Could cardiovascular disease risk stratification and management in rheumatoid arthritis be enhanced?

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The markedly enhanced risk of atherosclerotic cardiovascular disease (CVD) in rheumatoid arthritis (RA) is well documented.1 2 This prompted a European League Against Rheumatism (EULAR) task force to make a commendable effort in producing recommendations for cardiovascular risk management in patients with inflammatory arthritis.3 These included the application of the systematic coronary risk evaluation score (SCORE), a multiple major traditional risk factor assessment equation. In addition, the EULAR task force recommended applying a multiplier of 1.5 in patients with RA that met 2 of 3 criteria consisting of (1) a disease duration >10 years, (2) rheumatoid factor or anticyclic citrullinated peptide positivity and (3) the presence of extra-articular manifestation, thereby creating the modified (m) SCORE.

Risk factor assessment algorithms, including the SCORE and the Framingham risk equation, are recommended worldwide as part of CVD risk management in the population at large.4 5 These equations allow for stratifying subjects into low, intermediate, high and very high risk groups. With regard to CVD risk management, lifestyle factors should be addressed in all individuals. The use of cardiovascular drugs, particularly antihypertensive and lipid-lowering agents should be considered in those at high or very high risk as these interventions markedly reduce CVD event rates in such persons. Patients with established CVD, diabetes and chronic kidney disease are at high or very high risk and hence, risk factor equation application is not indicated.

Nonetheless, approximately a third of CVD events are not attributable to major CVD risk factors.6 Congruent with this, although multiple risk factor equations are useful in determining the overall CVD risk among different populations, they often underestimate the actual risk in individual subjects. This is particularly evident in those who are at moderate risk according to major risk factor assessment equations.4 5 Consequently, based on reported evidence, two approaches that can refine CVD risk stratification are currently considered helpful in both European and American guidelines on CVD risk management.6 7 First, the use of biomarkers, particularly high-sensitivity C reactive protein concentrations, and second, cardiovascular imaging, including multidetector tomography coronary artery calcification scores (CACS) and carotid ultrasound; for the first time, carotid plaques are recognised to represent very high risk in the latest European guidelines on CVD prevention in clinical practice,8 where cardiovascular risk assessment is also not necessary because the patient is categorised into secondary prevention equivalent to patients with established CVD. Taking into account that patients with RA have two to three times more frequent asymptomatic carotid atherosclerosis compared with persons without RA,7–12 this will have a major impact on correct classification and hence treatment in patients with RA.

Would traditional risk factors as included in the mSCORE be expected to reliably reflect the actual CVD risk in RA? Recently reported evidence suggests that this may not be the case. One study showed that the mean Framingham score was as low as 7% (low risk) in RA patients with carotid artery plaque despite it being associated with a 10-year incident CVD event rate of ≥39%.10 Indeed, Crowson and colleagues11 recently reported that the risk of CVD events is twofold and 65% higher than the Framingham score predicts in women and men with RA, respectively. The Reynolds risk score that additionally includes high-sensitivity C reactive protein concentrations and a family history of premature CVD revealed similar shortcomings.11 Using the area under the receiver operating characteristic curve in logistic regression analysis, traditional and non-traditional CVD risk factors associated similarly and additively with plaque prevalence.14 Solomon and colleagues15 subsequently confirmed that the same applied when the risk of incident CVD events was examined. The associations of traditional risk factors with CVD event rates are weakened in RA.16 Indeed, the relation between lipids and CVD is at most inconsistent17 and in one report was in fact paradoxically inverse, in RA.18 A recent investigation disclosed that in contrast to their white counterparts, black Africans with RA experience no major conventional risk factor–atherosclerosis and systemic inflammation–atherosclerosis relations.19 This further argues against the reliance on risk factor profiles as currently recommended in evaluating actual CVD risk.

Treatment with methotrexate reduces the risk for CVD events by ~20% in RA.20 Indeed, systemic inflammation among patients with RA contributes substantially to increased CVD risk both through its adverse impact on traditional risk factors and direct effects on the vasculature.21 22 Therefore, effective CVD risk management likely comprises not only adequate treatment of conventional risk factors but also tight disease activity control in RA.

With regard to the multiplier application as recommended by the EULAR task force,7 other recent reports revealed that the enhanced CVD risk is unlikely to be restricted to those patients with a disease duration of >10 years, neither to those who experience rheumatoid factor positivity and presumably also not to the small subgroup with extra-articular manifestations.23 The EULAR task force acknowledged that their approach was conservative.3 Taken together, evidence that was mostly reported after the EULAR recommendations for CVD risk management were published raises the possibility that their application could result in a substantial proportion of patients with RA at high risk for CVD remaining unidentified.23

However, are cardioprotective drugs effective in CVD risk management in RA? Indeed, there is a lack of hard evidence regarding CVD prevention in patients with RA and therefore many questions remain unanswered. In this regard, it is both noteworthy and promising that in a post hoc analysis of two prospective trials that assessed the impact of intensive compared with conventional treatment with statins on a CVD outcome, patients with and without inflammatory joint disease were found to experience comparable lipid-lowering effects and reduced CVD.
risk.24 Also, in a preventive cardio-rheuma
clinic, two-thirds of patients referred for
CVD risk evaluation required CVD pre-
vention,11 which further reinforces the
need for identifying patients at high risk.
RA patients often sustain background
marked systemic inflammation, altered
lipid parameters and exposure to poly-
pharmacy, all of which can influence
optimal lipid-lowering treatment in CVD
prevention. Despite the presence of these
factors, treatment to lipid targets was suc-
scessful in as many as ~90% of patients
with RA who required interventions with
cardiovascular drugs.11 Experience and
studies on clinical CVD prevention are
warranted.

Corrales et al25 compared the abilities of
the mSCORE; carotid ultrasound deter-
mined advanced atherosclerosis and CACS
in the identification of patients with RA
who sustain high or very high CVD risk in
the absence of established high or very high
risk. Upon using the EULAR task force
multiplier, the proportion of patients with
high or very high risk increased by only
3.1%, that is, from 11.6% to 14.7%. High
CACS (>100) were observed in a mostly
similar proportion of all patients, that is,
17.9%, and in none with an mSCORE of
<1% (low risk). By contrast, 73.7% of all
patients had ultrasonographically con-
firmed advanced atherosclerosis.
Remarkably, this comorbidity was observed
not only in 85% of patients at moderate risk
(mSCORE>1 and <5%) but also in 33.3% of those with an mSCORE<1%.
CACS and ultrasound findings correlated
significantly. Nevertheless, even among the
41.2% with no detected coronary artery
calciﬁcation, 57.5% had carotid plaques.
Finally, in keeping with these ﬁndings,
upon employing the presence of high/very
high risk as determined by an mSCORE>5,
a CACS of >100 or ultrasonographically
determined advanced atherosclerosis as
outcome variable, the sensitivities of an
mSCORE>5, CACS>100 and ultrasono-
graphically determined advanced athero-
sclerosis were 19.4%, 23.6% and 97.2%,
respectively. The ﬁndings on ultrasound in
the Corrales study are largely similar to
those recently reported by the same group
in a larger cohort.26

Overall, in the Corrales study, by con-
sidering ultrasound ﬁndings in addition to
the EULAR recommendations, the pro-
portion of patients stratified as being at
high or very high CVD risk increased
from 22.1% to 77.9% or 3.5-fold. Most
importantly, in routine clinical settings
these patients would generally not receive
adequate preventive CVD risk treatment
with the serious consequences this has.
Moreover, if up to a third of patients with
RA without established high CVD risk and
considered to be at low risk are actually at
very high risk, it would appear at least
reasonable to perform carotid ultrasound
not only in those at intermediate risk but
also in those with low risk according to
the mSCORE. Although the respective
proportion was only 13% in the previ-
ously reported Corrales study,26 even the
absence of identiﬁable carotid artery
plaque by ultrasound still does not fully
exclude the possibility of prevalent signiﬁcant
coronary artery disease.27

Could carotid artery plaque associate
with lower incident CVD event rates and
why would CACS be less sensitive in dis-
cerning high risk in RA? Both carotid artery
atherosclerosis and CACS predict incident
CVD events beyond other risk factors in
RA.28–30 Vulnerable plaques are more echo-
lucent and typically have a lipid-rich core,
macrophages and a low collagen content.31
By contrast, plaques that are less vulnerable
to rupture are more echogenic and contain
more collagen, dense ﬁbrous tissue and
various amounts of calciﬁcation and repre-
sent more advanced disease.31 Patients with
RA experience a disease activity-related
increased vulnerable plaque burden.12 It is
therefore highly unlikely that reliance on
the presence of carotid plaque translates
into an overestimate of CVD risk in RA,
and it is indeed expected that CACS are less
sensitive in this context. The latter is,
however, also recognised in non-RA
subjects.32

Upon considering the potential use of
carotid ultrasonography in CVD risk
stratiﬁcation in RA, the following issues
are equally relevant. In contrast to deter-
mining CACS, ultrasonography is inex-
 pensive, does not require radiation and is
considered cost-effective.31 Could the
additional use of biomarkers34–37 be pref-
erable to vascular imaging upon evaluat-
ing CVD risk in RA? Biomarkers of CVD
risk are valuable in examining atherogenic
mechanisms in RA34–36 but the identiﬁca-
tion of those that predict CVD events
beyond other risk factors in this disease is
in its early stages at present and requires
intensive and careful exploration.37 Also,
employing (presumably) a panel of useful
biomarkers is likely to enhance the
involved costs to a larger extent than per-
forming carotid ultrasonography.
Nevertheless, plaque represents advanced
atherosclerosis and hence biomarkers that
reﬂect enhanced arteriogenesis in RA may
well be needed to timely reclassify patients
with RA in CVD risk groups and identify
those at high risk at a stage prior
to plaque occurrence. Finally, whereas
plaque associates closely with coronary
artery disease, increased carotid intima-
media thickness (CIMT) represents mostly
high blood pressure-mediated arterial
media hypertrophy and relates more
strongly to left ventricular hypertrophy.31
Omission of CIMT results in the Corrales
study would not be anticipated to alter the
ﬁndings as only one of the patients
with a CIMT >0.9 mm did not have
plaque.

The article by Corrales and colleagues
does not allude to the limitations of their
investigation that do, however, require
further elucidation. Their cross-sectional
design precludes drawing inferences on
the direction of causality and, accordingly,
the role of carotid ultrasonography in
CVD risk assessment and management
and reduction of cardiovascular event
rates needs evaluation in a longitudinal
study. Also, since the mean disease dura-
tion was 10.8 years it remains to be clari-
ﬁed whether carotid ultrasound is as help-
ful among patients with early disease
versus those with long-standing disease in
enhancing CVD risk stratiﬁcation.

Improved risk stratiﬁcation alone will
not reduce cardiovascular event rates,
unless it is accompanied by adequate CVD
risk management in RA. Recently
reported retrospective data suggest that
the latter often does not occur38 and
traditional risk factors are underdiagnosed
and undertreated in RA,22 a situation
that could in itself contribute to enhanced
CVD risk. This deﬁciency is amply con-
ﬁrmed in a prospectively designed cross-
sectional investigation on CVD risk factor
control in 836 patients with RA by
Primdahl and colleagues,39 as also
reported in Annals of Rheumatic Diseases.
Most striking is that among the 644
patients without established CVD or dia-
betes, inadequate blood pressure and lipid
control were documented in 35.8% and
55.4% of participants, respectively. Even
more concerning is that among those with
CVD and diabetes, these proportions
were as high as 36.2% and 84.2% and
73.6% and 80.9%, respectively. Clearly,
effective and innovative measures aimed
at improving systematic evaluation and
management CVD risk factor pro-
ﬁles by healthcare providers in
patients with RA are urgently needed. In
line with the ﬁndings in the Corrales
study,25 upon applying the EULAR task
force multiplier,3 the proportion of
patients with high or very high risk
increased by only 3.6%, that is, from
12.6% to 16.2%.

Perhaps the most pertinent issue that
requires clariﬁcation here is: who should


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https://doi.org/10.1136/annrheumdis-2013-203911


take the responsibility to manage CVD risk in patients with RA? Enrolment in a preventive clinic with cardiologist involvement as currently done in a centre in Oslo, Norway, is likely to constitute one promising option in this regard.11 However, the establishment of such clinics may not be possible in less well-resourced countries. The Primdahl study investigators fully informed the patient, relevant hospital department and treating general practitioner (GP) about the participant’s risk profile and subsequently referred the patient to their GP. In this regard, in The Netherlands, the GP now assesses and manages CVD risk in patients with RA, a process that is facilitated by embedding of recommendations in the corresponding relevant guideline.49 Again for patients who form part of less affluent societies, this may not be feasible as it involves extra direct and indirect costs. Should, at least in some settings, the treating rheumatologist manage CVD risk in addition to obtaining optimal disease activity control?41 At the very least, population or/country-specific factors, including socioeconomic status, need to be accounted for in designing optimal and feasible CVD risk management strategies in RA.

In conclusion, whereas the mortality gap between patients with RA and the general population reportedly continues to widen,42 considering the findings in the Corrales and Primdahl studies could contribute to the implementation of potentially effective strategies in our attempts at reducing cardiovascular risk in RA.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

PHD and AGS contributed equally.


Received 1 June 2013 Revised 15 July 2013 Accepted 24 July 2013 Published Online First 9 August 2013

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Published Online First on April 20, 2022 by guest. Protected by copyright.