# Management of dyslipidaemia in high-risk patients with recent-onset rheumatoid arthritis: targets still not met despite specific recommendations. Results from the ESPOIR cohort during the first five years of follow-up

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## Abstract

### Objective

*Reduction of LDL-cholesterol (LDLc) is essential to decrease the cardiovascular mortality in rheumatoid arthritis (RA). Between 2005 and 2010, French recommendations for dyslipidaemia defined the LDLc target based on the number of cardiovascular risk factors. In 2006, it was recommended to consider LDLc objectives with RA being counted as an additional cardiovascular risk factor. Our objective was to assess lipid target achievement between 2006 and 2010 in a cohort of patients with recent-onset RA.*

### Method

*814 patients were included between 2002 and 2005 in a French cohort of patients with early arthritis and a high probability of RA (ESPOIR). Repeated cross-sectional analyses for cardiovascular risk factors, cholesterol levels were performed every year from 2006 to 2010 to determine lipid profile and achievement of the LDLc goal according to the French guidelines.*

### Results

*On the 620 patients analysed at the first point, 77% were female, 89.8% fulfilled the ACR criteria for RA and 2.7% received a statin. The proportion of patients failing to achieve the LDLc target did not improve following the publication of specific RA guidelines in 2006 (15.3 to 22.5% between 2006 and 2010). In patients with the highest cardiovascular risk, more than 58% did not reach the LDLc target.*

### Conclusion

*Specific recommendations for RA published in 2006 decreased LDLc target but did not improve management of dyslipidaemia in daily life which remained suboptimal particularly in patients at highest risk.*

**Key words**

rheumatoid arthritis, cardiovascular risk, dyslipidaemia, statin

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## Introduction

Rheumatoid arthritis (RA) leads to an increase risk in cardiovascular (CV) morbidity and mortality compared with the general population, and CV complications of RA cause death in one half of the cases (1–3). RA is an independent risk factor that is as critical as diabetes (4–7). RA patients must be considered to be at high CV risk. Several studies demonstrate that although dyslipidaemia management is essential for reducing CV morbidity and mortality (8,9), such management is insufficient in RA patients (10,11).

From 2005 to 2010, French dyslipidaemia management guidelines were based on the recommendations of the AFSSAPS (the French Health Products Safety Agency) (12), and since 2011, on the recommendations of the European Society of Cardiology (ESC) (13). These guidelines combine the LDL-cholesterol (LDL-c) level (therapeutic target) with the CV risk assessed by examining traditional risk factors (age, gender, tobacco use, hypertension, diabetes and family history).

In RA, the increased CV risk is only partially explained by traditional risk factors. The chronic inflammation and metabolic changes that accompany RA accelerate atherosclerosis and increase CV risk. The increased risk is greater in patients with long-standing RA and presence of rheumatoid factor or anti-CCP and extra-articular manifestations (14). Among patients with recent-onset RA, although some data did not show increased risk for CV mortality (15), others studies have demonstrated premature increased myocardial infarction risk as soon as the RA is diagnosed in the year following diagnosis (16), and for the Mayo Clinic, even before patients fulfill RA diagnostic criteria (17).

In France, clinical practice guidelines based on published evidence and expert opinion have considered since 2006 RA as an additional risk factor for defining LDL-cholesterol objectives according AFSSAPS recommendations (12,18). Since 2010, the European League Against Rheumatism (EULAR) recommended assessing CV risk yearly in RA patients using risk equations, the SCORE equation or a nationally validated equation (19). The risk should thus be multiplied by 1.5 when RA fulfills two in three of the following conditions: disease duration of over 10 years, positive rheumatoid factor or presence of anti-CCP, extra-articular manifestations. Updated EULAR recommendations on CV risk management should be soon published and will include imaging markers for risk prediction as well as multiplying CV risk score by a factor of 1.5 regardless of determinants of the RA (20).

The objective of the present study was to assess achievement of the lipid objectives defined by the LDLc target according to French guidelines every year from 2006 to 2010 in a cohort of recent-onset RA patients (ESPOIR cohort) (12, 18).

## Methods

### *Study population*

The ESPOIR (*Evaluation et Suivi de POlyarthrites Indifférenciées Récentes*) cohort initiated by the *Société Française de Rhumatologie* (French Rheumatology Society) is a prospective, national, multicenter cohort (21). Patients aged over 18 and under 70, with a clinical diagnosis of RA as certain or probable or who had experienced at least two peripheral arthritis episodes, lasting from six weeks to six months, without taking corticosteroids and/or DMARDs for a period of more than two weeks were included from December 2002 to March 2005. These patients were then followed every six months for two years, and then every year. After two years, follow-up of the patients with a diagnosis other than RA or with undifferentiated arthritis was stopped. Repeated cross-sectional analyses for CV risk factors, LDL and HDL cholesterol levels were performed every year between 2006 and 2010 to determine the proportion of patients achieving the LDL-c goal according to the French guidelines considering RA as an additional risk factor from 2006.

### *LDL cholesterol targets by level of cardiovascular risk*

The risk factors needed to determine the LDL-c target according to French guidelines (12) were recorded yearly

**Table I.** Demographic, RA characteristics and cardiovascular risk factors during 5 years of follow-up [mean ± SD or number (%)].

| | 2006 n=620 | 2007 n=558 | 2008 n=530 | 2009 n=515 | 2010 n=486 |
|---|---|---|---|---|---|
| Gender female | 475 (77.0) | 433 (77.6) | 413 (77.9) | 400 (77.7) | 384 (79) |
| Age, years | 51 ± 12.1 | 52.1 ± 11.8 | 53.3 ± 11.8 | 54.4 ± 11.5 | 55.6 ± 11.4 |
| Males ≥ 50 years | 100/145 (69.0) | 88/125 (70.4) | 87/117 (74.4) | 88/115 (76.5) | 82/102 (80.4) |
| Females ≥ 60 years | 105/475 (22.1) | 108/433 (24.9) | 123/413 (29.8) | 131/400 (32.8) | 145/384 (37.8) |
| Smoking | 112 (18.1) | 103 (18.5) | 105 (19.8) | 104 (20.2) | 93 (19.1) |
| Diabetes | 29 (4.7) | 25 (4.5) | 27 (5.1) | 25 (4.9) | 26 (5.4) |
| History of CVD | 16 (2.6) | 15 (2.7) | 19 (3.6) | 18 (3.5) | 13 (2.7) |
| Hypertension | 134 (21.6) | 131 (23.5) | 135 (25.5) | 129 (25.1) | 140 (28.8) |
| Total cholesterol (g/L) | 2.07 ± 0.44 | 2.11 ± 0.43 | 2.15 ± 0.42 | 2.13 ± 0.45 | 2.13 ± 0.43 |
| HDLc (g/L) | 0.68 ± 0.22 | 0.66 ± 0.20 | 0.64 ± 0.19 | 0.65 ± 0.20 | 0.66 ± 0.20 |
| LDLc (g/L) | 1.18 ± 0.37 | 1.24 ± 0.37 | 1.28 ± 0.36 | 1.25 ± 0.38 | 1.24 ± 0.36 |
| HDLc <0.4 (g/L) | 41 (6.6) | 32 (5.7) | 36 (6.8) | 33 (6.4) | 22 (4.5) |
| HDLc ≥0.6 (g/L) | 370 (59.7) | 313 (56.1) | 273 (51.5) | 288 (55.9) | 275 (56.6) |
| FRS ≥ 20% | 13 (2.1) | 19 (3.4) | 18 (3.4) | 13 (2.5) | 13 (2.7) |
| Mean duration of 1st symptoms (years)[a] | 2.92 ± 1.03 | 4.05 ± 1.01 | 5.09 ± 1.00 | 6.07 ± 0.98 | 7.06 ± 1.00 |
| DAS28[a] | 2.92 ± 1.32 | 2.88 ± 1.34 | 2.75 ± 1.35 | 2.81 ± 1.34 | 2.66 ± 1.29 |
| AntiCCP antibodies | 294/611 (48.1) | 244/550 (44.4) | 234/515 (45.4) | 217/484 (44.8) | 197/443 (44.5) |
| Rheumatoid factor positivity[a] | 287/610 (47) | 262/550 (47.6) | 249/516 (48.3) | 233/485 (48) | 255/450 (56.7) |
| 1987 ACR criteria | 530/620 (85.5) | 492/558 (88.2) | 472/530 (89.1) | 462/515 (89.7) | 446/486 (91.8) |
| 2010 ACRcriteria | 557/620 (89.8) | 512/558 (91.8) | 492/530 (92.8) | 481/515 (93.4) | 453/486 (93.2) |
| DMARD | 491/620 (79.2) | 435/558 (78) | 409/530 (77.2) | 389/515(75.5) | 369/485 (76.1) |
| Current steroids[a] | 209/620 (33.7) | 160/558 (28.7) | 146/530 (27.5) | 132/515 (25.6) | 108/486 (22.2) |
| Cholesterol-lowering drug therapy | 17/620 (2.7) | 14/558 (2.5) | 13/530 (2.8) | 16/515 (3.1) | 12/486 (2.5) |

History of cardiovascular disease (CVD): myocardial ischaemia or stroke; CHD: coronary heart disease; FRS: Framingham risk score; [a]$p<0.05$.

from 2006 to 2010. They included age (male 50 years or over, female 60 years or over), tobacco use (current or quit less than three years ago), hypertension (treated or not), type 2 diabetes (treated or not), and HDL-c <0.40 g/L (1 mmol/L) regardless of gender. Information on family history of premature coronary heart disease, which is one of the risk factors, was not available for this cohort. If HDL-c ≥0.60 g/L (1.5 mmol/L): subtract "one risk" from the risk level score. The LDL-c target was determined considering RA as an additional risk factor as recommended (18). LDL-c concentrations must be under 2.20 g/L (5.7 mmol/L) in the absence of any risk factors; under 1.90 g/L (4.9 mmol/L) with one single risk factor; under 1.60 g/L (4.1 mmol/L) with two risk factors and under 1.30 g/L (3.4 mmol/L) with three or more risk factors. In high CV risk patients (patients with a documented history of CV disease, high-risk type 2 diabetes with renal impairment or at least two risk factors), LDL-c concentrations must be less than 1 g/L (2.6 mmol/L) (13). The LDL-c target must also be less than 1 g/L when the CV event risk score calculated with the Framingham equation is ≥ 20%.

*Statistical analysis*

Statistical analysis was performed using Stata 13 software (StataCorp LP, College Station, TX, US). The tests were two-sided, with a type I error set at $\alpha$=0.05. Baseline characteristics were presented as mean (±standard-deviation) or median [interquartile range] according to statistical distribution for continuous data (assumption of normality assessed using the Shapiro-Wilk test) and as the number of patients and associated percentages for categorical parameters. Longitudinal analyses (repeated measures) were performed using mixed models (linear for quantitative dependent variable and generalised linear – logit – for dichotomous dependent variable as the change in dyslipidaemia prevalence), perfectly appropriate to model the non-independence of data considering patient effect as random-effect. Multivariate analyses were performed with an adjustment on age, gender, disease duration, DAS28, Rheumatoid factor positivity, steroid use (as fixed effects) and center (as random-effect). Then, sub-groups analyses were proposed according to gender. For non-repeated measures, usual statistical tests were performed: chi-squared or Fisher's exact tests for categorical variables and Anova or Kruskal-Wallis test if assumptions of Anova were not met (normality and homoscedasticity verified using Bartlett test) for quantitative parameters. Finally, to take into account the missing data, a sensitivity analysis was performed to characterise the statistical nature of missing data and to propose the most appropriate imputation method (estimates using Verbeke and Molenberghs).

## Results

*Study population*

The ESPOIR cohort included a total of 813 patients from December 2002 to March 2005. Of these patients, data were available for 620 patients in 2006. In this first year, 530 patients (85.5%) fulfilled the 1987 American College of Rheumatology (ACR) criteria (22) and 557 (89.8%) the 2010 ACR/European League Against Rheumatism (EULAR) criteria (23). In 2007, 558 patients could be analysed, in 2008: 530, in 2009: 515, and in 2010: 486. Over 90% of patients met ACR/EULAR criteria for RA (Table I). Table I summarises the main characteristics of the population studied each year from 2006 to 2010. The 620 patients analyzed at the

first year were mainly female (77%). They were 51±12.1 years old and mean symptom duration was 2.92±1.03 years. The 28-joint Disease Activity Score (DAS28) was 2.92±1.32. Seventy-nine percent (79%) received a DMARD and 33.7% received steroids. Forty-eight per cent (48%) had anti-CCP antibodies and 47% had rheumatoid factor (RF), and this increased significantly to 56.7% after 5 years of follow-up (Table I). During follow-up, the DAS28 decreased significantly as did the proportion of patients receiving steroids (Table I).

Three per cent (3%) of the patients were treated with statins and this did not significantly vary during the follow-up.

*Lipid target achievement*

The proportion of patients failing to achieve the recommended LDL-c target did not improve during the 5 years of follow-up: 15.3 % in 2006; 18.5 % in 2007; 22.5 % in 2008; 19.4 % in 2009, 18.5 % in 2010 (Fig. 1A). As described previously, sensitivity analysis was performed to take into account possible impact of missing data on results. Similar results were obtained (data not shown). It was in men that the prevalence of unachieved LDL-c targets was higher, regardless of the year of follow-up (2006: 24.8 % *vs*. 12.4%, $p<0.001$; 2007: 34.4% *vs*. 13.9%, $p<0.001$; 2008: 34.2% *vs*. 19.1%, $p=0.001$; 2009: 29.6% *vs*. 16.5%, $p=0.001$; 2010: 28.4% *vs*. 15.9% $p=0.004$) (Fig. 1B). The proportion of patients not achieving the target LDL-c level varied according to the level of CV risk. Although nearly all patients without risk factors had an LDL-c level within the target, the number of patients failing to achieve the therapeutic objective progressively increased with the number of risk factors. Among patients with only one risk factor, no more than 5 % did not have the target LDL-c level, while over 58% of high risk patients did not achieve therapeutic objectives (Table II). Inertia was calculated for the 353 patients with a longitudinal follow-up during the five years (Table III). Inertia was defined as the failure to achieve LDLc target the next year. A total of 26 (7 %) patients in 2006, 30 (8%) in 2007, 38 (11%) in 2008, 28 (8%) in 2009 had LDLc inertia without significant change during the follow-up (Table III). There was a higher proportion of inertia among patients at highest risk (3 associated risk-factors and high risk).

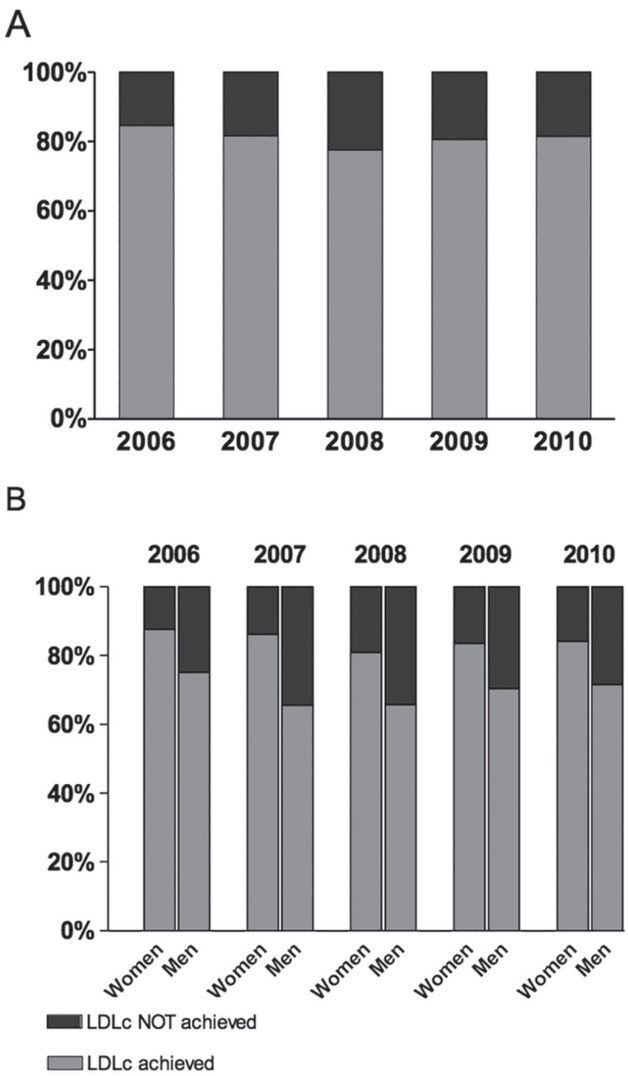


**Fig. 1.** Achievement of LDL-cholesterol objectives according to the French guidelines in with recent-onset rheumatoid arthritis during the 5 years of follow-up
**A**: all patients
**B**: by sex

## Discussion

Specific RA guidelines published in 2006 considering RA as an additional risk factor did not increase the proportion of patients who reached the LDL-c target. Management of dyslipidaemia remains suboptimal in France since the LDL-c target was not achieved in 15 to 22% of RA patients, and particularly in those patients with the highest CV risk. More males and more than half of patients with high CV risk did not reach the lipid target. It should be noted that specific guidelines published in 2006 for RA taking into account the excess of CV risk (18), led to a decrease in LDLc target but did not improve the proportion of patients reaching the target LDLc level. RA should be regarded as a condition leading to very high CV disease risk, even in the early stages of the disease (16). The increased CV risk is only partially explained by traditional risk factors, and the systemic inflammation associated with RA promotes atherogenesis and exacerbates established cardiovascular risk factors (24). In order to predict 10-year CV mortality risk, different equations were developed with algorithm combination taking into account the traditional CV risk factors such as age, sex, smoking status, hypertension, genetic, LDLc levels. In RA patients, although CV risk prediction scores correlated with vascu-

**Table II.** Proportion of patients in whom LDLc target was not achieved according to the level of cardiovascular risk. Number (%).

| Level of risk according to French Guidelines (LDLc target) | 2006 (n=620) | 2007 (n=558) | 2008 (n=530) | 2009 (n=515) | 2010 (n=486) |
|---|---|---|---|---|---|
| No risk factors (5.7 mmol/L=2.2 g/L) | 0/146 (0) | 0/122 (0) | 0/96 (0) | 0/103 (0) | 0/82 (0) |
| 1 risk factor (4.9 mmol/L=1.9 g/L) | 5/192 (3) | 5/169 (3) | 8/161 (5) | 5/139 (4) | 2/135 (1) |
| 2 risk factors (4.1 mmol/L=1.6 g/L) | 27/165 (16) | 30/141 (21) | 28/137 (20) | 34/148 (23) | 23/140 (16) |
| ≥3 risk factors (3.4 mmol/L=1.3 g/L) | 30/69 (43) | 44/86 (51) | 48/85 (56) | 30/79 (38) | 37/81 (46) |
| High risk (2.6 mmol/L=1 g/L) | 33/48 (69) | 24/40 (60) | 35/51 (69) | 31/46 (67) | 28/48 (58) |

**Table III.** Proportion of patients with inertia year over year among the 357 patients with a longitudinal follow-up during the 5 years. Inertia was defined as the failure to achieve LDLc target the next year. Number (%).

| Failure to achieve LDLc by risk category (LDLc target) | 2006 | 2007 | 2008 | 2009 | 2010 |
|---|---|---|---|---|---|
| No risk factors (5.7 mmol/L=2.2 g/L) | 0/101 | 0/90 | 0/71 | 0/78 | 0/66 |
| 1 risk factor (4.9 mmol/L=1.9 g/L) | 1/98 (1) | 3/104 (3) | 4/112 (4) | 4/99 (4) | 2/100 (2) |
| Patients with inertia | 0/1 (0) | 1/3 (33) | 1/4 (25) | 1/4 (25) | NA |
| 2 risk factors (4.1 mmol/L=1.6 g/L) | 13/97 (13) | 15/92 (16) | 18/94 (19) | 21/101 (21) | 10/95 (10) |
| Patients with inertia | 5/13 (38) | 5/15 (33) | 7/18 (39) | 8/21 (38) | NA |
| ≥3 risk factors (3.4 mmol/L=1.3 g/L) | 18/39 (46) | 26/48 (54) | 33/56 (59) | 21/52 (40) | 25/61 (41) |
| Patients with inertia | 14/18 (78) | 18/26 (69) | 21/33 (64) | 12/21 (57) | NA |
| High risk (2.6 mmol/L=1 g/L) | 16/22 (73) | 14/23 (61) | 13/24 (54) | 16/27 (59) | 20/35 (57) |
| Patients with inertia | 7/16 (44) | 6/14 (43) | 9/13 (69) | 7/16 (44) | NA |

lar function and morphologic changes (25), CV risk is underestimated by the SCORE, Framingham and new Pooled Cohort equations even after applying a 1.5 multiplication factor depending on RA characteristics as recommended by EULAR (26–28). Further studies are needed to clarify the effect the new American College of Cardiology/American Heart Association guidelines would have by expanding the proportion of RA patients recommended for therapy (29), but clinical inertia may limit the benefit of expanded statin therapy recommendations. In addition to having their CV risk underestimated, RA patients are under treated both in primary and secondary prevention (11, 30, 31). RA was associated with significantly less frequent initiation of statins compared with non-RA patients after myocardial infarction (31). In our study, as in the French general population, the proportion of patients who did not achieve cholesterol goals varied with the level of CV risk (32). A majority of patients with multiple risk factors and patients with the highest risk did not attain the LDL-c targets recommended by French guidelines and an even higher proportion did not attain targets stipulated by the ESC guidelines (32). The initiation of statin therapy is nevertheless associated with a lower risk of mortality in patients with RA (33). This treatment-risk paradox may be explained by clinical inertia due to fear of muscle toxicity (34, 35), underestimation or ignorance of the CV risk. Clinical inertia can be defined as physician error in initiating or intensifying treatment when indicated (36). Clinical inertia results from a combination of patient, health care professional and health care system factors. Statin induced myotoxicity, being female, the presence of comorbidities and the use of multiple, complex medications such as DMARDS or biologics may contribute to clinical inertia in RA patients. Statin induced myotoxicity includes myalgia, asymptomatic raised CK, rarely myositis or rhabdomyolysis, mostly self-limited resolving within weeks to months of discontinuing the medication. A metanalysis including 35 randomised trials did not show significant increase risk of CK elevations, rhabdomyolysis or myalgias contrasting with the 5–20% incidence seen in observational studies (35). Risk factors are related to the patient (advanced age, female gender, Asian descent, low body mass index, intense exercise, excess alcohol consumption, drug abuse, untreated hypothyroidism, diabetes, impaired renal or hepatic function, intercurrent infections or vitamin D deficiency), to drug interactions (protease inhibitors, macrolide antibiotics, azole antifungals, non-dihydropyridine calcium channel blockers, cyclosporine, amiodarone, grapefruit or cranberry juice) and to statin itself, hydrophilic statins being less myotoxic than lipophilic statins. Rheumatologists identify and manage CV risk factors less frequently than primary care physicians do, but RA patients saw their rheumatologist as often or more often than their primary care physician (37, 38). In addition, primary care physicians less frequently manage CV risk factors in RA patients than in the general population or in patients with type 2 diabetes (37). Key barriers to managing dyslipidaemia include inadequate knowledge when estimating CV risk. In addition to improving cholesterol guidelines for RA patient management, educating rheumatologists on screening and identifying high-risk

patients should be improved by including imaging and laboratory markers for risk prediction (20, 39, 40). Nurse-led programs on RA comorbidity management might be useful to facilitate the identification and management of cardiovascular risk factors by primary care general practitioners and/or rheumatologists (41).

## Conclusion

Regardless of the specific recommendations for managing CV risk in RA patients and more widespread cholesterol screening, dyslipidaemia management remains suboptimal, especially among those patients at the highest risk. Failure to achieve lipid target in most high-risk patients raises the question of the identification of patients with the highest CV risk and of the clinical inertia defined as no treatment initiation or intensification when indicated. In this context, it is still unclear whether the expansion by the new recommendations of the indications for statin therapy would expand lipid target achievement. Nurse-led programmes on RA comorbidities should be considered in addition to expanding cholesterol guidelines.

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