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# Risk factors associated with a decrease ≥2 g/dL in haemoglobin and/or ≥10% haematocrit in osteoarthritis patients taking celecoxib or a nonselective NSAID plus a PPI in a large randomised controlled trial (CONDOR)

A. Lanas*, J. L. Goldstein†, F. K. L. Chan‡, C. M. Wilcox§, D. A. Peura¶, C. Li**, G. H. Sands** & J. M. Scheiman††

*CIBERehd. IIS Aragón, Universidad de Zaragoza, Zaragoza, Spain.
†Northshore University HealthSystem, Evanston, IL, USA.
‡The Chinese University of Hong Kong, Hong Kong, China.
§University of Alabama, Birmingham, AL, USA.
¶University of Virginia, Charlottesville, VA, USA.
**Pfizer Inc, New York, NY, USA.
††University of Michigan, Ann Arbor, MI, USA.

**Correspondence to:**
Prof. A. Lanas, CIBERehd. IIS Aragón, Universidad de Zaragoza, Zaragoza, Spain.
E-mail: angel.lanas@gmail.com

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## SUMMARY

### Background
Nonsteroidal anti-inflammatory drugs are associated with gastrointestinal (GI) damage. The Celecoxib vs. Omeprazole and Diclofenac for At-Risk Osteoarthritis and Rheumatoid Arthritis Patients (CONDOR) trial showed that a haemoglobin drop ≥2 g/dL adjudicated as either of defined or presumed GI origin was the most frequent component/event for the composite GI primary end point. This adverse event is potentially clinically relevant in long-term NSAID treatment.

### Aim
To define potential risk factors associated with a decrease in haemoglobin/haematocrit.

### Methods
*Post hoc* analysis of the CONDOR trial was conducted in the intention-to-treat population. Clinically significant blood loss was defined as: (i) a haemoglobin drop ≥2 g/dL and/or a haematocrit drop ≥10%; and (ii) blood loss adjudicated as either of defined or presumed GI origin. Fifteen risk factors were evaluated by stepwise logistic regression. Each factor had to be significant at <0.20 α to be included in the model.

### Results
A total of 64/3774 (1.7%) osteoarthritis (OA) patients had decreased haemoglobin/haematocrit and were adjudicated to the GI endpoint. Significant risk factors, at the 0.20 α level found to be associated with clinically significant blood loss in OA patients included [odds ratio (80% CI)] baseline C-reactive protein (CRP) levels [2.27 (1.46–3.53)], history of gastritis and history of GI intolerance [1.55 (1.06–2.28)], positive *Helicobacter pylori* at screening [1.54 (1.07–2.22)], increasing age [1.17 (1.04–1.32)] and body mass index [BMI; 1.03 (1.00–1.06)].

### Conclusions
Monitoring for decreases in haemoglobin should be considered for all OA patients and especially those with an increased age, BMI, history of gastritis and GI intolerance, CRP levels >1 mg/dL and/or positive *H. pylori* status, as this may affect their clinical management.

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## INTRODUCTION

Nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) plus a proton pump inhibitor (PPI) or cyclooxygenase (COX)-2 selective NSAIDs are similarly effective in reducing the risk of upper gastrointestinal (GI) events in patients at high GI risk.[1] With average cardiovascular (CV) risk, current guidelines recommend the use of a COX-2-selective NSAID for patients at GI risk who need NSAIDs.[2] However, there is strong evidence suggesting that all NSAIDs are associated with damage in the upper and lower GI tracts. The intestinal damage associated with the use of NSAIDs includes the development of increased mucosal permeability, inflammation, erosions, ulcers, malabsorption, strictures, perforation and blood loss that can be either acute or chronic in nature and with/without identified mucosal lesions.[3]

A decrease in haemoglobin of $\geq 2$ g/dL has previously been suggested as a clinically relevant marker of mucosal damage[4] and has been evaluated as an end point of clinical interest in several GI outcome studies.[5–8] While the clinical relevance of a $\geq 2$ g/dL decrease in haemoglobin is currently the subject of active debate,[3] this measurement serves as a potential marker of NSAID damage throughout the entire GI tract.

In two large scale, independent randomised controlled outcome trials [Celecoxib vs. Omeprazole and Diclofenac for At-Risk Osteoarthritis and Rheumatoid Arthritis Patients (CONDOR)[1] and Celecoxib Long-term Arthritis Safety Study (CLASS) (non-aspirin using sub-population)[9]], clinically significant decreases in haemoglobin occurred, in non-aspirin using patients, in a similar fashion over time despite differences in trial design.[10] These findings support the clinical reproducibility of this outcome, related to continuous long-term NSAID treatment.

The CONDOR trial[1] showed that independent of the use of a PPI, both COX-2 selective NSAIDs and nonselective NSAIDs were associated with clinically significant blood loss, predefined as decreases in haemoglobin $\geq 2$ g/dL and/or haematocrit drop $\geq 10\%$. In fact, the decrease in haemoglobin $\geq 2$ g/dL adjudicated as of defined GI origin or presumed GI origin was found to be the main component of the composite primary GI end point in the CONDOR trial (92 of 101 predefined Clinically Significant Upper and Lower GI Events). We considered it important to define the risk factors for this component of the primary outcome, clinically significant blood loss, since it may be relevant for the management of patients treated with NSAIDs in clinical practice.

Therefore, a *post hoc* analysis of data from the CONDOR trial was conducted to identify potential risk factors for a clinically significant blood loss, defined as: (i) a haemoglobin drop $\geq 2$ g/dL and/or a haematocrit drop $\geq 10\%$; and (ii) blood loss adjudicated as either of defined or presumed GI origin.

## MATERIALS AND METHODS

This was a *post hoc* analysis of the CONDOR trial in which clinically significant blood loss was investigated. Clinically significant blood loss was predefined in the CONDOR trial as: (i) haemoglobin drop $\geq 2$ g/dL and/or a haematocrit drop $\geq 10\%$; and (ii) blood loss was adjudicated as either defined or presumed GI origin, based on all the available clinical data. This same definition is used in this analysis.

The CONDOR trial (NCT00141102) was a double-blind, parallel-group, multicentre, international trial that randomised a total of 4484 patients to receive either oral celecoxib 200 mg twice a day or diclofenac slow release (SR) 75 mg twice a day plus omeprazole 20 mg once a day for 6 months. Patients had osteoarthritis (OA) and/or rheumatoid arthritis (RA) with a high risk of GI adverse events, were *Helicobacter pylori* negative and were not allowed to use aspirin. A detailed description of the study design has been published previously.[1, 3]

Members of an independent, blinded adjudication committee (FKLC, JG, AL, JS) determined whether the primary end point was attained according to the predefined criteria in the primary analysis of the CONDOR data.[1] The GI event was adjudicated as clinically significant blood loss of defined GI origin when the bleeding source was identified. Without a defined source, if there was no clinical or laboratory evidence of a non-GI source of blood loss, the event was adjudicated as clinically significant blood loss of presumed occult GI origin, including possible small-bowel blood loss.

### Data analysis

From the collected baseline data, 15 potentially relevant risk factors for the clinically significant blood loss in OA/RA patients were identified based on previous studies demonstrating risk factors for upper GI events[11, 12] and lower GI tract (increasing age and prior lower GI event) of NSAID users.[13, 14] Potential demographic risk factors included increased age (continuous variable), race (white, black, Asian, Hispanic, other), and gender (female vs. male). The risk factors found to be relevant in the medical history included *H. pylori* status at screening (positive vs. negative testing based on local standards per protocol), primary diagnosis (RA vs. OA), history of upper GI complications (yes vs. no), history of



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gastritis and GI intolerance (yes vs. no), prior PPI use within 6 months of randomisation (yes vs. no), alcohol consumption (did not drink vs. drank), body mass index (BMI; continuous variable), documented history of lower GI disorders (ulcerative colitis, Crohn's disease, small-bowel perforation, large-bowel perforation, small-bowel obstruction, large-bowel obstruction, bowel carcinoma, and/or haemorrhoids) (yes or no), prior steroid use within 6 months of randomisation (yes vs. no) and patient-reported history of anaemia (yes vs. no). Potentially relevant baseline laboratory data included baseline haemoglobin (g/dL; continuous variable) and baseline C-reactive protein (CRP) level (>1 vs. $\leq$1 mg/dL).

Analysis was conducted in the intention-to-treat (ITT) population, including all patients randomly allocated to treatment.[1] In CONDOR, patients treated with celecoxib had fewer haemoglobin drops than patients treated with diclofenac SR plus omeprazole (15 vs. 77 patients)[1]; however, as there were only 15 events in the celecoxib arm, an independent analysis of risk factors for a $\geq$2 g/dL haemoglobin drop by study arm was not feasible.

A descriptive statistical summary of the data was first conducted and presented by the binary response variable. To evaluate the potentially relevant risk factors, a stepwise logistic regression model with adjustment for treatment was used. Each risk factor had to be statistically significant at 0.20 $\alpha$ level to be included as a risk factor during the selection process and in the final model.[15]

Odds ratios, 80% CIs and associated *P* values ($\chi^2$ testing) for the potentially relevant risk factors identified were calculated. The significance was taken to higher level ($P < 0.20$, 80% CI level) as the CONDOR trial was not designed and not powered for testing these risk factors.

In a preliminary analysis, the OA/RA cohort was first analysed with the inclusion of both baseline haemoglobin value and primary diagnosis (OA vs. RA) in the model. However, as a result of the observation of a low correlation between baseline haemoglobin level and haemoglobin change from baseline ($\rho = 0.27$), the baseline haemoglobin level was removed from the logistic regression model. Steroid use was also determined to be a confounding factor due to an imbalance in steroid use within the RA population. To avoid this confounding factor and to provide a clearer understanding of the risk factors associated with a decrease in haemoglobin/haematocrit in OA patients, further analyses were carried out on the OA population only, who comprised the majority of patients in CONDOR (3774/4484). The limited number of patients with RA in the study prevented reliable analysis of risk factors for this subset of patients.

## RESULTS

A total of 136/4484 OA and RA patients in the ITT population had a $\geq$2 g/dL decrease in haemoglobin and/or $\geq$10% decrease in haematocrit and the events were sent for adjudication. Of these 136 OA/RA patients, 92 were adjudicated as having 'Clinically Significant Upper and Lower GI Events' (Figure 1).

The final risk factors included in the model were: baseline CRP levels (>1 mg/dL vs. $\leq$1 mg/dL); positive *H. pylori* at screening (yes vs. no); age; history of gastritis and GI intolerance (yes vs. no), BMI, race, gender, prior PPI use, alcohol consumption, history of upper GI complications, history of lower GI disorders and history of anaemia.

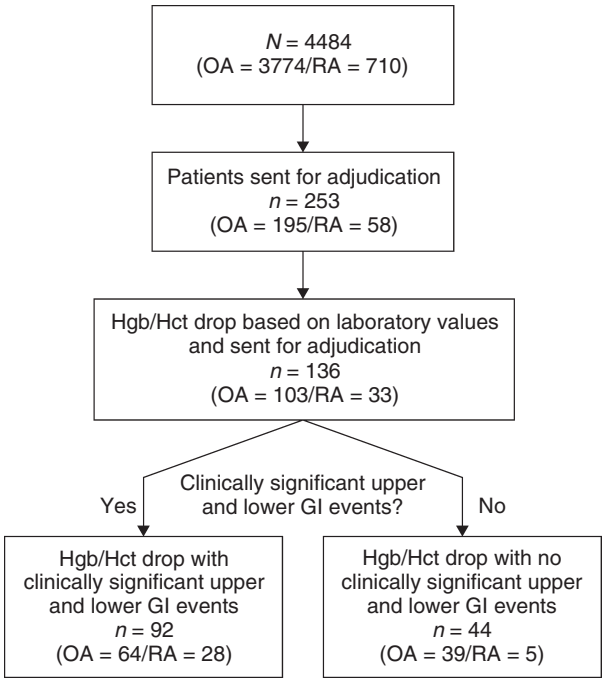


**Figure 1 |** Flow diagram of patients with OA/RA referred for adjudication for a decrease in haemoglobin $\geq$2 g/dL and/or haematocrit $\geq$10% from baseline. Clinically significant upper and lower GI events defined as a composite of clinically significant events occurring throughout the GI tract. Components were gastroduodenal, small-bowel or large-bowel haemorrhage; gastric-outlet obstruction; gastroduodenal, small-bowel or large-bowel perforation; clinically significant anaemia of defined GI or presumed occult GI origin (including possible blood loss from the small bowel) and acute GI haemorrhage of unknown origin (including presumed small-bowel haemorrhage). Clinically significant anaemia was defined as a decrease in haemoglobin of $\geq$2 g/dL, or a decrease in haematocrit of $\geq$10%.

**Table 1 |** Descriptive summary of baseline demographics, medical history and laboratory values for OA patients in the CONDOR trial

| | ≥2 g/dL decrease in Hgb and/or ≥10% decrease in Hct and confirmed cases (*N* = 3774) | |
|---|---|---|
| | Yes 64 (1.70) | No 3710 (98.30) |
| Demographic characteristics | | |
| Age | | |
| *N* | 64 | 3710 |
| Mean (s.d.) | 67.2 (7.51) | 65.7 (7.33) |
| Median | 67.0 | 66.0 |
| Range | 45.0–88.0 | 26.0–93.0 |
| Race | | |
| White | 35 (54.69) | 2172 (58.54) |
| Black | 2 (3.13) | 96 (2.59) |
| Asian | 5 (7.81) | 363 (9.78) |
| Other | 4 (6.25) | 333 (8.98) |
| Hispanic | 18 (28.13) | 746 (20.11) |
| Gender | | |
| Female | 55 (85.94) | 3068 (82.70) |
| Male | 9 (14.06) | 642 (17.30) |
| Medical history | | |
| *Helicobacter pylori* status at screening | | |
| Negative | 46 (71.88) | 2967 (79.97) |
| Positive | 18 (28.13) | 743 (20.03) |
| History of upper GI complications | | |
| No | 54 (84.38) | 3102 (83.61) |
| Yes | 10 (15.63) | 608 (16.39) |
| History of gastritis and GI intolerance | | |
| No | 49 (76.56) | 3097 (83.48) |
| Yes | 15 (23.44) | 613 (16.52) |
| Prior PPI use within 6 months of randomisation | | |
| No | 53 (82.81) | 3137 (84.56) |
| Yes | 11 (17.19) | 573 (15.44) |
| Alcohol consumption | | |
| Did not drink | 56 (87.50) | 2995 (80.73) |
| Drank | 8 (12.50) | 715 (19.27) |
| BMI (continuous variable) | | |
| *N* | 64 | 3697 |
| Mean (s.d.) | 30.1 (6.37) | 29.1 (5.20) |
| Median | 28.2 | 28.4 |
| Range | 20.3–48.4 | 14.1–70.0 |
| History of lower GI disorders | | |
| No | 58 (90.63) | 3414 (92.02) |
| Yes | 6 (9.38) | 296 (7.98) |
| Prior steroid use within 6 months of randomisation | | |
| No | 64 (100) | 3683 (99.27) |
| Yes | 0 | 27 (0.73) |
| History of patient-reported anaemia | | |
| No | 63 (98.44) | 3598 (96.98) |
| Yes | 1 (1.56) | 112 (3.02) |
| Baseline laboratory data | | |
| Baseline haemoglobin (g/dL) (continuous variable) | | |
| *N* | 64 | 3687 |
| Mean (s.d.) | 14.1 (1.27) | 13.6 (1.10) |
| Median | 14.2 | 13.6 |
| Range | 11.7–17.0 | 9.9–18.9 |
| Baseline CRP level | | |
| ≤1 mg/dL | 53 (82.81) | 3397 (92.06) |
| >1 mg/dL | 11 (17.19) | 293 (7.94) |

Values are *n* (%) unless otherwise specified.

The baseline characteristics for the OA patients are shown in Table 1. A total of 3774 patients were analysed in the OA cohort. Of these patients, 64 had a ≥2 g/dL decrease in haemoglobin and/or ≥10% decrease in haematocrit adjudicated as a 'Clinically Significant Upper and Lower GI Event.' The logistic regression analysis in the OA cohort showed the significant risk factors, at the 0.20 $\alpha$ level, for clinically significant blood loss were: baseline CRP levels (>1 mg/dL vs. ≤1 mg/dL); positive *H. pylori* at screening (yes vs. no); age; history of gastritis and history of GI intolerance (yes vs. no) and BMI for

**Table 2 |** Risk factors for clinically significant decreases in haemoglobin (≥2 g/dL) and/or haematocrit (≥10%) in OA patients

| Risk factors | Odds ratio | 80% CI | *P* value* |
|---|---|---|---|
| CRP (>1 mg/dL vs. ≤1 mg/dL) | 2.27 | 1.46–3.53 | 0.0169 |
| Positive *H. pylori* at screening (yes vs. no) | 1.54 | 1.07–2.22 | 0.1263 |
| Age† (continuous variable) | 1.17 | 1.04–1.32 | 0.0845 |
| History of gastritis and GI intolerance (yes vs. no) | 1.55 | 1.06–2.28 | 0.1446 |
| BMI‡ (continuous variable) | 1.03 | 1.00–1.06 | 0.1762 |

* Significance taken to upper level ($P < 0.20$, 80% CI level) as study was not designed for testing risk factors.

† Odds ratio estimate for every 5-year increase.

‡ Odds ratio estimate for every unit increase.



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developing clinically significant decreases in haemoglobin ($\geq$2 g/dL) and/or haematocrit ($\geq$10%) for these OA patients (Table 2). Race, gender, prior PPI use, alcohol consumption, history of upper GI complications, history of lower GI disorders and history of anaemia were not found to be predictive of clinically significant decreases in haemoglobin.

Additional analysis was conducted to determine if steroid use was associated with a haemoglobin drop. In the RA population, steroid use was associated with a $\geq$2 g/dL haemoglobin drop (11/403 patients without steroid use vs. 17/307 patients with steroid use; $P = 0.0569$). No patients in the OA population with steroid use had a $\geq$2 g/dL haemoglobin drop.

## DISCUSSION

In this *post hoc* analysis of the CONDOR trial, 64 OA patients treated with celecoxib or diclofenac SR plus omeprazole had a $\geq$2 g/dL decrease in haemoglobin and/or $\geq$10% decrease in haematocrit with an observed 'Clinically Significant Upper and Lower GI Event.' Among the 15 risk factors studied in this analysis, the risk factors found to be associated with blood loss in OA patients included increasing age, baseline CRP levels, *H. pylori* at screening, history of gastritis and GI intolerance and increasing BMI. While the significance of BMI as a risk factor was modest, this represents the first information on BMI as a predictive factor for blood loss throughout the GI tract in NSAID users. The reason for that is unclear, but it may represent the known association of obesity with more comorbidities.

Numerous risk factors previously have been identified to be associated with bleeding in the upper GI tract (prior ulcer disease, use of multiple or high-dose NSAIDs, increasing age, anticoagulant treatment and *H. pylori* infection)[11, 12] or lower GI tract (increasing age and prior lower GI event) of NSAID users.[14, 16] The current analysis confirms these observations that increasing age and *H. pylori* at screening were found to be predictive of $\geq$2 g/dL decrease in haemoglobin due to either confirmed or presumed GI blood loss. *Helicobacter pylori* at screening and history of gastritis and GI intolerance should in principle be linked to blood loss from the upper GI tract and both should be within the same clinical spectrum. However, upper GI complications were not found to be an associated risk factor, likely due to their infrequent occurrence in the trial.

Idiopathic anaemia has been linked to *H. pylori* infection in multiple studies.[17] Although patients with active *H. pylori* infection were not enrolled in the study, the proportion of patients with a positive *H. pylori* infection who underwent eradication before enrolment was high (876/4484 or ~20%).[1] Whether this population represents one with a higher risk of developing a haemoglobin drop due to blood loss from the GI tract—wherever the lesion in the GI tract develops—when taking NSAIDs with pre-existing iron deficiency or lower iron deposits, needs to be proved, but they were clearly identified as susceptible to developing blood loss in this study.

History of gastritis and GI intolerance or dyspepsia has been found to be linked to a higher risk or to be a marker of gastroduodenal damage.[18, 19] This is especially relevant in areas where *H. pylori* infection is common. Patients in this trial were recruited in countries with high *H. pylori* infection rates and the presence of *H. pylori* infection was one of the main exclusion criteria. In any case, the current data cannot provide a clear reason to explain why both *H. pylori* infection and GI intolerance were identified as risk factors for haemoglobin drops due to GI blood loss, and requires further exploration. The CONDOR study design might have led to missed lesions in these patients (erosions, small ulcers) that could be responsible for the observed blood loss, since GI investigations/endoscopies were not always performed immediately after stopping the NSAID. Upper GI tract lesions potentially explaining haemoglobin drops do not exclude the presence of other lesions in the small bowel. This could not be demonstrated as the small bowel was not examined in CONDOR trial.

C-reactive protein was found to be the risk factor with the strongest association with the primary diagnosis. There is a growing body of evidence suggesting that development of OA is accompanied by inflammation, and that high-sensitivity (hs) CRP is a sensitive marker of systemic inflammation in these patients,[20] which may put them at a higher risk of developing GI adverse events. Some previous studies have demonstrated that elevated hs-CRP is associated with disease progression and a higher incidence of disease symptoms in patients with OA.[21–24] Nevertheless, in the CONDOR trial data were collected on CRP, not hs-CRP, and therefore we cannot confirm whether this specific CRP marker was the one actually associated with the outcome. In the current analysis, baseline CRP levels of >1 mg/dL were identified as a positive predictor of clinically significant GI blood loss. Indeed, there is evidence that serum CRP levels are associated with poor outcomes in patients with GI bleeding. In patients hospitalised with upper and lower GI bleeding, elevated serum CRP levels at hospital

admission were associated with greater mortality.[25] Although the current findings suggest CRP is a risk factor for clinically significant decreases in haemoglobin, further studies are needed to determine the specific contribution of CRP in OA disease pathogenesis.

Race, gender, prior PPI use, alcohol consumption and history of anaemia were not found to be predictive of clinically significant decreases in haemoglobin nor was the history of upper GI complications. In the CONDOR trial[1] and in previous studies[26, 27] where patients were treated with celecoxib or NSAID plus PPI a similar reduction in the number of upper GI complications was observed between the two treatments. Therefore, as all patients were treated with two equally effective treatments for the prevention of upper GI complications, it may explain why, in this trial, a history of previous upper GI bleeding was not singled out as a risk factor for GI blood loss.

We believe that the data presented in this *post hoc* analysis of the CONDOR trial are relevant to the real-life clinical situation facing many physicians prescribing NSAIDs today. First, the data are determined from a randomised clinical trial.[1] The analysis focuses on clinically significant blood loss (predefined as haemoglobin drop of $\geq 2$ g/dL and/or haematocrit drop of $\geq 10\%$) adjudicated as having confirmed or presumed a GI aetiology, as demonstrated by being included in the composite primary end point for the CONDOR trial, 'Clinically Significant Upper and/or Lower GI Events.' An analysis of pooled studies with patient-reported outcomes data showed those patients with haemoglobin decreases of $\geq 2$ g/dL were associated with no improvement in function irrespective of treatment group.[28] Furthermore, the clinical validity of a fall in haemoglobin levels of $\geq 2$ g/dL has been confirmed by its inclusion among the criteria for "major bleeding" by the Control of Anticoagulation Subcommittee of the International Society on Thrombosis and Haemostasis[29] and it has also been used as criteria for "major bleeding" in large CV outcome clinical trials.[30, 31] Secondly, the presence of even low-normal haemoglobin values has been shown to have a detrimental effect on clinical outcomes, particularly in elderly patients. Anaemia resulting from significant reductions in haemoglobin is associated with poorer physical performance, increased disability, more hospitalisations, impaired quality of life and a higher risk of CV events and overall mortality.[32–36] An analysis of pooled studies examining patient-reported outcomes data showed that those arthritis patients with haemoglobin decreases of $\geq 2$ g/dL failed to improve functional status irrespective of treatment group.[28]

The limitations associated with this *post hoc* analysis are the same as those described in the CONDOR trial.[1] The main limitations included excluding aspirin users and patients with a positive *H. pylori* status at screening, and adjudicating presumed occult GI bleeding by exclusion, rather than by direct confirmation of blood loss.[1] A further limitation included excluding the RA population. Although this criterion reduced the confounding effect of steroid use, the results cannot be extrapolated to patients with RA. Another limitation is the collection of CRP measurements rather than hs-CRP. Therefore, we could not confirm whether this specific CRP marker was the one actually associated with the outcome. In addition, as the CONDOR trial was not designed for testing risk factors, the significance could only be taken to the upper level of $P < 0.20$ and an 80% CI level.

In conclusion, the results of this analysis suggest OA patients with high GI risk should be considered for monitoring for potential decreases in haemoglobin, particularly in those with an increased age, BMI, history of gastritis and GI intolerance and/or positive *H. pylori* status, as this may affect their clinical management. This is especially relevant for OA patients with CRP levels >1 mg/dL. Based on these results, it appears to be clinically relevant to evaluate the risk factors that may predict decreases in haemoglobin levels in OA patients at particularly high GI risk, receiving treatment with NSAIDs.

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