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Application of the European Society of Cardiology, Adult Treatment Panel III and American College of Cardiology/American Heart Association guidelines for cardiovascular risk management in a French cohort of rheumatoid arthritis

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ABSTRACT

Background: Patients with rheumatoid arthritis (RA) have greater rates of cardiovascular mortality and RA is an independent cardiovascular risk factor. For the management of cholesterol, the American College of Cardiology/American Heart Association (ACC/AHA) developed new guidelines for the general population. None of the European or American guidelines are specific to RA. The European League Against Rheumatism (EULAR) recommends applying a coefficient to cardiovascular risk equations based on the characteristics of RA. Our objective was to compare the three different sets of guidelines for the eligibility of statin therapy in RA-specific population with very high risk of cardiovascular disease.

Methods and results: We calculated the proportion of patients eligible for statins according to the guidelines of the European Society of Cardiology (ESC), the Adult Treatment Panel III (ATP-III) and the ACC/AHA in a French cohort of statin-naïve RA patients at least 40 years age. Of the 547 women and 130 men analyzed, statins would be recommended for 9.1% of the women and 26.4% of the men, 15.6% of the women and 53.1% of the men, 38.8% of the women and 78.5% of the men, according to the ESC, ATP-III and ACC/AHA guidelines respectively.

Conclusions: In RA patients, as has been observed in the general population, discordance in risk assessment and cholesterol treatment was observed between the three sets of guidelines. The use of the new ACC/AHA guidelines would expand the eligibility for statins and may be applied to RA population a condition at very high risk of cardiovascular disease.

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Rheumatoid Arthritis (RA) leads to an increase in mortality compared with the general population and cardiovascular disease accounts for approximately half of the death [1–3]. RA itself is an independent risk factor for cardiovascular disease that carries as much weight as diabetes [4–7]. Then, RA should be regarded as a condition at very high risk of cardiovascular disease. In the general population, strategies for preventing cardiovascular disease are based on calculations of 10-year cardiovascular mortality risk using the Systematic Coronary Risk Evaluation (SCORE) in Europe and the Framingham score in the United States on the basis of traditional risk factors. In RA, the increased cardiovascular risk is only partially explained by traditional risk factors and inflammation not included as a parameter in SCORE or Framingham equations, may account for the excess cardiovascular risk. The systemic inflammation associated with RA promotes atherogenesis and exacerbates established cardiovascular risk factors. Other factors associated with an increased cardiovascular risk in RA are disease duration, rheumatoid factor or anti-cyclic citrullinated peptide (anti-CCP) positivity, severe disease with extraarticular manifestations. How to capture the extra risk beyond the traditional risk factors in clinical practice is a debated

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[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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issue [8]. Over the course of RA, The European League Against Rheumatism (EULAR) guidelines for the management of cardiovascular risk recommend an annual assessment depending on the SCORE equation or validated national risk equations [9]. The risk score should be then multiplied by 1.5 when RA has two of the following three characteristics: disease progression of over 10 years, positive rheumatoid factor or anti-CCP, and extra-articular symptoms [9]. While the European Society of Cardiology (ESC) guidelines recommend statin therapy for primary prevention on the basis of a combined assessment of low-density lipoprotein cholesterol (LDLc) level and the 10-year risk of cardiovascular mortality using the SCORE equation [10], the Adult Treatment Panel-III (ATP-III) guidelines were based on the combination of LDLc and the 10-year risk of coronary heart disease only as calculated with the Framingham risk calculator [11]. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines have just been updated and a new equation evaluating the risk of all hard atherosclerotic cardiovascular disease (ASCVD) in the general population was validated [12]. In a cohort of patients with definite RA, we calculated the proportion of patients eligible for statins according to the guidelines of the ESC, ATP-III and ACC/AHA by applying a coefficient of 1.5 to the risk equations if necessary, as recommended by the EULAR. Our objective was to compare the three different sets of guidelines for the eligibility of statin therapy in RA-specific population with very high risk of cardiovascular disease.

1. Methods

1.1. Study population

COMEDRA is a multicenter French cohort study evaluating the impact of nurse-led program on the management of comorbidities in patients with RA [13]. The study included the report of pre-existing comorbidities, the presence of risk factors and the implementation of the recommendation for the detection and/or management of such comorbidities. Patients with RA according to the 1987 American College of Rheumatology criteria, aged between 18 and 80 and with disease considered by the treating rheumatologist to have been stable for at least three months, were recruited from March 2011 to December 2011. Each patient gave their free, informed consent to take part and the local French authorities approved the study. The eligibility for statin therapy was assessed for each patient aged 40 years or older not receiving statins.

1.2. Cardiovascular risk stratification

The 10-year risks for cardiovascular mortality (ESC), coronary heart disease (ATP-III) and ASCVD (ACC/AHA) were calculated for each individual on the basis of the three equation scores using online calculators [14–16]. A coefficient of 1.5 was applied when a patient presented two of the following three characteristics: disease progression for over 10 years, rheumatoid factor or anti-CCP positivity and extra-articular signs and symptoms [9]. The recommended thresholds were used for the application of the European (ESC), ATP-III and ACC/AHA statin treatment guidelines. Based on each guideline, the patients were classified into 3 categories: "no treatment", "treatment considered", "recommended treatment". eTables 1–3 in the Supplementary data presents the details of these 3 treatment categories by each guideline.

ESC guidelines are based on the SCORE equation, which determines the 10-year cardiovascular mortality risk of a first fatal atherosclerotic event including heart attack, stroke or other occlusive arterial disease [10]. The guidelines were validated in the French population. The SCORE equation was determined for each patient using an online calculator [14] because this is what is used to consider the HDL cholesterol, a major cardiovascular risk factor which frequently decreases in RA [17]. The other parameters of this equation are age, gender, tobacco use, systolic blood pressure and cholesterol. This equation validated in patients 40 to 65 years of age identifies patients with very high (SCORE > 10%), high (5% < SCORE < 10%) or moderate (1% < SCORE < 5%) cardiovascular risk [10]. Initiating statin treatment is recommended when cardiovascular risk is >10% and LDL cholesterol is >1.8 mmol/l (0.7 g/l) and when cardiovascular risk is >5% and <10% and LDL cholesterol is >2.5 mmol/l (1 g/l) [10]. Initiating stains may also be considered in patients with cardiovascular risk of >10% and LDL cholesterol of <1.8 mmol/l (0.7 g/l), when cardiovascular risk is >5% and <10% and LDL cholesterol is <2.5 mmol/l (1 g/l), when cardiovascular risk is >1% and <5% and LDL cholesterol is >2.5 mmol/l (1 g/l) and when cardiovascular risk <1% and LDL cholesterol is >4.9 mmol/l (1.9 g/l) [10].

ATP-III guidelines are based on 10-year coronary heart disease risk. The risk factors taken into consideration in this equation are age, sex, tobacco use, HDL-cholesterol, hypertension and blood pressure treatment. The risk was determined with the online calculator [15]. It is recommended to initiate statins in patients with a calculated risk of >20% when their LDL cholesterol is >100 mg/dl (2.5 mmol/l), when LDL cholesterol is >130 mg/dl (3.4 mmol/l) and calculated risk is 10% to 20% and there are two other cardiovascular risk factors, when LDL cholesterol is >160 mg/dl (4.1 mmol/l), calculated risk is <10% and there are two other cardiovascular risk factors, and when LDL cholesterol is greater than 190 mg/dl (4.9 mmol/l) [11]. Statin treatment may also be considered in patients with a calculated risk >20% when LDL cholesterol is <100 mg/dl (2.5 mmol/l), when LDL cholesterol is 100 to 129 mg/dl (2.5 and 3.4 mmol/l) and calculated risk is 10% to 20% and there are two other cardiovascular risk factors, and when LDL cholesterol is 160 to 189 mg/dl (3.4–4.9 mmol/l) [11].

ACC/AHA guidelines are based on the 10-year atherosclerotic cardiovascular disease risk (the Pooled Cohort Equations) that determines the risk of fatal and non-fatal myocardial infarction, other coronary heart disease (CHD) mortality and stroke [12]. The risk was determined with the online calculator [16]. It is recommended to initiate statins in all patients with clinical atherosclerotic cardiovascular disease or with elevation of LDL cholesterol ≥190 mg/dl (4.9 mmol/l) [12]. It is recommended to initiate statins in patients 40–75 years of age with diabetes and LDL cholesterol greater than 70 mg/dl, and in patients with a cardiovascular risk of 7.5% or higher, 40–75 years of age and LDL cholesterol greater than 70 mg/dl [12]. Statins can be considered in patients whose calculated risk is 5% to 7.5% [12].

1.3. Statistical analyses

Statistical analysis was performed using Stata 13 software (StataCorp LP, College Station, TX, US). Baseline characteristics were presented as mean (±standard-deviation) or median (interquartile range) for continuous data (assumption of normality assessed using the Shapiro–Wilk test) and as the number of patients and associated percentages for categorical parameters. Comparisons of the three equation scores were made using the Stuart–Maxwell test for categorical parameters. The tests were two-sided, with a Type I error set at $\alpha = 0.05$. Since the SCORE equation was validated for the population aged 40–65 years, an additional sub-group analysis was performed by age.

2. Results

2.1. Study population

There were 970 patients enrolled in the COMEDRA study. Among this initial population, patients were excluded because they were receiving a statin (n = 168), were under the age of 40 (N = 49) or because there were missing data (n = 76). The 677 analyzed patients were mainly women (N = 547, 80.8%) with a mean RA disease duration of 11.4 (6.5–19.8) years (Table 1). The RA characteristics and the cardiovascular risks are presented in Table 1 for all patients and in Tables 2 and 3 for patients aged 40–65 and those over the age of 65. The EULAR coefficient needed to be applied in 59.9% of the patients.

2.2. Treatment recommendations based on the different guidelines

Based on the ESC guidelines, 9.1% of the women and 26.1% of the men were included in the "treatment recommended" category. The "treatment considered" group comprised 43.9% of the women and 60.8% of the men and the "no treatment" category 47% of the women and 13.1% of the men (Fig. 1A, Table 4 and eTable 1 in the Supplementary data).

Using the ATP-III guideline, 15.5% of the women and 53.1% of the men were categorized in the "treatment recommended" group, 11.7% of the women and 18.4% of the men in the "treatment considered" group and 72.8% of the women and 28.5% of the men in the "no treatment" category (Fig. 1A, Table 4 and eTable 2 in the Supplementary data).

Based on the ACC/AHA guidelines, the "treatment recommended" group included 38.8% of the women and 78.5% of the men. The "treatment considered" group comprised 11.5% of the women and 7.7% of the men, the "no treatment" category 49.7% of the women and 13.8% of the men (Fig. 1A, Table 4 and eTable 3 in the Supplementary data).

The same differences between the three guidelines were observed whether considering subjects 40 to 65 years of age or patients over 65 years of age (Fig. 1B and C). In contrast to the SCORE equation, Framingham risk scoring and the Pooled Cohort Risk Assessment equation can also be used in patients over the age of 65. For these patients and according to the ACC/AHA guidelines, all men and 93.2% of women should receive statin therapy.

Table 1
Characteristics of all patients.

	Total N = 677	Women N = 547 (80.8%)	Men N = 130 (19.2%)
Age, years; mean ± SD	58.7 ± 9.4	58.5 ± 9.4	59.4 ± 9.3
Disease course duration, years; median [Q1–Q3]	11.4 [6.5–19.3]	12.7 [7.3–20.2]	7.4 [4.3–13.4]
Positive RF or anti-CCP; n (%)	566/674 (84.0)	454/545 (83.3)	112/129 (86.8)
Erosive RA; n (%)	500/671 (74.5)	409/543 (75.3)	91/128 (71.1)
DAS28 score (ESR); mean ± SD	3.06 ± 1.27	3.17 ± 1.24	2.57 ± 1.28
DAS28 score (CRP); mean ± SD	2.83 ± 1.13	2.89 ± 1.13	2.57 ± 1.06
mHAQ score; mean ± SD	0.40 ± 0.44	0.41 ± 0.45	0.33 ± 0.39
RAID; mean ± SD	2.95 ± 2.03	3.04 ± 2.07	2.54 ± 1.80
Current DMARD; n (%)			
None	13 (1.9)	12 (2.2)	1 (0.8)
Biological only	118 (17.4)	94 (17.2)	24 (18.5)
Conventional synthetic only	182 (26.9)	147 (26.9)	35 (26.9)
Biological and synthetic	364 (53.8)	294 (53.7)	70 (53.8)
Current MTX; n (%)	481 (71.0)	389 (71.1)	92 (70.8)
Current corticosteroid intake; n (%)	248 (36.6)	195 (35.6)	53 (40.8)
Current corticosteroid intake (prednisone dose, mg/day; mean ± SD)	5.4 ± 5.3	5.1 ± 5.7	6.3 ± 3.4
Cardiovascular disease, n (%)	35 (5.2)	20 (3.7)	15 (11.6)
Diabetes, n (%)	35 (5.2)	23 (4.2)	12 (9.2)
Diabetes treatment, n (%)	32/35 (91.4)	20/23 (87.0)	12/12 (100.0)
Family history of CHD, n (%)	99 (14.6)	76 (13.9)	23 (17.7)
Smoking, n (%)	106 (15.7)	77 (14.1)	29 (22.3)
Systolic blood pressure (mm Hg); mean ± SD	124.8 ± 16.1	124.0 ± 16.3	128.2 ± 14.8
Diastolic blood pressure (mm Hg); mean ± SD	75.9 ± 11.3	75.5 ± 10.9	77.5 ± 12.5
Antihypertensive, n (%)	195 (28.8)	161 (29.4)	34 (26.2)
Antihypertensive treatment at baseline (n = 195)	182 (93.3)	149 (92.5)	33 (97.1)
Body mass index (kg/m2); mean ± SD	25.1 ± 4.8	24.7 ± 4.8	26.7 ± 4.5
Total cholesterol (g/l); mean ± SD	2.17 ± 0.45	2.19 ± 0.44	2.11 ± 0.47
HDL cholesterol (g/l); mean ± SD	0.67 ± 0.19	0.70 ± 0.18	0.57 ± 0.19
LDL cholesterol (g/l); mean ± SD	1.33 ± 0.38	1.33 ± 0.38	1.35 ± 0.40
Triglyceride (g/l); mean ± SD	1.07 ± 0.65	1.06 ± 0.66	1.12 ± 0.62
Fasting glucose (g/l); mean ± SD	0.97 ± 0.46	0.94 ± 0.40	1.09 ± 0.62
Fasting glucose (g/l) for current corticosteroid intake; mean ± SD	0.96 ± 0.52	0.90 ± 0.43	1.15 ± 0.74
Need to apply the coefficient of 1.5 as recommended by EULAR, n (%)	402/671 (59.9)	340/544 (62.5)	62/127 (48.8)

Table 2
Characteristics of patients 40 to 65 years of age.

Patients 40 to 65 years of age	Total N = 510	Women N = 415 (81.4%)	Men N = 95 (18.6%)
Age, years; mean ± SD	54.6 ± 6.8	54.5 ± 6.9	55.1 ± 6.5
Disease course duration, years; median [Q1–Q3]	10.7 [6.1–18.4]	11.4 [6.7–18.8]	7.8 [4.2–13.4]
Positive RF or anti-CCP; n (%)	429/509 (84.3)	347/414 (83.8)	82 (86.3)
Erosive RA; n (%)	366/506 (72.3)	301/412 (73.1)	65/94 (69.1)
DAS28 score (ESR); mean ± SD	2.98 ± 1.26	3.09 ± 1.24	2.48 ± 1.25
DAS28 score (CRP); mean ± SD	2.78 ± 1.11	2.83 ± 1.12	2.55 ± 1.03
mHAQ score; mean ± SD	0.37 ± 0.43	0.38 ± 0.43	0.33 ± 0.40
RAID; mean ± SD	2.88 ± 2.03	2.97 ± 2.08	2.51 ± 1.76
Current DMARD; n (%)			
None	10 (1.9)	9 (2.2)	1 (1.1)
Biological only	83 (16.3)	66 (15.9)	17 (17.9)
Synthetic only	135 (26.5)	116 (27.9)	19 (20.0)
Biological and synthetic	282 (55.3)	224 (54.0)	58 (61.0)
Current MTX; n (%)	372 (72.9)	302 (72.8)	70 (73.7)
Current corticosteroid intake; n (%)	183 (35.9)	145 (34.9)	38 (40.0)
Current corticosteroid intake (prednisone dose, mg/day; mean ± SD)	5.3 ± 6.0	5.2 ± 6.6	5.7 ± 3.0
Cardiovascular disease, n (%)	20 (3.9)	11 (2.7)	9 (9.5)
Diabetes, n (%)	22 (4.3)	17 (4.1)	5 (5.3)
Diabetes treatment, n (%)	21/22 (95.5)	16/17 (94.1)	5/5 (100.0)
Family history of CHD, n (%)	76 (14.9)	58 (14.0)	18 (18.9)
Smoking, n (%)	98 (19.2)	70 (16.9)	28 (29.5)
Systolic blood pressure (mm Hg); mean ± SD	122.6 ± 15.5	121.6 ± 15.4	127.2 ± 15.0
Diastolic blood pressure (mm Hg); mean ± SD	75.7 ± 11.4	75.2 ± 10.9	77.7 ± 13.1
Antihypertensive, n (%)	118 (23.1)	96 (23.1)	22 (23.2)
Antihypertensive treatment at baseline (n = 118)	112 (94.9)	91 (94.8)	21 (95.5)
Body mass index (kg/m2); mean ± SD	25.1 ± 4.8	24.8 ± 4.8	26.5 ± 4.2
Total cholesterol (g/l); mean ± SD	2.17 ± 0.43	2.17 ± 0.41	2.16 ± 0.50
HDL cholesterol (g/l); mean ± SD	0.67 ± 0.19	0.69 ± 0.18	0.57 ± 0.20
LDL cholesterol (g/l); mean ± SD	1.31 ± 0.36	1.30 ± 0.34	1.34 ± 0.43
Triglyceride (g/l); mean ± SD	1.04 ± 0.67	1.02 ± 0.66	1.13 ± 0.69
Fasting glucose (g/l); mean ± SD	0.96 ± 0.48	0.93 ± 0.42	1.09 ± 0.67
Fasting glucose (g/l) for current corticosteroid intake; mean ± SD	0.95 ± 0.56	0.92 ± 0.50	1.11 ± 0.76
Need to apply the coefficient of 1.5 as recommended by EULAR, n (%)	296/505 (58.6)	247/413 (59.8)	49/92 (53.3)

Table 3
Characteristics of patients over 65 years of age.

>65 years-old	Total N = 167	Women N = 132 (79.1%)	Men N = 35 (20.9%)
Age, years; mean ± SD	71.0 ± 4.0	70.9 ± 3.9	71.2 ± 4.3
Disease course duration, years; median [Q1–Q3]	14.7 [7.5–22.7]	15.7 [10.3–23.3]	6.5 [4.4–16.8]
Positive RF or anti-CCP; n (%)	137/165 (83.0)	107/131 (81.7)	30/34 (88.2)
Erosive RA; n (%)	134/165 (81.2)	108/131 (82.4)	26/34 (76.5)
DAS28 score (ESR); mean ± SD	3.29 ± 1.27	3.42 ± 1.22	2.82 ± 1.33
DAS28 score (CRP); mean ± SD	2.98 ± 1.18	3.09 ± 1.17	2.61 ± 1.14
mHAQ score; mean ± SD	0.48 ± 0.48	0.53 ± 0.49	0.31 ± 0.36
RAID; mean ± SD	3.14 ± 2.03	3.28 ± 2.04	2.63 ± 1.93
Current DMARD; n (%)			
None	3 (1.8)	3 (2.3)	0 (0.0)
Biological only	35 (21.0)	28 (21.2)	7 (20.0)
Synthetic only	47 (28.1)	31 (23.5)	16 (45.7)
Biological and synthetic	82 (49.1)	70 (53.0)	12 (34.3)
Current MTX; n (%)	109 (65.3)	87 (65.9)	22 (62.9)
Current corticosteroid intake; n (%)	65 (38.9)	50 (37.9)	15 (42.9)
Current corticosteroid intake (prednisone dose, mg/day; mean ± SD)	5.5 ± 2.8	4.8 ± 1.9	7.7 ± 3.9
Cardiovascular disease, n (%)	15 (9.0)	9 (6.8)	6 (17.6)
Diabetes, n (%)	13 (7.8)	6 (4.5)	7 (20.0)
Diabetes treatment, n (%)	11/13 (84.6)	4/6 (66.7)	7/7 (100.0)
Family history of CHD, n (%)	23 (13.8)	18 (13.6)	5 (14.3)
Smoking, n (%)	8 (4.8)	7 (5.3)	1 (2.9)
Systolic blood pressure (mm Hg); mean ± SD	131.6 ± 16.1	131.7 ± 16.6	131.0 ± 13.9
Diastolic blood pressure (mm Hg); mean ± SD	76.6 ± 10.9	76.5 ± 11.0	76.9 ± 11.0
Antihypertensive, n (%)	77 (46.1)	65 (49.2)	12 (34.3)
Antihypertensive treatment at baseline (n = 77)	70 (90.9)	58 (89.2)	12 (100.0)
Body mass index (kg/m2); mean ± SD	25.2 ± 4.8	24.7 ± 4.6	27.1 ± 5.3
Total cholesterol (g/l); mean ± SD	2.18 ± 0.49	2.23 ± 0.52	1.97 ± 0.34
HDL cholesterol (g/l); mean ± SD	0.69 ± 0.18	0.72 ± 0.17	0.56 ± 0.15
LDL cholesterol (g/l); mean ± SD	1.39 ± 0.44	1.40 ± 0.47	1.38 ± 0.27
Triglyceride (g/l); mean ± SD	1.15 ± 0.58	1.17 ± 0.62	1.09 ± 0.38
Fasting glucose (g/l); mean ± SD	0.98 ± 0.39	0.94 ± 0.35	1.11 ± 0.48
Fasting glucose (g/l) for current corticosteroid intake; mean ± SD	0.96 ± 0.37	0.87 ± 0.10	1.25 ± 0.68
Need to apply the coefficient of 1.5 as recommended by EULAR, n (%)	106/166 (63.9)	93/131 (71.0)	13 (37.1)

3. Discussion

Our study showed that the proportion of patients with RA requiring statin therapy varies considerably with the guidelines, from 9.1 to 38.8% for women and 26.2 to 78.5% for men by applying, when necessary, a coefficient according to the EULAR guidelines. It is with the new ACC/AHA guidelines that the greatest number of patients would require statin treatment. These same differences had already been observed in the general population [18,19]. The performances of the different cardiovascular risk equations were recently evaluated [19]. In a Dutch cohort of 4209 patient aged 55 years or older, 95.6% of men and 65.8% of women would require statin treatment according to the ACC/AHA guidelines, 52% of men and 35.5% of women with the ATP-III guidelines and 66.1% of men and 39.1% of women with the ESC guidelines [19]. In this study, the three models overestimated risk with respect to the observed events. Differences between the 3 guidelines involve the fact that Framingham score takes into account only risk of coronary heart disease whereas Pooled Cohort and SCORE equations include also stroke. ESC guidelines do not take into account the increased risk after 65 years-old. Compared with the ATP-III guidelines, the ACC/AHA guidelines place more importance on 10-year predicted risk than on LDLc levels, and have greater sensitivity, especially in the elderly population (>60 years of age) but with less specificity [20]. Except in secondary prevention, in all patients with elevation of LDL cholesterol ≥ 190 mg/dl and in patients with diabetes, new ACC/AHA guidelines base the recommendation for statin therapy on the solely threshold of cardiovascular risk of 7.5% rather than on specific LDL cholesterol targets. Finally, in secondary prevention, ACC/AHA guidelines recommend statin therapy for all patients whereas some can be categorized as “treatment considered” or “treatment not recommended” with ATP-III or ESC guidelines.

Cardiovascular risk management in RA raises specific problems. In contrast to the general population, the risk equations can underestimate the cardiovascular risk, especially in elderly patients with RA with the presence of rheumatoid factor and an elevated sedimentation rate [21] or when the observed risk is low or moderate [22]. Therefore, approximately 30% of cardiovascular events are observed in patients with a low calculated risk [22]. This is explained by the fact that the cardiovascular risk observed in RA depends both on RA activity and cardiovascular risk factors [23,24]. Even if a coefficient is applied, the SCORE equation underestimates RA cardiovascular risk [25]. Indeed, in a study of 327 RA patients, only five patients were reclassified as high or very high risk when applying the coefficient suggested by EULAR. In contrast carotid intima–media thickness >0.90 mm or the presence of carotid plaques was observed in 63% of moderate risk patients, enabling these patients to be reclassified as high cardiovascular risk patients [25]. The new Pooled Cohort equation was better than SCORE to identify patients with high cardiovascular risk when carotid intima–media thickness for the detection of subclinical atherosclerosis was used as the gold standard test (58% vs 16% respectively, $P < 0.0001$) [26]. However, it failed to identify 42% of patients with subclinical atherosclerosis [26]. In addition, inflammatory status can induce quantitative and qualitative changes in lipid profile in RA leading to misinterpretation of lipid levels [17,27]. The lower impact of the LDLc in the ACC/AHA guidelines suggests better sensitivity for these guidelines that lipid-profile-based cardiovascular risk stratification in particular when control of inflammation is not achieved.

Although cardiovascular disease contributes to half of the mortality occurring during RA [1], lipid-lowering agents are underused in RA despite management guidelines to reduce LDLc levels as recommended by ATP III [28,29]. In the present RA cohort, only 17.7% of patients aged 40 to 65 and 25.8% of patients over the age of 65 received a statin, while

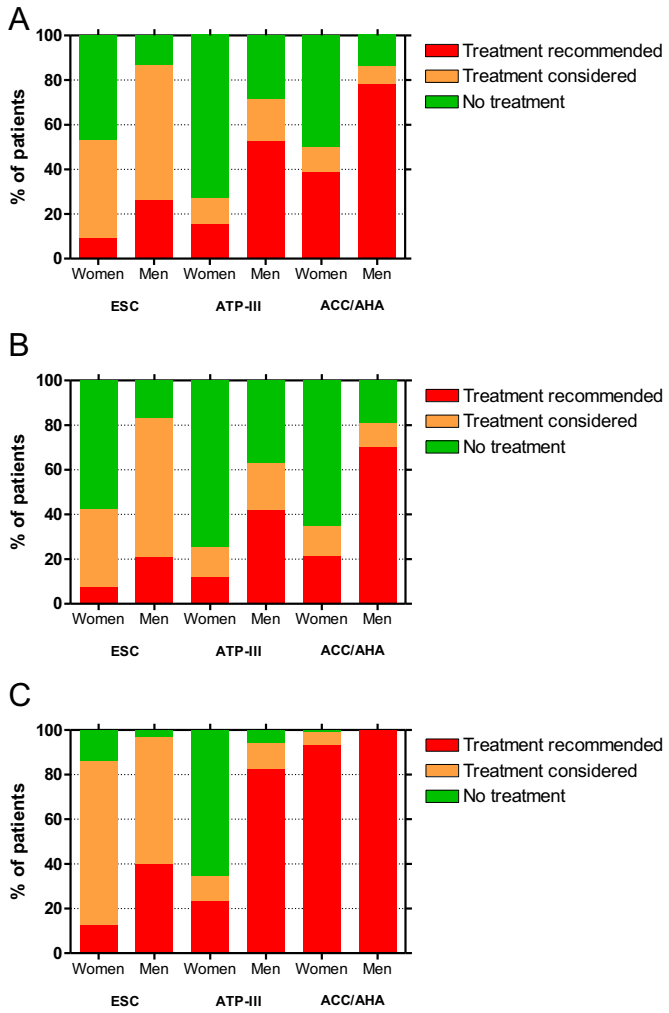

Fig. 1. Treatment recommendations for COMEDRA study participants based on the 2012 ESC, 2004 ATP-III and 2013 ACC/AHA guidelines. A: All patients, B: Age 40–65 years, and C: Age >65 years.

according to the ACC/AHA guidelines, 46.4% of patients should have received a statin. In addition, 5.2% of the patients with a history of cardiovascular disease or diabetes warranting statin treatment were not taking any, regardless of the guidelines. In the general population, statin therapy is a key factor in reducing cardiovascular risk [30]. There are no large-scale controlled studies on the effect of statins as primary cardiovascular risk prevention in RA. In a Scottish cohort of 430 RA, including 181 statin-exposed and 249 statin-unexposed patients, with a mean follow-up period of 3.90 and 3.14 years, statins reduced total cholesterol by 16% and were associated in primary prevention with reduced cardiovascular events (HR: 0.45 [0.20–0.98]) and concomitant decrease in all-cause mortality (OR: 0.43 [0.20–0.92]) [31]. As secondary prevention, the decrease in cholesterol with statins and relapse in MI are identical, regardless of whether or not the patients have RA, and discontinuing statins is accompanied by a high risk of stroke [32,33]. Finally, it was demonstrated that baseline systemic inflammation or lipid levels did not influence the dose of statin needed to reach LDLc target [34].

Table 4
Treatment recommendations based on different guidelines (all patients).

	ESC	ATP-III	ACC/AHA	P value
Women (n = 547)				
Treatment recommended	50 (9.1)	85 (15.5)	212 (38.8)	<0.001
Treatment considered	240 (43.9)	64 (11.7)	63 (11.5)	<0.001
No treatment	257 (47.0)	398 (72.8)	272 (49.7)	<0.001
Men (n = 130)				
Treatment recommended	34 (26.1)	69 (53.1)	102 (78.5)	<0.001
Treatment considered	79 (60.8)	24 (18.4)	10 (7.7)	<0.001
No treatment	17 (13.1)	37 (28.5)	18 (13.8)	<0.001

Strength of the study includes the application and the comparison of the 3 different guidelines in a specific RA population at very high or high total cardiovascular risk comparable to the risk in patients with diabetes, by introducing a 1.5 multiplication factor depending on RA characteristics. An important limitation is that our study does not provide information on the agreement for each model between the predicted and the observed risks.

Our study confirmed in RA the differences observed in the general population with the three types of guidelines. In the specific case of RA, the importance of cardiovascular mortality and the underestimation of risk by the SCORE and Framingham equations support the use of the new expanded treatment recommendations of the ACC/AHA. Further studies are needed to clarify the effect the new guidelines would have by expanding the proportion of RA patients recommended for therapy. In addition, a RA-specific cardiovascular risk model may improve the cardiovascular risk prediction [35].

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Competing interests

None.

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Patient consent obtained.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2015.01.069.

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