidence base and summarises current literature on the opportunities and limitations of non-invasive CVD imaging modalities and how their application may improve risk stratification of CVD in patients with RA.

### **EPIDEMIOLOGY OF CARDIOVASCULAR DISEASE IN RHEUMATOID ARTHRITIS**

Rheumatoid arthritis affects up to 1% of the general population and is associated with increased mortality. This is predominantly, though not exclusively due to an accelerated process of atherosclerosis affecting the coronary and cerebral arterial systems[2]. There is a 50% increase in CV mortality amongst patients with RA[3], similar in magnitude to that associated with diabetes[4].

### **CARDIOVASCULAR RISK STRATIFICATION IN RA**

Cardiovascular risk stratification enables estimation of a patient's percentage risk of developing a defined CV endpoint over a given period of time through the development of a CVD risk algorithm. Insights gained by studies investigating CV risk calculation in RA also provide a greater understanding of the interaction between autoimmunity/inflammation and traditional risk factors for CVD over time. Development of accurate CVD risk algorithms could identify which patients might benefit most from management of risk factors for CVD and enable more effective CVD management pathways.

The need for effective and expedient risk stratification and management of CVD risk factors specific to patients with RA is recognised in international, European League Against Rheumatism (EULAR) recommendations, as well as expert opinion [5,6]. The most recent of these[6] are summarised in Figure 1. Consistent with the EULAR guidelines, the 2016 European Society of Cardiology (ESC) guideline on CVD prevention in clinical practice [7] highlights the value of systematic CV risk assessment in individuals at high risk including those with "comorbidities increasing CV risk." In addition to clinical history and risk stratification in the general population and in RA patients can in principle be undertaken by two methods; with CVD risk algorithms systems based on clinical and biochemical parameters or using non-invasive cardiovascular imaging techniques.

### **Clinical Cardiovascular Disease Risk Algorithms**

Numerous clinical CVD risk algorithms have been proposed for both general and RA populations.

Crowson et al. assessed the accuracy of 10-year CV risk assessment using the Framingham and Reynolds clinical CVD risk algorithms when applied to an RA cohort[8]. The observed CV risk in RA patients was found to be twofold higher than was estimated by both of these CVD risk calculators. Using a similar study design, Arts et al. assessed the accuracy of 4 clinical risk algorithms (Framingham, Reynolds, SCORE and Q-Risk II) when applied to an RA population[9]. These risk algorithms were found either to underestimate (Framingham, Reynolds and SCORE) or overestimate risk (Q-Risk II) in RA patients.

Efforts have been made to address the inaccuracies of CVD risk algorithms. Solomon et al. devised the ERS-RA risk calculator incorporating RA specific CV risk factors, however, performance was less than perfect with a tendency towards reclassifying a patient's predicted CV risk downwards rather than upwards[10]. The modified SCORE system has been proposed as a means of improving CV risk stratification[5] and involves a multiplication factor of 1.5 applied to the calculated SCORE risk to RA patients with high risk features. However, this CVD risk calculator has not been prospectively evaluated in RA patients so that its validity is as yet unproven[11]. Additionally, it frequently underestimates CVD risk in patients estimated at intermediate risk of developing CVD[6]. In patients estimated at intermediate risk of developing CVD or in those with a risk close to the decisional thresholds (as indicated in the ESC guidelines), additional tests or tools can improve risk stratification. Here, non-invasive CV imaging may have an important role[7].

## **CARDIOVASCULAR IMAGING MODALITIES**

Current CV imaging modalities allow detailed evaluation of the structure and function of the heart and systemic arterial systems. This enables detection of atherosclerotic disease, which accounts for the majority of excess CV mortality in RA. Some imaging methods can detect other CV manifestations of RA such as valvular abnormalities, left ventricular (LV) dysfunction and inflammatory processes affecting the CV system (Figure 2). The ideal imaging technique in the assessment of CVD risk in patients with RA would be able to address the following objectives:

- Accurate prediction of CV mortality
- Early, subclinical detection of atherosclerosis
- Longitudinal evaluation of interval change in CVD, allowing on-going individualised adjustment to a patient's RA and CVD specific treatment
- Detection of impact of atherosclerosis and other manifestations of CVD

The following section reviews how ultrasound (US), computerised tomography (CT), positron emission tomography (PET) and cardiovascular magnetic resonance (CMR) can contribute to CVD risk stratification and highlights their existing application and potential for CVD risk calculation in RA patients. Their relative strengths and weaknesses are summarised in Figure 3.

### **Non-invasive Assessment of Arterial Stiffness**

Arterial stiffness is a recognised surrogate measure of increased CVD risk[12] and reflects a generalised process of vascular ageing and atherosclerosis. Arterial stiffness is most commonly measured by aortic pulse wave velocity (aPWV) and augmentation index (Aix)[13] with a transcutaneous device (such as the Sphygmocor device[14]) to assess the pulse pressure waveform. Alternative measures of arterial stiffness include aortic distensibility [15,16] and brachial-ankle elasticity index (baEi)[17].

### **Ultrasound**

Ultrasound provides accurate and reproducible measurements of anatomical structures without harmful ionising radiation. Applications include assessment of carotid intima-media thickness (cIMT) and demonstration of atherosclerotic plaque within the carotid artery.

High resolution US images are used to detect the presence of atherosclerotic plaque and to measure cIMT of a patient's common carotid artery which corresponds to the combined thickness of the intima and media[18]. Carotid intima-media thickness progressively thickens with atherosclerosis, representing a generalised measure of atherosclerosis burden and providing early evidence of CV

risk in subclinical patient populations[19]. Absolute thickness of >0.9mm or greater than the 75<sup>th</sup> percentile is considered high CV risk[20].

### **Computed Tomography**

Computed tomography can be used for coronary artery calcium score (CAC) or coronary angiography (CTCA).

CAC score is a simple test to estimate the degree of calcification within the coronary arteries with excellent correlation with total coronary calcium burden in histological samples[21] and is a direct measure of (early) atherosclerosis[22]. A score of 0 is associated with low CV risk, whereas scores above 1 are associated with an incremental increase in risk[23]. The American College of Cardiology recommends the use of CAC score to guide risk assessment where an individual's level of CVD risk is unclear using traditional clinical CVD risk algorithms[24] and a similar recommendation is made in ESC guidance[7].

CTCA allows direct anatomical visualisation of the coronary arteries to detect atherosclerotic disease. Its ability to visualise the coronary arteries, typically measuring 3-4mm in diameter, stems from its high spatial resolution[25,26]. CTCA is primarily used to assess patients with low to intermediate pre-test probability of significant coronary artery disease[27], but could potentially be used in the CV risk assessment of patients with RA. With current methodology, the radiation exposure from CTCA is in the region of 3-4 millisievert or below[28]. The typical radiation dose associated with CAC scoring is less than 1 millisievert, making it a viable option for CV risk assessment[29].

### **Positron Emission Tomography**

Positron emission tomography myocardial perfusion imaging detects uptake of positron-emitting radiotracers in the heart and enables accurate measurement of LV volumes and quantitation of blood flow (perfusion of blood into the myocardium). Perfusion to the myocardium may be assessed either globally i.e. the LV as a whole or individually at the level of each of the standard 17 LV segments. Decreased myocardial perfusion may indicate obstructive coronary artery disease or reduced flow at the level of the coronary microcirculation. Studies have demonstrated the usefulness of PET-CT to identify ruptured and high-risk atherosclerotic plaques in patients with symptomatic coronary and carotid artery disease[30]. Although not widely available, PET may be used for patients with suspected angina[27]. PET has also been shown to predict CV mortality in patients with coronary artery disease[31] and could potentially be applied to the CV risk stratification of other high risk patient groups such as those with RA. Limitations include its expense, availability of tracers, use of ionising radiation and limited assessment of cardiac structures.

### **Cardiovascular Magnetic Resonance**

Cardiovascular magnetic resonance imaging provides a comprehensive assessment of CV structure and function without the use of ionising radiation. It provides the most accurate and reproducible quantitation of left and right ventricular volumes, mass and ejection fraction of all CV imaging modalities[32].

A key advantage of CMR is its provision of 'tissue characterisation' of the myocardium; detailed information regarding the structure and composition of the ventricular myocardium allowing detection and diagnosis of a wide range of myocardial diseases[33]. This is commonly achieved using late gadolinium enhancement imaging (LGE) to detect areas of infarction or focal fibrosis[34]. More diffuse forms of fibrosis may be assessed using T1 mapping (magnetic relaxation property of

the myocardium) and extracellular volume (ECV) quantification (estimate of the ECV volume as a proportion of the myocardium)[35]. Both have the potential to be used in prognostication and to track progression of a disease over time and/or after the introduction of new therapies[36].

Chronic myocardial ischaemia can be assessed using myocardial perfusion at rest and during pharmacological vasodilator stress [37]. In the assessment of angina, CMR is recommended to assess and plan treatment in patients at intermediate pre-test probability of having significant coronary artery disease[27].

Limitations include its expense and contraindications for patients with retained metal objects or older metallic medical prostheses.

## **CURRENT EVIDENCE SUPPORTING NON-INVASIVE CV IMAGING IN RA**

### **Measures of Arterial Stiffness**

Both aPWV and Aix are associated with increased CVD risk in hypertension[38][39], diabetes[40] and the general population[41] in large patient cohorts. In the context of RA, one modest sized study of 113 RA patients demonstrated significantly lower aPWV and Aix values in patients in remission (n= 31) compared with active disease (n=82), although this was a cross-sectional analysis[42]. Another recent study of 138 RA patients demonstrated increased that aPWV (as well as carotid plaque and CIMT) were predictive of CV events over a mean follow-up period of 5.4 years, with a hazard ratio per unit (m/s) increase in aPWV of 1.85[43].

The predictive value of baEI in CV risk assessment has been extensively investigated in the general population. A meta-analysis of 18 studies involving 8169 participants with a wide spectrum of CV risk factors concluded that the presence of high baEI corresponded with a pooled relative risk of 5.36 and 2.45 respectively for CV mortality and all-cause mortality versus low baEI[44]. The mean follow-up period of the included studies was 3.6 years and the study populations included end stage renal disease, diabetes, hypertension and patients with previous CV events, however, this did not include any studies with RA populations. Although no longitudinal outcome studies have been conducted with RA patients, meta-analysis suggests that baEI is reduced in RA[45].

### **Carotid Ultrasound**

A limited number of studies have demonstrated prognostic outcomes using non-invasive imaging in RA cohorts. Evans et al prospectively assessed 599 patients with established RA without a history of acute coronary syndrome (ACS) after undergoing carotid US[46]. Patients with no atherosclerotic plaque had a new incidence of ACS of 1.1 per 100 patient years and those with unilateral and bilateral atherosclerotic plaque had ACS incidence rates of 2.5 and 4.3 respectively. Ajeganova demonstrated similar results in a retrospective analysis of 105 patients with new onset, treatment naïve RA[47]. Bilateral atherosclerotic plaque was associated with a hazard ratio of 6.3 of developing ACS compared with patients without atherosclerotic plaque. In the same study, CIMT was no different in patients who developed ACS compared with those who did not. Prospective 5-year outcomes were assessed in a series of 47 patients with RA without risk factors of clinical evidence of CVD after initial screening using carotid US, of whom 17 subsequently experienced an adverse CV outcome during follow up[48]. Carotid intima-media thickness was highly accurate in predicting adverse CV events, with an area under the receiver operating curve (AUC) of 0.93. Presence of atherosclerotic plaque detected by US was slightly less accurate with an AUC of 0.9.



Meta-analyses assessing cIMT versus clinical CVD risk algorithms to modified SCORE CV risk calculation. Coralles et al.[49] assessed 370 consecutive patients with established RA with no history of CVD and stratified them according to modified score risk as low, intermediate, high and very high CVD risk. All patients underwent carotid US to assess cIMT and the presence of atherosclerotic plaque. Only 12% of low risk patients had evidence of increased cIMT and/or carotid plaque consistent with high CV risk, whereas 65% of the moderate and 85% of the high and very high groups were found to have increased cIMT and/or carotid plaque. This demonstrates the utility of CV imaging in the CVD risk estimation of intermediate risk patients, as conventional CVD risk algorithms such as the modified SCORE system underestimate risk in this cohort. The same group showed that a high cIMT was significantly more frequent than a high (>100) coronary calcium score in high or very high risk patients [50]. Whilst the limited accuracy of the clinical CVD risk algorithms against which they were validated must be acknowledged, these studies suggest that cIMT may be a more sensitive predictor of CV risk than coronary calcium score. However, this remains to be confirmed in a longitudinal study.

### **Alternative Imaging Modalities**

One recent CMR study of 39 RA patients reported higher T1 and ECV values in RA versus controls[51]. Increases in ECV have been shown to be associated with increased mortality[52], thus both T1 and ECV have the potential to be used as 'biomarkers' in RA to predict CV risk as well as tracking treatment response over time[53].

Another potential indicator of disease severity and treatment response measurable by echocardiography and CMR is LV mass. Giles et al[54] demonstrated reduced LV mass by CMR in 75 patients with established RA versus controls. These findings were corroborated by a large echocardiography study of 200 patients[55], as well as preliminary findings from a CMR study assessing treatment naïve patients with a new diagnosis of RA[56]. There are some conflicting reports of higher LV mass in patients with RA in echocardiography studies[57,58], however, this probably reflects the relatively low accuracy of echocardiography-derived LV mass measurement in general (not specific to these studies) and the small sample sizes of the currently available reports.

Carotid ultrasound and baEI currently provide the most robust and best-validated estimates of future development of CVD in patients with RA, however, neither represents the 'ideal' technique as outlined earlier in this review. The presence of aortic plaque (particularly when bilateral) in the carotid artery appears a promising predictor of future ACS events, though it is unclear whether it is as strong in predicting other CV events. Whilst cIMT is validated specifically in RA patient cohorts, in effect it provides only a single, non-dynamic measurement as serial measurements have not been shown to be helpful in on-going CV risk calculation in the same patient[59] and results of small scale prospective studies are conflicting. Additionally, carotid US does not assess ventricular or valvular function, both of which are common, clinically significant complications of RA. Despite extensive prognostic outcome data in other diseases associated with high CVD risk, the prognostic value of baEI in RA has not yet been assessed in longitudinal studies.

### **CONCLUSION**

Rheumatoid arthritis is associated with increased risk of CV mortality compared with the general population. Much of this relates to atherosclerotic disease, however, RA is associated with many other disease processes affecting the CV system, which further contribute to increased CV mortality.

There are currently very limited prognostication data specific to RA patients enabling CVD risk stratification. The risk profile is different from patients without RA and not well estimated using



conventional clinical CVD risk algorithms. There is reasonable evidence for using carotid US in patients estimated at intermediate risk of CV mortality. Newer imaging techniques such as CMR and CT offer the potential to improve risk stratification further, however, longitudinal data with hard CVD outcomes are currently lacking.

Risk stratification is crucial in RA and assessment should be performed as early as possible in the disease.

## **FUTURE DIRECTIONS**

Molecular imaging (such as PET) allows visualisation of biological targets within the heart by revealing the location and degree of uptake of specific molecules. Hybrid techniques including PET-CT and PET-MRI which theoretically combine the advantages of both approaches are being assessed[60]. Future approaches using molecular imaging may allow the ability to track uptake of radiolabelled therapeutic agents, providing information on disease activity and treatment efficacy[61]. Advancements are also being made in the development of ‘hyperpolarised’ molecules for use in CMR which can be used to assess their intracellular metabolism rather than uptake of the molecules within the tissues of the CV system[62]. This could aid diagnosis of specific diseases and improve quantitation of myocardial perfusion.

Perhaps the ‘holy grail’ in assessing atherosclerotic plaque using CV imaging is the identification of ‘vulnerable plaque’. Composition of plaque varies greatly from one patient to another. The ideal imaging technique would not only assess the degree of coronary artery stenosis (a poor predictor of future plaque rupture and thus future MI), but also identify high-risk characteristics of atherosclerotic plaque predictive of future MI and other CV events. Molecular imaging shows early promise, however, further work is required to improve the prognostic value of this and other techniques[63].

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The authors have no competing interests to declare

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#### **FIGURE LEGENDS:**

- Figure 1. Summary of current recommendations on CVD risk stratification in RA.
- Figure 2. Coronal CMR image of the heart and aorta depicting where pathophysiological processes may occur in RA patients.
- Figure 3. Advantages and disadvantages of cardiovascular imaging modalities in RA (PET image from Positron Emission Tomography Myocardial Perfusion Imaging for Diagnosis and Risk Stratification in Obese Patients. *Current Cardiovascular Imaging Reports* 2015; 8: 9304. Arasaratnam P. Reproduced with permission of Springer).