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Coronary heart disease is associated with a worse clinical outcome of hand osteoarthritis: a cross-sectional and longitudinal study

Alice Courties, Jérémie Sellam, Emmanuel Maheu, Christian Cadet, Yoann Barthe, Fabrice Carrat, Francis Berenbaum

ABSTRACT

Objective: To determine whether cardiometabolic factors are associated with hand osteoarthritis (HOA) symptoms, radiographic severity and progression in a post hoc analysis of the phase III Strontium ranelate Efficacy in Knee OsteoarthrItis triAl (SEKOIA) trial, designed to determine the effect of strontium ranelate on knee osteoarthritis (OA).

Methods: Among the 1683 patients randomised in the SEKOIA study, 869 with radiographic HOA at baseline (rHOA ≥2 joints with Kellgren-Lawrence grade ≥2) were included in a cross-sectional analysis. For longitudinal study, we included only the 307 patients with rHOA at baseline from the placebo group. We evaluated whether baseline symptomatic HOA, radiographic severity and clinical and rHOA progression were associated with coronary heart disease and/or metabolic diseases (obesity, diabetes and hypertension, dyslipidaemia) by multivariate regression analysis.

Results: At baseline, 869 patients (72% women) were included in the cross-sectional analysis; 26% were symptomatic. On multivariate analysis, symptomatic HOA was associated with coronary heart disease (OR 3.59, 95% CI (1.78 to 7.26)) but not metabolic diseases. After a mean follow-up of 2.6 years, for the 307 participants in the placebo group, on multivariate analysis, worse clinical HOA outcome was associated with coronary heart disease (OR 2.91, 95% CI (1.02 to 8.26)). The slow radiographic progression did not allow for revealing any associated factors.

Conclusions: Symptomatic HOA and worse HOA clinical course are associated with coronary heart disease. These results strengthen the systemic component of HOA and the association between OA pain and cardiac events.

INTRODUCTION

Hand osteoarthritis (HOA) is a heterogeneous disorder because of its multiple risk factors such as inheritance, ageing, gender and obesity. In addition, HOA has been associated, although not always, with metabolic disorders (ie, diabetes, hypertension or dyslipidaemia), delineating the metabolic OA phenotype. Furthermore, cardiovascular disease (CVD) and mortality are more frequent in people with OA than without OA. A recent meta-analysis reported higher risk of CVD, especially heart failure and ischaemic heart disease, with OA than without OA but with a high heterogeneity in the design of the studies included. The relationship between CVD and OA has been attributed to disability, preventing people from exercising, therefore with increased cardiovascular risk.

However, some studies have suggested a direct relationship between CVD and osteoarthritis (OA), independent of increased body weight and physical activity, which suggests a systemic association via a common
low-grade inflammation state. Indeed, HOA, which does not affect physical activity, has been independently associated with atherosclerosis or cardiac events.\textsuperscript{10}–\textsuperscript{11} However, most of these studies compared CVD and metabolic disease outcomes between patients with and without HOA but did not evaluate their association with HOA symptoms or severity, which may be more representative of systemic inflammation.

To better understand the association between metabolic diseases, CVD and OA, we investigated an association of cardiometabolic diseases with symptomatic HOA, radiographic severity and/or progression of HOA in a post hoc study of data from the Strontium ranelate Efficacy in Knee Osteoarthritis triAl (SEKOIA; ISRCTN41323372), which carefully assessed HOA.

**PATIENTS AND METHODS**

**Study design and patient population of SEKOIA**

SEKOIA is a randomised phase III, multicentre, placebo-controlled study evaluating the structural effect of strontium ranelate in knee OA. The design of this study has been previously described.\textsuperscript{12} Briefly, 1683 Caucasian patients $\geq 50$ years old with symptomatic and primary knee OA fulfilling the American College of Rheumatology criteria with Kellgren-Lawrence (KL) knee grade 2 or 3 and minimum joint space 2.5–5 mm were randomised between April 2006 and March 2008. There were three treatment groups: strontium ranelate 1 g/day, strontium ranelate 2 g/day and placebo. The randomisation was stratified on centre and gender. Analgesics and non-steroidal anti-inflammatory drugs were permitted if stopped at least five half-lives before each visit to allow for proper symptom assessment. Patients were followed annually for 3 years, with the last visit on February 2011. The results of the main study have been previously reported.\textsuperscript{13}

The study conformed to the principles of the Declaration of Helsinki; it was approved by the Ethics Committee or Institutional Review Board of every site. All patients provided written informed consent before randomisation. The trial is registered (ISRCTN41323372).

**Population of the ancillary study**

All patients with radiographic HOA (rHOA) defined as a KL score $\geq 2$ for at least two joints at baseline were included in the cross-sectional analysis. For the longitudinal analysis, to avoid any treatment bias, we excluded patients from the treatment group and included only patients with rHOA from the placebo group at baseline.

**HOA evaluation**

For this post hoc ancillary study, bilateral anteroposterior hand radiographs taken at baseline and at the end of follow-up were scored with blinding to treatment group and in chronological order. Two expert readers (EM and CC) scored half of the radiographs each, independently, by using the KL hand score (grade 0–4) for the following joints: proximal interphalangeals (PIPs 2–5), first interphalangeal (IP-1), distal interphalangeals (DIPs 2–5), metacarpophalangeals (MCPs 1–5), first carpometacarpal and scaphotrapezial. The KL hand score ranged from 0 to 128 (128 being the worst).\textsuperscript{14} Presence of erosive joints was determined by using the phase E (erosive phase) or R (remodelling phase) of the Verbruggen anatomical scoring system to analyse PIPs 2–5, IP-1, DIPs 2–5 and MCPs 1–5.\textsuperscript{15} Intrarreader and inter-reader reproducibility were excellent, with intraclass correlation coefficient $>0.8$ for inter-reader reproducibility and $>0.9$ for intrarreader reproducibility.

Clinical evaluation of pain and disability due to HOA was assessed by the AUStralian/CACanadian (AUSCAN) pain score,\textsuperscript{16} stiffness and function scores and total AUSCAN score as well as the Functional Index for HOA (FIHOA).\textsuperscript{17} For the AUSCAN, each of the three subscale scores was corrected to 100, for a range from 0 to 300 for the total score. Presence of pain was assessed by the question ‘Did you have pain in your hands during the past 48 hours?’, with a binary answer (yes/no).

**Definition of symptomatic HOA and clinical progression**

In the cross-sectional analysis, symptomatic HOA was defined by a FIHOA score $\geq 5$ and hand pain in the past 48 hours (FIHOA$\geq 5$+presence of HOA pain). The FIHOA$\geq 5$ threshold was used because it discriminates between symptomatic and non-symptomatic HOA.\textsuperscript{18} In the longitudinal analysis, clinical progression was defined by deterioration in FIHOA score between baseline and the end of follow-up (FIHOA final minus FIHOA initial $\geq 0$). The secondary clinical outcomes were AUSCAN pain score, used as a continuous variable, to determine baseline clinical symptom intensity and AUSCAN pain deterioration for clinical symptom changes.

**Definition of radiographic severity and radiographic progression**

We defined radiographic severity by using the KL hand score as a continuous variable. Radiographic progression was defined by a change in KL total score over each reader’s smallest detectable difference (SDD). The secondary structural radiographic outcomes were presence of at least one erosive joint on both hands based on the Verbruggen score (phase E or R) and the occurrence of a new erosive joint in the cross-sectional and longitudinal analysis, respectively.

**Collected clinical data**

At baseline, the following demographic variables were collected from medical files, self-reported data and patient medications by SEKOIA study investigators without information on delay between the disease and the randomisation: age, gender, body mass index (BMI),
menopause status, alcohol consumption and tobacco use and comorbidities such as diabetes mellitus, hypertension, dyslipidaemia, depression, coronary heart disease (defined as acute myocardial infarction, angina pectoris, arteriosclerosis coronary artery, coronary artery disease/insufficiency/oclusion/stenosis/thrombosis, coronary heart disease, myocardial infarction and myocardial ischaemia), stroke and lower limb arthritis. Obesity was defined as BMI ≥ 30 kg/m².

Statistical analysis
Data were analysed by using SAS V.9.3 (SAS Institute, Cary, North Carolina, USA). Continuous variables are described as mean±SD or median (quartile 1–3) and categorical variables as frequencies and percentages. Comparison of cross-sectional and longitudinal data involved Fisher’s exact and Wilcoxon tests. In the cross-sectional analysis, we used unadjusted logistic regression to analyse the following factors associated with symptomatic HOA (FIHOA score ≥5+pain): age, sex, menopause, obesity, history of diabetes, hypertension, dyslipidaemia, coronary heart disease (as described previously), depression, stroke, alcohol consumption, tobacco use, and rHOA and knee OA features. Linear regression was used to assess associations with AUSCAN pain and KL hand score, and logistic regression was used to assess an association with presence of at least one erosive joint. All factors associated on univariate analysis at p<0.20 were retained in multivariate models and if not, were systematically adjusted on age and BMI because of the known association of these variables with HOA.

In the longitudinal analysis, we used unadjusted linear regression to analyse whether the same factors were associated with AUSCAN pain deterioration and deterioration in radiographic KL hand score and logistic regression for factors associated with deteriorated FIHOA score and the occurrence of a new erosive OA joint. All factors associated on univariate analysis at p<0.20 were retained in multivariate models. p Value <0.05 was considered statistically significant.

In all linear regression models, the dependent variable was transformed (log or square root as indicated for each analysis) as appropriate to avoid a strong departure from the normality assumption. No multiple corrections were performed because this study was exploratory and planned to study the association between cardiometabolic diseases and HOA.

RESULTS
Population characteristics
Among the 1683 patients randomised in the SEKOIA study, 1371 were included in the trial’s full analysis set for the knee study; among these 1371 patients, 390 did not have rHOA, 108 had no hand radiography follow-up and 4 had missing data and thus were excluded. Overall, 869 participants had rHOA and were included in our cross-sectional analysis; 18 had a missing KL hand score. AUSCAN and FIHOA scores were not available for 75 and 372 patients, respectively.

After a mean follow-up of 2.6±0.7 years, 307 patients in the placebo group were included in the longitudinal analysis; 276 with a final AUSCAN score, 164 with an FIHOA score and 272 with a Verbruggen score. Characteristics of cross-sectional and longitudinal study populations are summarised in table 1. Mean age for the cross-sectional population was 64±7 years and mean BMI was 29.6±4.7 kg/m²; 72% were women. Cross-sectional and longitudinal populations did not differ in characteristics.

Factors associated with symptomatic HOA on cross-sectional analysis
For the 479 patients with data available on clinical symptoms (ie, presence of HOA pain+FIHOA≥5), 126 (26%) were symptomatic.

On univariate analysis, the presence of coronary heart disease, menopause, depression, alcohol consumption and radiographic severity (ie, baseline KL hand score and number of erosive joints) was associated with symptomatic HOA (table 2). Except for alcohol consumption, all factors remained significantly associated with clinical symptoms on multivariate analysis. All these factors were also significantly associated with AUSCAN pain score (n=778 patients) in the multivariate model (see online supplementary file 1). We did not find any association between metabolic diseases alone or combined (ie, obesity, diabetes mellitus, hypertension and dyslipidaemia) and symptomatic HOA (data not shown).

Factors associated with rHOA severity on cross-sectional analysis
On univariate analysis, age, menopause, BMI ≥ 30 kg/m², alcohol consumption, previous tobacco use, presence of HOA clinical symptoms and baseline KL knee score were associated with more structural damage as indicated by a high baseline KL hand score. On multivariate analysis, age, presence of HOA clinical symptoms and baseline KL knee score remained independently and significantly associated with KL hand score (table 3). Obesity and HOA severity judged by KL hand score were associated but not significantly (p=0.07). Moreover, erosive HOA was associated with increased age (OR=1.04, 95% CI (1.00 to 1.07)) and presence of menopause (OR=2.13, 95% CI (1.10 to 4.1); see online supplementary file 2).

Factors associated with clinical HOA deterioration
Mean FIHOA did not significantly change between baseline and the end of follow-up (3.9±4.8 vs 3.2±4.4) because some patients showed worsened condition and others improved condition. However, 23% of patients (n=38/164) showed clinical deterioration. After a mean of 2.6±0.7 years of follow-up, FIHOA score deterioration was associated with coronary heart disease (OR=2.91

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(95% CI 1.02 to 8.26); table 4). The secondary clinical outcome, worsened AUSCAN pain score, was associated with only low baseline AUSCAN score (data not shown).

Factors associated with HOA progression
Radiographic progression, defined by a deteriorated KL score above the SDD of each reader, was weak and affected only 5/295 patients (2%) after a mean follow-up of 2.6±0.7 years, which did not allow for determining associated factors. Finally, 32/273 patients (n=10%) showed a new erosive joint, which was associated with increased baseline KL and AUSCAN scores (see online supplementary file 3).

DISCUSSION
In this cohort of generalised OA (ie, knee plus hand OA), coronary heart disease was associated with presence of HOA symptoms and worse clinical outcome, after a mean of 2.6 years. No other metabolic diseases such as dyslipidaemia or diabetes were associated with HOA symptoms or progression.

We had the advantage of analysing data for a large population in which HOA was carefully assessed with longitudinal evaluation and with standardised data available for confounding factors. Thus, we could evaluate the association of HOA with CVD and metabolic diseases. Few studies have reported on determinants of HOA severity and progression,19 especially in terms of

Table 1 Baseline demographic, clinical and radiographic characteristics of patients for cross-sectional and longitudinal analyses

|                         | Cross-sectional, n=869 | Longitudinal, n=307 | p Value |
|-------------------------|------------------------|----------------------|---------|
| Age (years), mean±SD    | 64.0±7                 | 63.8±7.1             | 0.56    |
| Sex                     | 622 (72)               | 213 (69)             | 0.94    |
| Women, n (%)            | 489 (78)               | 166 (54.1)           | 0.50    |
| Menopause               | 247 (28)               | 86 (28)              |         |
| BMI (kg/m²), mean±SD    | 29.6±4.7               | 29.5±5               | 0.55    |
| BMI<30, n (%)           | 502 (58)               | 172 (56)             |         |
| BMI≥30, n (%)           | 366 (42)               | 127 (41)             |         |
| Comorbidities, n (%)    |                        |                      |         |
| Diabetes                | 82 (9)                 | 30 (10)              | 0.91    |
| Hypertension            | 413 (48)               | 135 (44)             | 0.28    |
| Dyslipidaemia           | 245 (28)               | 89 (29)              | 0.82    |
| Coronary heart disease  | 81 (9)                 | 35 (11)              | 0.32    |
| Stroke                  | 16 (2)                 | 7 (2)                | 0.63    |
| Depression              | 81 (9)                 | 30 (10)              | 0.82    |
| Alcohol consumption, n (%) |                      |                      |         |
| No                      | 422 (49)               | 135 (44)             |         |
| Previous use            | 16 (2)                 | 6 (2)                |         |
| Yes                     | 431 (50)               | 158 (51)             | 0.57    |
| Tobacco use, n (%)      |                        |                      |         |
| No                      | 567 (65)               | 188 (61)             |         |
| Previous use            | 222 (26)               | 86 (28)              |         |
| Yes                     | 80 (9)                 | 25 (8)               | 0.53    |
| Clinical variables      |                        |                      |         |
| FIHOA                   | 0–30, median [Q1, Q3]  | 2.0 [0.0–7.0]         | 0.90    |
| ≥5+pain, n (%)          | 126 (26)               | 45 (15)              | 0.83    |
| AUSCAN, median [Q1, Q3] | 77.3 [23.4–156]        | 77.5 [18.7–158]      | 0.90    |
| Overall (0–300)         | 25 [5.6–54.6]          | 26.4 [4.8–55.8]      | 0.84    |
| Pain (0–100)            | 20 [4–54]              | 20 [4–56]            | 0.81    |
| Stiffness (0–100)       | 25.9 [7.2–52.2]        | 25.4 [5.9–53.9]      | 0.76    |
| Function (0–100)        |                        |                      |         |
| KL hand score (0–128), median [Q1, Q3] | 18 [12–27] | 17 [12–28] | 0.75    |
| Number of erosive joints (phase E or R, Verbruggen score), median [Q1, Q3] | 2 [1–4] | 1 [1–3] | 0.45    |
| KL knee grade 2, n (%)  | 532 (61)               | 194(63)              | 0.47    |
| KL knee grade 3, n (%)  | 336 (39)               | 105 (24)             |         |

AUSCAN, AUStalian-CANadian; BMI, body mass index; FIHOA, Functional Index for Hand Osteoarthritis; KL, Kellgren-Lawrence; Q1, Q3, quartile 1, quartile 3.
cardiometabolic disorders. Our multivariate analysis revealed coronary heart disease associated with HOA symptoms and worse clinical evolution but not radiographic severity and progression.

This study strengthens the association between OA pain and CVD. Previous studies have shown associations between HOA diagnosis and subclinical atherosclerosis, CVD and mortality, but few focused on their association with HOA pain and reported conflicting results. Massengale et al found a negative but significant association between hand pain and coronary heart disease, which limits the interpretation of these results. Furthermore, hand pain was assessed by a visual analogue scale, whereas we used a more complete score reflecting also functional disability. Recently, Haugen et al observed an association of asymptomatic but not rHOA with increased rate of incident coronary heart disease (by twofold) as compared with non-HOA participants. Our study confirms these findings in a population with generalised OA and suggests that coronary heart disease is also associated with worse clinical outcome. However, in contrast with Haugen et al, our comparator was patients with asymptomatic rHOA and we did not include participants without HOA. Likewise, within a population with rHOA, the presence of pain and functional impairment was associated with coronary heart disease. Such a result suggests that the systemic component of HOA preferentially involves clinical symptoms over structural severity.

The underlying mechanisms behind this observational association between HOA pain and coronary heart disease raised further assumptions. Confounding factors such as obesity, metabolic diseases or ageing could explain such an association, in that they are risk factors for HOA and CVD. Indeed, Dahaghin et al reported that metabolic disorders had a cumulative and harmful effect on rHOA risk. Recently, these data were confirmed by Visser et al, who demonstrated that HOA alone was closely linked to systemic metabolic diseases, in contrast with knee OA or a combination of knee and HOA, which are preferentially associated with weight. This finding agrees with our results, because the populations we studied all had knee OA due to the inclusion criteria of SEKOIA. Consequently, the association between

| Table 2 Logistic regression analysis of factors associated with symptomatic HOA on cross-sectional analysis |
| --- |
| **n (%) or mean±SD** | **Univariate analysis** | **Multivariate analysis** |
| **OR (95% CI)** | **p Value** | **OR (95% CI)** | **p Value** |
| --- | --- | --- |
| **Age** | 63.9±7.2 | 1.00 (0.97 to 1.03) | 0.92 |
| **Sex** |  |  |  |
| Men (reference) | 21 (17) | 1 |  |
| Menopausal women | 86 (68) | 3.33 (1.96 to 5.65) | <0.001 |
| Non-menopausal women | 19 (15) | 1.87 (0.94 to 3.72) | 0.94 |
| **BMI≥30 vs <30 kg/m²** | 54 (43) | 1.07 (0.71 to 1.61) | 0.76 |
| **Comorbidities** |  |  |  |
| Diabetes | 16 (13) | 1.46 (0.77 to 2.76) | 0.25 |
| Hypertension | 57 (45) | 1.08 (0.71 to 1.62) | 0.73 |
| Dyslipidaemia | 38 (30) | 1.09 (0.70 to 1.71) | 0.69 |
| Coronary heart disease | 20 (16) | 2.37 (1.27 to 4.42) | 0.01 |
| Depression | 22 (17) | 2.46 (1.35 to 4.48) | <0.01 |
| Stroke | 4 (3) | 1.25 (0.38 to 4.14) | 0.71 |
| **Alcohol consumption** |  |  |  |
| No/previous use (reference) | 81 (64) | 1 |  |
| Yes | 45 (36) | 2.09 (1.38 to 3.19) | <0.001 |
| **Tobacco use** |  |  |  |
| No (reference) | 93 (74) | 1 |  |
| Previous use | 25 (20) | 1.52 (0.67 to 3.43) | 0.32 |
| Yes | 8 (6) | 1.01 (0.41 to 2.47) | 0.99 |
| **Clinical variables** |  |  |  |
| AUSCAN | 186±68 |  |  |
| **Radiographic variables** |  |  |  |
| Baseline KL hand score | 22±17 | 1.03 (1.02 to 1.05) | <0.001 |
| Number of erosive joints (Verbruggen score) | 3±3.8 | 1.2 (1.08 to 1.33) | <0.001 |
| Baseline KL knee score | II: 82 (65) | 1.24 (0.81 to 1.88) | 0.32 |
| III: 44(35) |  |  |  |

*Systematic adjustment on age and BMI.
Statistically significant results are in bold.
AUSCAN, AUStralian-CANadian; BMI, body mass index; HOA, hand osteoarthritis; KL, Kellgren-Lawrence.
coronary heart disease and symptomatic HOA is not biased by metabolic disturbances.

Symptomatic HOA and coronary heart disease may share a systemic low-grade inflammation state. The level of high sensitivity C reactive protein and presence of synovitis are greater in patients with symptomatic HOA than without symptomatic HOA, so OA-related pain could result in part from low-grade inflammation. As well, systemic inflammation promotes atherosclerosis and coronary heart disease development. However, this observational cross-sectional study could not allow for determining a causal association between HOA and coronary heart disease and we did not have assessments of blood inflammatory biomarkers.

Finally, in contrast with knee OA, the coronary heart disease–HOA symptoms relationship could not be due to functional disability because HOA involves non-weight-bearing joints. Since all patients had symptomatic knee OA, we performed a subanalysis including adjustment on knee OA symptoms (ie, WOMAC score), which did not attenuate the association between HOA symptoms, clinical progression and coronary heart disease. Furthermore, Eymard et al²⁵ studying the SEKOIA population, found an association between knee OA severity and cardiometabolic disorders and no association between baseline WOMAC score and CVD.

Finally, we accounted for the knee radiographic severity in all analyses because the association between HOA and coronary heart disease was independent of the KL knee score. Of note, the discussion addressing the risk of cardiac events with strontium ranelate was unrelated to this study because our longitudinal analysis involved only the placebo group and coronary heart disease was considered at the time of inclusion in SEKOIA, not after.

On multivariate cross-sectional analysis, we also found an association, although not significant, between obesity and radiographic severity defined by the KL hand score, independent of symptoms. The association between obesity and HOA has often been reported, although sometimes with conflicting results. However, in a meta-analysis, Yusuf et al³ demonstrated a twofold greater risk of HOA for obese than non-obese participants. The association between obesity and HOA radiographic diagnosis or severity could be explained by the endocrine capacity of adipose tissue to produce adipokines, known to have a harmful role on cartilage. No other metabolic disorder was associated with HOA severity and progression.

Longitudinal analysis of radiographic progression confirmed that the use of the KL score change at the patient level is not a sensitive method to discriminate patients with and without radiographic progression (ie,

| Table 3  | Linear regression analysis with log transformation of factors associated with baseline KL hand score |
|-----------------|---------------------------------------------------------------|
|                | Univariate analysis                                    | Multivariate analysis*                              |
|                | β (95% CI)             | p Value              | β (95% CI)             | p Value              |
| Age                  | 0.022 (0.02 to 0.03) | <0.001               | 0.022 (0.01 to 0.03) | <0.0001               |
| Sex                  |                       |                       |                       |                       |
| Men                 |                       |                       |                       |                       |
| Menopausal women    | 0.11 (−0.01 to 0.24) | 0.06                  |                       |                       |
| Non-menopausal women| 0.08 (−0.08 to 0.24) | 0.31                  |                       |                       |
| BMI≥30 vs <30 kg/m²  | 0.07 (−0.04 to 0.18) | 0.19                  | 0.1 (−0.01 to 0.2)    | 0.07                  |
| Comorbidities       |                       |                       |                       |                       |
| Diabetes            | 0.065 (−0.11 to 0.24) | 0.48                  |                       |                       |
| Hypertension        | −0.02 (−0.12 to 0.09) | 0.75                  |                       |                       |
| Dyslipidaemia       | −0.03 (−0.15 to 0.09) | 0.63                  |                       |                       |
| Coronary heart disease | 0.01 (−0.17 to 0.2)  | 0.87                  |                       |                       |
| Depression          | −0.1 (−0.29 to 0.07)  | 0.23                  |                       |                       |
| Stroke              | 0.04 (−0.3 to 0.38)   | 0.81                  |                       |                       |
| Alcohol consumption |                       |                       |                       |                       |
| No                  |                       |                       |                       |                       |
| Previous use        | 0.17 (−0.42 to 0.76)  | 0.57                  |                       |                       |
| Yes                 | −0.1 (−0.21 to 0.01)  | 0.07                  |                       |                       |
| Tobacco use         |                       |                       |                       |                       |
| No                  |                       |                       |                       |                       |
| Previous use        | −0.11 (−0.24 to 0.02) | 0.08                  |                       |                       |
| Yes                 | −0.08 (−0.28 to 0.13) | 0.46                  |                       |                       |
| Clinical variables  |                       |                       |                       |                       |
| FIHOA≥5+pain        | 0.21 (0.09 to 0.33)   | <0.001               | 0.2 (0.09 to 0.32)    | <0.001               |
| Radiographic variables |                       |                       |                       |                       |
| Baseline KL knee score | 0.15 (0.04 to 0.26) | 0.008               | 0.1 (−0.001 to 0.21) | 0.05               |

*Systematic adjustment on age and BMI. Statistically significant results are in bold.
BMI, body mass index; FIHOA, Functional Index for Hand Osteoarthritis; KL, Kellgren-Lawrence; NS, no significance.
2% of patients with progression). Otherwise, when we defined radiographic progression by number of patients with a new erosive joint (corresponding to a progression at the joint level), 10% of patients had radiographic progression, which was associated with baseline radiographic severity. Previous analysis based on the same SEKOIA population showed that with radiographic progression defined at the joint level, by at least one worsened joint with KL or Verbruggen scores, the rate of radiographic progression increased to 52% and 51%, respectively.\(^{28}\) Likewise, radiographic progression of HOA should be assessed at the joint and not the patient level.\(^{28-30}\) However, whatever the method used, radiographic progression was mild because of the short follow-up to assess structural progression. As well, Bijsterbosch \textit{et al} \(^{31}\) reported very weak progression of osteophytes and nodes after a follow-up of 2 years but more frequent at 6 years.\(^{32}\) Our study has some limitations. First, HOA assessment started after the beginning of the study, which explains some of the high rate of missing data for the FIHOA at baseline that was analysed in almost 500 patients, however. This situation could have introduced some bias because of fewer postmenopausal women in the group with clinical data available than in the group without FIHOA available. Second, our longitudinal study exploring the risk factors of HOA progression may have been affected by colliding bias because we included patients with HOA at inclusion.\(^{33}\) We did not try to overcome this issue because we had no longitudinal data for patients without HOA at baseline. However, a large number of known or potential risk factors for HOA were analysed, and coronary heart disease was associated with symptoms at baseline according to the main (as well as secondary) clinical outcomes and with worsening during the follow-up—a finding that is unlikely to result from the colliding bias described above. Finally, some data, known to be associated with HOA, such as grip strength or joint hyperlaxity, were lacking at the baseline examination, but they probably did not affect the systemic association with coronary heart disease. As well, the association between CVD and other OA localisations besides the knee (previously investigated by Eymard \textit{et al} \(^{25}\)) and hand was not planned and thus not evaluated in this study.

In conclusion, we found coronary heart disease associated with HOA symptoms and poor clinical outcome. Yet, the underlying mechanisms of such an association are not fully understood. Such results strengthen the relationship between CVD and HOA and emphasise the need to better delineate the metabolic OA phenotype among overall OA disease.

Table 4  Longitudinal analysis: logistic regression analysis of baseline determinants of clinical progression defined by worsened FIHOA score

|                          | Univariate analysis | Multivariate analysis |
|--------------------------|---------------------|-----------------------|
|                          | OR (95% CI)         | p Value               | OR (95% CI)         | p Value               |
| Age                      | 1.0 (0.97 to 1.04)  | 0.38                  |                      |                      |
| Sex                      | Ref                 |                       |                      |                      |
| Menopausal women         | 0.75 (0.4 to 1.44)  | 0.39                  |                      |                      |
| Non-menopausal women     | 1.16 (0.52 to 2.6)  | 0.71                  |                      |                      |
| BMI\(\geq30\) vs \(<30\)kg/m\(^2\) | 1.38 (0.79 to 2.39) | 0.25                  |                      |                      |
| Comorbidities            |                     |                       |                      |                      |
| Diabetes                 | 0.84 (0.35 to 2.01) | 0.69                  |                      |                      |
| Hypertension             | 1.1 (0.64 to 1.9)   | 0.72                  |                      |                      |
| Dyslipidaemia            | 1.16 (0.65 to 2.1)  | 0.61                  |                      |                      |
| Coronary heart disease   | 2.39 (1.03 to 5.58) | \(0.04\)              | 2.91 (1.02 to 8.26)  | \(0.045\)            |
| Depression               | 0.44 (0.18 to 1.05) | 0.06                  |                      |                      |
| Stroke                   | 0.91 (0.19 to 4.47) | 0.91                  |                      |                      |
| Alcohol consumption      |                     |                       |                      |                      |
| No                       | 1.57 (0.05 to 53.27)| 0.8                   | 1.01 (0.64 to 1.9)   | 0.73                  |
| Yes                      |                     |                       |                      |                      |
| Tobacco use              |                     |                       |                      |                      |
| No                       | 0.84 (0.45 to 1.59) | 0.6                   | 1.41 (0.39 to 5.09)  | 0.59                  |
| Yes                      |                     |                       |                      |                      |
| Clinical variables       |                     |                       |                      |                      |
| FIHOA                    | 0.77 (0.72 to 0.83) | \(<0.001\)           | 0.956 (0.88 to 1.038)| \(0.28\)             |
| Radiographic variables   |                     |                       |                      |                      |
| KL hand score            | 0.99 (0.97 to 1.01) | 0.27                  |                      |                      |

Statistically significant results are in bold.
FIHOA, Functional Index for Hand Osteoarthritis; KL, Kellgren-Lawrence.
