# Lipid management in rheumatoid arthritis: a position paper by the Cardiovascular Pharmacotherapy Working Group of European Society of Cardiology

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# Abstract

Rheumatoid arthritis (RA) is associated with increased cardiovascular morbidity, partly due to alterations in lipoprotein quantity, quality and cell cholesterol trafficking. Although cardiovascular disease significantly contributes to mortality excess in RA, cardiovascular prevention has been largely insufficient. Because of limited evidence, optimal strategies for lipid management (LM) in RA have not been determined yet, and recommendations are largely based on expert opinions.

In this position paper, we describe abnormalities in lipid metabolism in RA and introduce a new algorithm for estimation of cardiovascular risk (CVR) and LM in RA. The algorithm stratifies patients according to RA-related factors impacting CVR (such as RA activity and severity and medication) and therefore enables a more nuanced approach than other current methods. We propose strategies for monitoring of lipid parameters and treatment of dyslipidemia in RA (including lifestyle, statins and other lipid-modifying therapies, and disease modifying anti-rheumatic drugs). These opinion-based recommendations are meant to facilitate LM in RA until more evidence is available.

# Keywords

Rheumatoid arthritis; cardiovascular risk; atherosclerosis; lipid management; statins; inflammation.

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## Background

## Increased cardiovascular risk (CVR) in rheumatoid arthritis (RA)

RA, an autoimmune disease affecting 0.5-1% of the population (predominantly women), is associated with 50% increase in cardiovascular morbidity and mortality (1-5). RA patients younger than 50 years have been observed to have relative risk of 2.6 (6). The main cause of premature cardiovascular disease (CVD) in RA is accelerated atherosclerosis, with increased plaque burden, plaque vulnerability and thrombogenesis (3, 7). Although some traditional CVR factors (CVRFs) are increased in RA, they do not fully explain the CVD excess because of the significant role of other mechanisms, e.g. inflammation, in its development (3, 5, 7-10).

CVR in RA is related to RA activity and severity (including articular, extraarticular and systemic inflammation, positivity for anti-citrullinated protein antibodies and rheumatoid factor, physical disability, joint damage) (3, 4, 8, 9, 11-20).

Although CVR can be increased early during the disease course, long RA duration has been reported to enhance CVR, probably due to the cumulative inflammatory activity (9, 11, 19, 21). The effects of inflammation are also likely to explain the link between low body mass index (BMI) and increased CVR in RA (5).

RA is associated also with other conditions that may augment CVR, e.g., stress, depression, and other adverse psychosocial factors, chronic kidney disease, hypothyroidism, sleep apnea, periodontitis, hyperuricemia, low vitamin D levels and use of non-steroidal anti-inflammatory drugs and glucocorticoids (9, 17, 22-24).

Cardiovascular prevention (CVP), including hypertension and dyslipidemia treatment, has been found to be frequently unsatisfactory in RA (even with respect to recommendations for the general population, not adjusted for the RA-related CVR excess) (25-28). This may be partly due to lack of evidence causing uncertainties regarding optimal CVP strategies in RA, low awareness of the problem, and inadequate organization of the CVP management. None of the previously proposed recommendations on CVP in RA has been uniformly and widely taken into clinical practice. Moreover, the predisposition to atypical/asymptomatic CVD in RA limits opportunities for secondary CVP (29-32).

Both the 2016 guidelines of the European Society of Cardiology on CVP (2016 ESC CVP-guidelines) and the 2018 American guidelines on cholesterol management state that RA should be considered a CVR enhancing factor but quantifying the magnitude of its effect has been challenging (33-35). Calculators for the general population, based only on traditional CVRFs, undervalue the importance of RA-specific CVRFs (8, 17, 36).

Among instruments developed to adjust CVR for the RA or inflammation related risk excess belong the 2010 and 2015/2016 European League Against Rheumatism [EULAR] methods, QRISK2, Expanded CVR Score for RA, ATACC-RA calculator and Reynolds Score. Whereas the 2015/2016 EULAR method has not been validated yet, the other methods do not appear to significantly improve CVR reclassification, and can either underestimate or overestimate CVR in RA (17, 32, 35-39). E.g., QRISK2, adjusting for RA by a multiplier of 1.4, was found to overestimate the risk (36, 39). Analogously, it is conceivable that the 2015/2016 EULAR approach, adjusting for RA indiscriminately by multiplying CVR score from calculators for the general population by 1.5, might overestimate CVR in some RA patients without significantly increased CVR. On the other hand, it might underestimate CVR in other RA subgroups, similar to the previous EULAR version (2010), which recommended use of the 1.5 multiplier only in selected RA subpopulations.

As RA is a heterogeneous disease with varying characteristics that affect CVR, it is plausible that a tailored approach to CVR estimation/CVP according to these factors would be beneficial.

Similar to the general population, some current studies signal decreasing cardiovascular morbidity in RA. Nevertheless, a large Swedish study did not observe any significant decline in the excessive relative risk of acute coronary events in RA during 1997-2014, despite progress in antirheumatic treatment and greater focus on CVP (18). Thus, there is still a great need for improvement of CVP strategies in RA.

## Disturbances in lipoprotein quantity and quality

One of the factors contributing to CVR in RA is altered lipid metabolism (3, 8, 40-46).

RA activity is associated with increased CVR but decreased cholesterol levels, leading to an U-shaped relationship between cholesterol quantity and cardiovascular morbidity (40, 42, 47-49). Nevertheless, the impact of inflammation should not lead to neglecting the importance of lipid management (LM) (50).

Importantly, RA activity is also related to qualitative proatherosclerotic modifications of HDL-C and LDL-C, and impaired cell cholesterol transport (40, 51, 52).

Hypertriglyceridemia (in particular triglycerides [TGs]>1.7 mmol/L [150mg/dL]) is a significant independent CVRF (33). In fact, the atheroprotective functions of HDL-C have been observed to be attenuated after adjustments for TGs (53). In RA, increased TG levels as well as their relationships to atherosclerosis and cardiovascular events have been reported (8, 19, 54-59). High TG levels might be especially harmful in patients with high disease activity (19). A lipid profile characterized by high TGs and low HDL-C may be of particular importance for CVR in RA (53).

Recent data suggest that RA may be associated with postprandial hyperlipidemia (60). This condition, characterized by protracted increased levels of TG-rich lipoproteins after food intake, is gaining increasing interest as it may have significant impact on CVD morbidity (61, 62).

RA has been reported to be associated with high lipoprotein (a) (Lp[a]) that may promote atherogenesis and thrombogenesis (5, 55, 63-65). Also other aspects of lipid homeostasis, including increased LDL-C/HDL-C ratio, oxidation of fatty acids and autoantibodies to modified lipoproteins, may influence atherogenesis in RA (5, 41, 63, 66-69).

Of note, while inflammation affects lipid metabolism, several of the aforementioned lipid abnormalities, including hypertriglyceridemia, hyperlipoproteinemia and alterations of HDL function and cell cholesterol transport, may promote inflammation (53).

## Effects of antirheumatic drugs on lipoproteins

Disease modifying antirheumatic drugs (DMARDs) can increase LDL-C and TC levels, which appears to be mainly secondary to inhibition of inflammation, although some DMARDs (e.g., IL-6 and JAK inhibitors) may specifically alter lipoprotein metabolism (3, 40, 70, 71). However, these effects can be offset by protective functions of these drugs, e.g. amelioration of inflammation, lipoprotein quality, cell cholesterol handling and Lp(a) levels (3, 72-75). Hence, none of these drugs has been proven to increase CVR; on the contrary, some antirheumatic regimens (including methotrexate and tumor necrosis factor inhibition) have been found to protect from CVD in RA (3, 76-78). Moreover, the DMARDs-induced dyslipidemia can be attenuated by statins and lifestyle interventions (79-81).

Notably, hydroxychloroquine has been reported to improve several CVRFs, e.g. to reduce TC, LDL-C and TG, increase HDL-C, and protect against statin-induced diabetes (82, 83). Thus, employing hydroxychloroquine in RA treatment might help to protect from CVD (83).

The proatherosclerotic actions of glucocorticoids (including alterations of lipoprotein levels and cell cholesterol handling) can be also partly counteracted by their anti-inflammatory properties (84). The association with increased CVR has been documented for high-dose (daily doses corresponding to >7.5 mg prednisone or high cumulative doses), but not low-dose glucocorticoid treatment (3, 24, 85, 86).

## Recommendations for LM in RA

Due to paucity of large randomized controlled trials (RCTs), and similar to other recommendations on LM in RA, this position statement is largely opinion-based, founded on the available evidence from RA and other populations, and has to be validated and adjusted with developing empirical knowledge. Nevertheless, it is important to take a position and try to improve LM in RA while awaiting results from future studies.

LM in RA can follow similar principles as those employed in diabetics, with adjustments for local opportunities. It can be provided by general practitioners, in collaboration with other providers, e.g. cardiologists, endocrinologists, lipidologists, dietitians and physical therapists, and might be facilitated by nurse driven clinics (33). Nevertheless, at least until CVP becomes well-integrated into management of RA patients, rheumatologists should take the lead, provide necessary information, and ensure that LM is performed correctly (17).

Education of patients (emphasizing lifestyle) and health care providers may reduce CVR in RA in a cost-effective way (87). It can be aided by web-based tools, such as “Love your heart” by the National Rheumatoid Arthritis Society of United Kingdom (88).

## Assessment of lipid profile and CVR

Because lipid-modifying therapy (LMT) is guided by lipid status and the total CVR, their assessment in RA is important. However, due to limited evidence, it is uncertain when the monitoring should start, what it should include, and how often it should be performed.

In some patients, exact CVR calculation is not necessary, e.g. in those with established CVD who should regardless receive the most intensive LMT. Nonetheless, assessment of modifiable CVRFs (e.g., hypertension and diabetes) is pertinent with respect to their management, and their monitoring should be adjusted to their severity and response to therapy.

The 2015/2016 EULAR recommendations suggest CVR assessment at least every five years in RA (17). More frequent assessment can be useful in patients with CVR close to thresholds mandating initiation or intensification of LMT (e.g., SCORE approaching 5%), and in those with rapidly progressing RA or other CVRFs (17, 33). Some experts advocate annual CVRF screening also in RA patients from the low and moderate ESC CVR-categories, given the relatively high occurrence of atherosclerosis even in these groups (31, 32). We suggest that annual lipid monitoring should be considered at least in “High-risk RA” (HR-RA; defined in Figure 1).

CVR re-evaluation should be considered upon substantial changes in factors influencing lipids and CVR, including lifestyle and treatment (e.g., initiation of DMARD and high-dose glucocorticoid treatment) (17). As LDL-C increases with decreasing inflammation, lipid status should be examined also when reduction of disease activity is achieved, e.g. 1-4 months after initiation of DMARDs. For interleukin-6 inhibitors, some recommendations propose lipid assessment 4-8 weeks after initiation of the treatment, and subsequently at 6 months intervals (89).

Lipid monitoring should be adjusted to the overall situation; e.g., stringent LM might not be indicated in individuals predisposed to adverse effects or with short life expectancy (33, 90).

The 2016 Canadian guidelines for dyslipidemia management recommend lipid screening at any age in certain conditions associated with increased CVR, e.g. in inflammatory conditions (91). EULAR does not state any age restrictions for CVR monitoring in RA (17). Due to the premature CVD onset in RA and benefits of CVP in young patients with high relative CVR (given the causal and cumulative effect of LDL-C in CVD), we support CVR screening in RA regardless of age.

Routine lipid screening should include TC, LDL-C, HDL-C, and TG concentrations (17). Because of the potential importance of TGs for CVR in RA, their evaluation appears sensible (TGs are usually measured for LDL-C calculations anyway). Combinations of different lipid parameters in RA might be more informative than the individual components (17, 53).

Because food intake influences cholesterol and TG concentrations, fasting assessment is ideal (34). Nevertheless, we agree with the 2016 ESC CVP-guidelines that non-fasting assessment is acceptable for routine screening (33). It may even provide opportunity to detect postprandial hyperlipidemia. However, if non-fasting TGs are ≥2.3 mmol/L (200 mg/dL), their fasting levels should be checked.

Non-HDL-C, calculated by subtracting HDL-C from TC, is not influenced by food intake and high TG levels, and can predict CVR more accurately than LDL-C (33). Thus, non-HDL-C might be superior to LDL-C for LMT guidance in RA, especially in patients with high TG and low HDL-C.

The 2016 ESC CVP-guidelines do not recommend general Lp(a) screening, but suggest its consideration in individuals with moderate ESC-CVR in order to refine risk evaluation, and in those with a family history of early CVD (33). The 2016 ESC/EAS guidelines on dyslipidemia emphasize that Lp(a) assessment should be systematically considered in certain individuals, e.g. in those with high CVR (92). As Lp(a) can improve CVR estimation (92), liberal Lp(a) assessment in RA (especially HR-RA) might be useful given the predisposition to high Lp(a) levels and the limited value of standard lipid parameters for CVR prediction.

Apolipoprotein B (apo B) levels and apo B/apo A1 ratio strongly predict CVR (33). However, as their analyses are costly and they add little to CVR estimation performed by non-HDL-C, they are not a part of the standard lipid screening.

There are no available tests for routine evaluation of lipoprotein quality yet, although novel methods for assessment of cell cholesterol efflux (reflecting HDL-C function) are promising.

## Proposed CVR stratification and LDL-C targets in RA

## Stratification of RA patients according to RA-related CVR enhancing factors

Herein we propose a new strategy for CVR stratification in RA. It is based on 2016 ESC CVP-guidelines and takes into consideration general and RA-specific CVRFs and carotid ultrasound (Figure 1). Adjustments for RA are built on similar strategies as those recommended for diabetes and its complications. In accordance with the 2016 ESC CVP-guidelines, we employ LDL-C as the primary treatment target (33). However, the algorithm can be easily adapted to non-HDL-C (Figure 1).

Because 2016 ESC CVP-guidelines are already widely in use, incorporation of the proposed algorithm into clinical practice could be feasible. Although our algorithm is based on SCORE (that uses age, gender, cholesterol levels, blood pressure, smoking and geographic area for CVR estimation), it can be adapted to national or other relevant CVR estimating tools for the general population. When using SCORE, the version that includes HDL-C should be preferably used (<http://www.heartscore.org>) (33).

The proposed algorithm stratifies RA according to RA-related characteristics influencing CVR (3, 4, 8, 9, 11-20, 24). “**Low-risk RA” (LR-RA)** is defined as seronegative, non-erosive RA in patients without extraarticular manifestations, in long-term (>1 year) remission (CDAI ≤ 2.8 or SDAI ≤3.3 or DAS28-ESR≤2.6), without active arthritis or persistently elevated C-reactive protein or erythrocyte sedimentation rate, with well-preserved physical function (HAQ-DI≤0.5), without high cumulative disease activity, not currently using glucocorticoids and without high cumulative glucocorticoid dose (≥40g). All other patients are classified as **HR-RA** (Figure 1). Because employing exact values of all the specific measures in planning LM might not be feasible, the RA stratification should be based on clinical judgment using physical examination, laboratory results, medical history and reports from the involved rheumatologists. Nevertheless, some of these measures are frequently assessed by rheumatologists, and their provision to providers administering LM may facilitate their decision-making.

Patients with LR-RA can follow CVP guidelines for the general population, but goal LDL-C of at least <3 mmol/L (115 mg/dL) should be considered in all individuals. In HR-RA, reclassification into a one-level higher CVR-category (implying lower goal LDL-C) should be considered (Figure 1).

Patients with low RA activity and remission can have residual inflammation that may promote atherogenesis (93-96). Therefore, we introduced relatively strict definition of LR-RA. Moreover, as of yet, patients with borderline profile between LR-RA and HR-RA should be treated as having HR-RA.

In theory, the proposed method might reduce undertreatment of the HR-RA and/or overtreatment of the LR-RA population compared to some of the current methods that do not significantly reclassify RA patients into higher CVR categories and/or do not distinguish between RA populations with different CVR levels. Nonetheless, prospective studies with hard CVD outcomes are necessary in order to determine the optimal strategy for CVR stratification and LM in RA. Despite difficulties with CVR estimation, we are likely to err less if we adopt a proactive approach and attempt to stratify CVR in RA at the current level of knowledge than if we avoid considering CVR-enhancing RA-related CVRFs while awaiting robust evidence.

## Subclinical CVD in RA and carotid ultrasound

Due to the high occurrence of unrecognized CVD in RA (29, 30), pro-active approach to CVD diagnosing is necessary for appropriate treatment and prevention. Subclinical atherosclerosis can be unmasked by detection of plaques on carotid ultrasound, which imply very-high CVR requiring a strict lipoprotein control (Figure 1) (33).

The occurrence of subclinical carotid plaques in RA is increased, and they strongly predict CV events (17, 97-101). However, carotid plaques in RA are not sufficiently predicted by current methods for CVR estimation (31, 32, 102). E.g., optimal cutoff values of SCORE and Framingham Score for predicting carotid plaques appear to be strikingly low (SCORE 0.5% and Framingham Score 7.3%) in some RA patients (103).

Carotid plaques were observed in 13% RA patients with low, 63% with moderate and 80% with high CVR according to SCORE adjusted for RA using the 2010 EULAR method, and in 24% of RA women with SCORE=0 (in 38% of those with concurrent hypercholesterolemia and/or age>49.5 years) (31, 32). Hence, carotid ultrasonography can be meaningful in RA patients from the low to high ESC CVR-categories, and particularly important in the moderate CVR-category. As the presence of plaques is related to RA-specific factors, including inflammation (17), their assessment may be especially relevant in HR-RA.

Carotid ultrasound is a relatively feasible, cheap and non-invasive method that can be performed by devices for musculoskeletal imaging. It seems therefore sensible to integrate it more broadly into the assessment of patients with dubious CVR, especially in HR-RA (if practical and economic settings allow for it).

Nonetheless, future research is needed as the effect of carotid-ultrasound guided LM on CVD morbidity/mortality in RA has not been determined yet.

CVR estimation may be also facilitated by other vascular parameters including ankle-brachial index (33, 97).

## General considerations regarding CVR estimation and LM

All diabetics >40 years of age should use statins, and this treatment may be considered also in younger diabetics with pronounced CVR (e.g., microvascular complications or multiple CVRFs) (33). It remains to be investigated if similar approach would be beneficial also in HR-RA.

It is important to emphasize that CVR calculators and guidelines in general are meant to facilitate, not to replace, clinical judgment (the used cutoffs are founded on health-economics evaluations, which may differ between different regions) (33). CVR estimation/LMT should be therefore individualized, taking into consideration the overall situation, including comorbidities, laboratory aberrations, treatment, psychosocial factors, lifestyle, BMI (low and high), waist circumference and biologic age (33).

## Lipid-modifying interventions

LMT in RA should at least follow recommendations for the general population. However, many RA patients, in particular HR-RA (Figure 1), might benefit from intensified LM, with lower LDL-C targets, due to the increased CVR in patients with active/severe RA, inverse relationship between RA activity and LDL-C levels, and cardioprotective effects of statins beyond their lipid-lowering functions.

Efficient control of RA activity is essential in order to reduce CVR, and may also improve some aspects of lipid homeostasis (3, 17).

## Heathy lifestyle

Healthy lifestyle has widespread beneficial effects, e.g. amelioration of lipid metabolism, other CVRFs and inflammation, and should be a cornerstone of LM/CVP (17, 33, 104). RA patients should receive adequate counseling and support (long-term if needed) according to recommendations for the general population, with emphasis on healthy diet, optimal weight/waist circumference, smoking abstention, increasing physical activity and restricting sedentary activities, and psychosocial interventions including stress management (33, 104, 105). An empathic multidisciplinary approach, considering RA-specific aspects, utilizing cognitive behavioral therapy and empowering the patient´s motivation, can be of significant importance (33, 104).

Adults should perform at least 150 min/week of moderate or 75 min/week of vigorous aerobic physical activity, or their equivalent combination (33). Benefits of physical activity have been demonstrated in RA populations: e.g., intensive aerobic and resistance training improved lipid profile, CVR, disease activity and functional status in RA (106). The choice of exercise program should be individualized according to the patients´ preferences (to increase adherence) and physical limitations (104). Patients should be informed that any physical activity (including daily-life activities) is better than none, and that more physical activity is better than some (33).

Diet should follow recommendations for the general population and provide appropriate amounts of calories and macro- and micronutrients in order to achieve optimal weight and avoid malnutrition (17, 33). If proper nutritional status cannot be achieved by diet, deficiencies (e.g. in vitamins) should be appropriately corrected by supplements. Sufficient intake of proteins and amino acids may attenuate inflammation-induced loss of muscle mass and its replacement by fat in RA (5).

In brief, diet should be rich in fiber, vegetables, fruits, berries, legumes, tree nuts, wholegrains, unsaturated fatty acids (in particular olive oil) and seafood (especially oily fish), whereas the content of animal fat, sugar, fructose, salt, processed food and trans-fat should be limited (33). Alcohol should be consumed in moderation (minimization/abstention can be necessary in some individuals such as those with hypertriglyceridemia or using hepatotoxic antirheumatics). The Mediterranean diet can be a good alternative in RA (17).

## Drugs improving lipid metabolism

## Drugs reducing LDL-C

## Statins

Statins are indicated if optimal lipid control cannot be achieved by lifestyle, and in selected patient populations (e.g., diabetics; Figure 1) (33).

In TRACE RA, an RCT examining 3002 RA patients without CVD, atorvastatin 40 mg daily was associated with significant improvement in lipoprotein levels compared to placebo and 34% reduction in major cardiovascular events, whereas safety profile was similar. Although the effect on cardiovascular events was not statistically significant (which might be due to the unexpectedly low event rate), its magnitude corresponded to statin effects in other populations. The event-rate reduction was related to decrease in LDL-C (107).

Post-hoc analyses of RCTs from the general population and observational studies indicate that statins are efficient in primary and secondary CVP and reduce mortality in RA (3, 108-112). Discontinuation of statin treatment is linked to increased total/cardiovascular mortality and cardiovascular morbidity (109, 113-115).

Rosuvastatin treatment, aimed to attain LDL-C ≤1.8 mmol/L, induced carotid plaque regression in RA patients within 18 months (116).

In a study of 49 227 RA patients, protection against ACS increased with cumulative dose and length of statin treatment, and was most prominent in rosuvastatin treated patients (112). Indeed, an early initiation of statin therapy, even in young individuals with a low absolute but high relative CVR, is likely to have the greatest long-term benefits due to the reduction of lifelong CVR (33).

Besides lipoprotein-lowering qualities, statins exert also other beneficial effects, including anti-inflammatory, antithrombotic and antioxidant actions, improvement of endothelial and HDL-C function, plaque stabilization, which may underlie the cardioprotective effects of statins even in non-hyperlipidemic individuals (117-120). These effects may be particularly important in RA. Further research is needed to clarify if statins might be beneficial in a large part of the RA population (in particular HR-RA), irrespective of cholesterol levels, similar to diabetes.

Statins cause various adverse effects including myalgias, hepatopathy, hyperglycemia, autoimmune conditions (including myositis/necrotizing autoimmune myopathy and RA), but serious adverse effects are very rare (121-123). Monitoring for adverse effects should follow recommendations for the general population. Of note, appropriate correction of vitamin D deficiency/insufficiency might help to reduce muscle symptoms in statin-users (124). The risk of hepatopathy may increase in combinations with hepatotoxic drugs. Nevertheless, atorvastatin in TRACE RA was well-tolerated despite combinations with potentially hepatotoxic DMARDs (107). Other studies also indicate that statin treatment in RA has acceptable safety profile, and that it may be cost-effective (22, 110, 125, 126). In addition, statins can induce beneficial side effects, including mitigation of RA activity (107, 125, 127-129).

Further research is needed to clarify which statin regimens are the most suitable in RA with respect to safety and cardioprotective and anti-inflammatory effects. Atorvastatin might be the drug of choice given the available evidence indicating its beneficial effects on CVD, lipids (decreasing LDL-C, TC and TGs) and inflammation, good safety profile and low costs (107, 129, 130). Rosuvastatin might also be a good alternative (112, 116, 130).

## Other drugs reducing LDL-C

Other LDL-C reducing drugs are used primarily in patients who do not sufficiently respond to statins or who do not tolerate them. Adding ezetimibe or PCSK9 inhibitors to statins appears to improve protection against cardiovascular events without any significant increase in adverse events (131).

**Ezetimibe** reduces cardiovascular morbidity by inhibition of intestinal lipid absorption (131). In RA, ezetimibe appears to have similar anti-inflammatory effects as statins, and to counteract endothelial dysfunction and vascular stiffness (118).

**Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitors** substantially reduces CVD morbidity (131-133). Alirocumab and evolocumab have been authorized for treatment of primary hyperlipidemias and secondary CVD prevention. Data on effects of these drugs in RA are missing.

**Fibrates** activate nuclear receptor peroxisome proliferator-activated receptor alpha, leading to multiple effects on lipid metabolism, e.g. reduction of serum TG, LDL-C and very low-density lipoprotein levels, and improvement of LDL-C quality (134, 135). Because of lack of data from RA populations, and given the small but reported risk of autoimmune adverse effects (e.g., autoimmune thrombocytopenia and hepatitis), fibrates should be used with care in RA (136). Nonetheless, there is increasing interest in fibrates in RA treatment due to their beneficial effects on postprandial hypertriglyceridemia and inflammation (137, 138).

## Treatment of other lipid abnormalities

Treatment of other lipid alterations should follow general recommendations (33, 34, 91, 92, 139). Among drugs reducing **TGs** belong statins, fibrates, ezetimibe, niacin and omega-3 fatty acids. Icosapent ethyl is a new promising hypertriglyceridemia treatment, that lowers risk of ischemic events and cardiovascular death, and is well-tolerated (140).

Treatment options for **hyperlipoproteinemia (a)** have been limited and included mainly niacin and apheresis (65). It is therefore noteworthy that novel lipid therapies, e.g. PCSK9 inhibitors, as well as DMARDs, may lower Lp(a) (132, 141, 142).

There are no indications that drugs **increasing HDL-C** levels protect against cardiovascular events (143). Except for DMARDs, there are so far no pharmaceutic drugs available for improving **cell cholesterol transport** (74).

**Conflict of interests:** none.

## Figure 1. Proposed CVR stratification and goal LDL-C in RA

CAD: coronary artery disease. CVD: cardiovascular disease. CVR: cardiovascular risk. CVRF: CVR factor. DM: diabetes mellitus. ESC CVR-category: CVR-categories according to the 2016 European CVP guidelines on CVD prevention (33). LDL-C: low density lipoprotein-cholesterol. LM: lipid management. PAD: peripheral artery disease. RA: rheumatoid arthritis.

In general, LM is stratified according to ESC CVR-categories into three levels. However, patients with CVR-enhancing RA-related factors (“High-risk RA”)l should be considered as having CVR-category that is one level higher compared to the general population. Use of carotid ultrasound can help to reclassify patients into very-high ESC CVR-category.

All diabetics >40 years of age should use statins. This treatment may be considered also in younger diabetics if they have pronounced CVR (e.g., microvascular complications or multiple CVRFs).

The suggested non-HDL targets for the very-high, high and low/moderate CVR category are <2.6, <3.3 and <3.8 mmol/L (<100, <130 and <145 mg/dL).

a Including cholesterol >8 mmol/L (>310 mg/dL; e.g., in familial hypercholesterolemia) or blood pressure ≥180/110 mmHg.

b Except for young people with type 1 DM without other major CVRFs who may be at low or moderate risk, and those specified in very-high ESC CVR-category.

c Glomerular filtration rate (GFR) 30–59 mL/min/1.73 m2.

d Including smoking, marked hypercholesterolemia or marked hypertension.

e GFR <30 mL/min/1.73 m2.

f <115 mg/dL.

g <100 mg/dL.

h 100-200 mg/dL.

i <70 mg/d.

j 70-135 mg/ dL.

k “Low-risk RA” is defined as seronegative, non-erosive RA in patients without extraarticular manifestations, in long-term (>1 year) remission (CDAI ≤ 2.8 or SDAI ≤3.3 or DAS28-ESR≤2.6), without acute arthritis and persistently elevated acute phase reactants (C-reactive protein or erythrocyte sedimentation rate), with well-preserved physical function (HAQ-DI≤0.5), without high cumulative disease activity, not currently using glucocorticoids and without high cumulative glucocorticoid dose (≥40g). All other patients are classified as “High-risk RA”.

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