Review

Long-term low dose glucocorticoid therapy in rheumatoid arthritis: a systematic review with meta-analysis on cardiovascular effects

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ABSTRACT

Objective. *Glucocorticoids (GCs) are widely used as first-line therapy in rheumatoid arthritis (RA) due to their rapid onset of action and strong efficacy. However, inappropriate use is associated with significant adverse effects. Long-term treatment with low doses has been considered relatively safe for most RA patients, although its cardiovascular (CV) impact remains controversial.*

Methods. *A systematic literature review was conducted using PubMed to evaluate the CV effects of long-term (≥12 months) low-dose GC therapy (<7.5 mg/day prednisone equivalent) in RA patients. Studies published between 2010 and 15 March 2026 were screened independently by two reviewers. Study quality was assessed using the Newcastle-Ottawa Scale for observational studies and the Cochrane Risk of Bias 2 tool for randomised controlled trials. A meta-analysis was performed to estimate pooled hazard ratios (HRs) with 95% confidence intervals.*

Results. *Ten studies were included in the review, of which five provided adjusted HRs suitable for meta-analysis. Long-term GC exposure even to low doses was associated with an increased risk of CV events (pooled HR 1.37; 95%CI 1.03-1.81; p=0.01). Substantial heterogeneity was observed among studies. Egger's test did not indicate significant publication bias.*

Conclusion. *Current evidence suggests that while short-term low-dose GC therapy may be relatively safe in selected RA patients, prolonged use and higher cumulative doses are associated with a slight increased CV risk, particularly in individuals with existing risk factors or comorbidities.*

Introduction

Glucocorticoids (GCs) are the most used anti-inflammatory and immunosuppressive drugs in the treatment of chronic immune-inflammatory rheumatological diseases (1). The first use of cortisone dates to 1949, when Drs Philip S. Hench, Edward C. Kendall, Charles H. Slocumb and Howard F. Polley (Mayo Clinic, Rochester, MN, USA) presented a case series of patients suffering from rheumatoid arthritis (RA), treated with cortisone (17-hydroxy-11-dehydrocorticosterone: compound E), with dramatic improvement in disease activity (2). In 1950 Drs. Philip S. Hench, Edward C. Kendall and Tadeusz Reichstein awarded the Nobel Prize in Physiology or Medicine "*for their discoveries relating to the hormones of the adrenal cortex, their structure and biological effects*" (3).

In 1955, the first data on the use of prednisone (PDN) in the treatment of RA was published (4). Of note, PDN allowed fewer side effects related to sodium retention than cortisone, maintaining the same clinical efficacy (4). In the following decades, the use of GCs spread to virtually all inflammatory musculoskeletal disorders and autoimmune connective tissue diseases, proving to be irreplaceable, almost in the initial phases, due to their rapid onset of action and effectiveness (5). However, it soon became evident that high cumulative GCs doses were associated with significant adverse effects, such as the development of insulin resistance/iatrogenic type II diabetes, intercurrent infectious events, frailty fractures and cardiovascular (CV) diseases (6).

The treatment of RA was therefore revolutionised by the discovery of the first conventional disease-modifying anti-

rheumatic drug (cDMARD), methotrexate, in 1988, and later by biological DMARDs (bDMARDs, with etanercept as the first, in 1998), followed in 2012 by targeted synthetic DMARDs (tsDMARDs) (7). New and promising therapeutic mechanisms are currently under investigation (8).

At this time, European and American guidelines for the treatment of RA consider GCs a bridging strategy while awaiting the full efficacy of cDMARDs (and, when needed, bDMARDs/tsDMARDs) (9,10). However, RA patients often remain on long-term treatment with low doses of GCs (11). This is due to the optimisation of daily doses, now far lower than in the past (*i.e.* usual less than of 5 mg per day of PDN equivalent), and the use of nighttime, programmed-release formulations designed to counter the circadian rhythms of the inflammatory response (12, 13).

Moreover, a daily low dose of GCs (<7.5 mg/day of PDN equivalent) has been defined by the European Alliance of Associations for Rheumatology (EULAR) as acceptable in terms of the risk/benefit ratio for most patients (14). This definition of 'low risk' has therefore generated considerable interest and numerous systematic literature reviews (SLRs) aimed at confirming or refuting efficacy and safety profile of chronic GCs for RA patients. Although an increased risk of infections and of frailty fractures has nonetheless been highlighted, the impact on the CV risk of each RA patient remains debated to date (15).

For this reason, current SLR with meta-analysis aims to analyse the most recent evidence available on the effects of long-term, low-dose GC therapy on the CV risk of RA patients, quantifying the risk to develop new CV events during time and providing detailed information for daily rheumatologic clinical practice.

Methods

Data source and search strategy

A SLR on the state of art on CV effects of low dose long-term use of GCs in RA patients has been performed according to the preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA) (Fig. 1) (16).

PubMed bibliographic database has been utilised for manuscript search until 15th March 2026. The search strategy employed a combination of Medical Subject Headings (MeSH): ("Arthritis, Rheumatoid" OR "Rheumatic Diseases") AND ("Antirheumatic Agents" OR "Glucocorticoids" OR "Prednisone" OR "Prednisolone") AND ("Cardiovascular Diseases" OR "Myocardial Infarction" OR "Stroke" OR "Hypertension" OR "Cause of Death" OR "Treatment Outcome").

Screening process and eligibility criteria

The initial screening of the manuscripts was independently performed by two authors, EG and RC, who reviewed titles and abstracts for relevance.

The inclusion criteria were structured around the PICO (Population, Intervention, Control, Outcomes) framework (17), as follows:

- Population (P): adult human patients (≥18 years) diagnosed with RA according to 2010 ACR/EULAR classification criteria
- Intervention (I): long-term treatment (defined as drug exposure for at least 12 months) with low-dose GCs (defined as an average dose of ≤7.5 mg/day of PDN equivalent)
- Control (C): RA patients not exposed to GCs or exposed for a short-term period (less than 12 months)
- Outcomes (O): all CV events incidents reported by the authors (*i.e.* myocardial infarction, stroke, or new-onset hypertension).

We included in the SLR original articles with different study designs, as observational cohorts, nested case-control studies and randomised clinical trials (RCTs). We excluded reviews, editorials and congress abstracts.

Any disagreements between reviewers during the screening process were settled through discussion until agreement was reached. Data extraction and analysis were then carried out using a predefined standardised template to ensure consistency and accuracy in the assessment of the included studies.

When quantitative data were available, they were collected and summarised across the included studies. Specifically, we evaluated the HR adjusted for confounders for CV events during the treatment of low dose GCs. The eligibility criterion of ≤7.5 mg/day of PDN equivalent was selected in accordance with the EULAR definition of long-term acceptable low-dose GC therapy (14).

Quality assessment

The methodological quality of the included studies was assessed using evaluation tools appropriate for their study design. For cohort and case-control studies, quality was appraised using the Newcastle-Ottawa Scale (NOS), which assigns a maximum of nine points across three domains: selection (up to four stars), comparability (up to two stars), and outcome or exposure assessment (up to three stars). Higher scores indicate better methodological quality (18).

According to our predefined criteria, studies scoring ≥7 were considered to have a low risk of bias, those with scores between 4 and 6 were classified as having a moderate risk of bias, and studies scoring ≤3 were regarded as having a high risk of bias.

The risk of bias of RCTs was assessed using the Cochrane Risk of Bias (RoB 2) tool (19). The tool evaluates five domains: randomisation process, deviations from intended interventions, missing outcome data, outcome measurement and selection of reported results. Each domain was rated as low risk, some concerns, or high risk, leading to an overall risk of bias judgement.

The assessment of quality was performed independently by two reviewers (EG and RC). Each rater scored all the subjects, and the consistency of their ratings were evaluated using the Intraclass Correlation Coefficient (ICC). Specifically, a two-way random-effects model with absolute agreement for the average measures was applied, corresponding to ICC(A,2). Statistical significance was tested with an F-test, and 95% confidence intervals (CI) were calculated for the ICC. All analyses were performed with R software.

Statistical analysis

The meta-analysis was performed to evaluate the CV risk associated with long-term, low-dose GCs therapy across

the included studies. For the purpose of quantitative synthesis, only studies providing adjusted hazard ratios were included in the meta-analysis. Studies reporting exclusively on new-onset arterial hypertension were retained within the systematic review for narrative synthesis but were not pooled. For quantitative synthesis, the individual study effect sizes were extracted or converted to the natural logarithm of the hazard ratio (LogHR) with their corresponding standard errors (SE). We calculated the pooled effect estimate using a random-effects model to account for potential variability between study populations. The results showed a pooled hazard ratio (HR) and a 95% CI. The presence and extent of heterogeneity among the studies were rigorously assessed. We employed the Cochrane Q-test to evaluate the null hypothesis of homogeneity and calculated the I^2 statistic to quantify the percentage of total variation across studies due to heterogeneity rather than sampling error. Furthermore, the between-study variance was estimated using the tau-squared (tau^2) statistic. To further explore the potential sources of the observed heterogeneity, a mixed-effects meta regression was conducted. In this model, study quality, as assessed by the NOS or the RoB 2 where appropriate, served as the primary moderator. We determined the proportion of heterogeneity accounted for by the quality scores using the R^2 statistic and evaluated the residual heterogeneity (residual I^2 and QE statistic) to assess the explanatory power of the model. A leave-one-out sensitivity analysis was performed to assess the robustness of the pooled estimate, sequentially excluding one study at a time and re-fitting the random-effects model on the remaining four studies (Supplementary Fig. S1). To contextualise the clinical relevance of the pooled HR, the Absolute Risk Difference (ARD) and Number Needed to Harm (NNH) were calculated using the formula $ARD = (HR - 1) \times I_0$, where HR represents the pooled hazard ratio and I_0 the baseline cumulative incidence of CV events in patients not receiving GCs. The 95% CIs for ARD and NNH were derived by applying the same formula to the lower and upper bounds of the pooled HR 95% CI, with NNH CI limits obtained as the inverse of the ARD CI limits. The selection of I^2 values requires justification; among the included studies, Coburn *et al*. (2024) was the only one providing stratified baseline CV event incidences from a GC-free control arm, and uniquely reporting these estimates according to CV risk profile. Two reference incidences were therefore applied: 1.1% per year for older, more comorbid patients (Medicare cohort) and 0.67% per year for younger, healthier patients (CDM cohort). This stratified approach was chosen to reflect the clinical heterogeneity of RA patients encountered in routine practice, where the absolute CV risk associated with GC therapy is expected to vary substantially according to the patient's baseline risk profile. ARD and NNH were calculated for both the pooled HR and the individual study HRs, to illustrate how absolute risk estimates vary across the range of effect sizes observed in the included studies. All statistical analyses were performed using R Statistical programme.

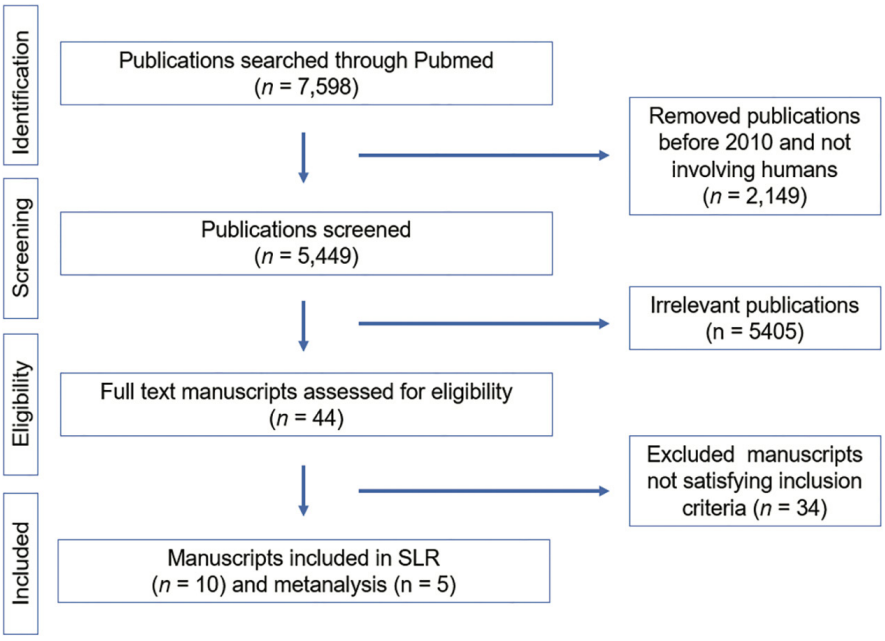

Fig. 1. Flowchart of the systematic literature review with metanalysis on cardiovascular effects of low-dose long term treatment with glucocorticoids in patients suffering from rheumatoid arthritis according to PRISMA guidelines. SLR: systematic literature review

Results

Search results

A total of 5,449 abstracts identified through PubMed Central database were screened, of which ten studies met the eligibility criteria and were included in the systematic review (Fig. 1). The literature search and study selection process are summarised in Figure 1. The ten included manuscripts were subsequently analysed, and data was extracted for the metanalysis. (Fig. 1). Five manuscripts were included in the quantitative analysis, as these were the only studies reporting HRs comparing low-dose GC use in RA patients with appropriate adjustment for relevant confounding factors.

Study characteristics and inter-rater reliability

The ten screened articles included RA patients from different continents (North America, Europe, Asia) (20-29). Eight manuscripts had retrospective design, one a prospective design and one was a double-blinded RCT *versus* placebo. All the characteristics are resumed in Table I.

The total scores assigned by EG and RC showed perfect inter-rater reliability, with an ICC (A,2) of 1.00, indicating complete agreement between the raters. All manuscripts received identical scores from both raters, demonstrating excellent consistency and concordance. Statistical tests for significance

Table I. Characteristics of the studies included in the systematic review and in the meta-analysis of the cardiovascular effects of long-term low-dose treatment with glucocorticoids in patients suffering from rheumatoid arthritis.

	Wilson, 2019	**Pujades Rodriguez, 2020**	**Roubille, 2021**	**Ocon, 2021**	**Costello, 2021**
Ref. number	20	21	22	23	24
Study design	Retrospective cohort and nested case-control	Retrospective, cohort	Observational, cohort	Retrospective, cohort	Retrospective, cohort
Country	United Kingdom	United Kingdom	France	United States of America	United Kingdom
RA patients, n	34,050	25,324	608	19,902	17,760
Age, years	52.2 (mean)	57 (median)	47.5 (mean)	57.82 (mean – RA without CV events); 65.44 (mean – RA with CV events)	56.3 (mean)
Females, n (%)	23,991 (70.5%).	18,361 (72.5)	480 (78.9)	15,399 (77.4)	12,101 (68 %)
RA patients treated with long-term low-dose GCs, n (%)	13,770 (40.4%) received at least one oral GC prescription.	Total oral GC users: 4,945 (subgroup on <5 mg dose not specified)	397 (65%)	19,902 (100%)	2,175 (12.3%) were continuous users of GCs over 2 years (data for the low-dose subgroup were not specifically reported.)
'Low-dose', mg/day of prednisone-equivalent	<5	1–4.9	1.9 (IQR 0.6-4.2)	1– <5	<5
Period of treatment	8.1 ± 16 years (mean±SD)	5 years (median)	44.6 months (mean)	12 months	2 years
Reported CV events	Thrombotic stroke Myocardial infarction	Atrial fibrillation Heart failure Acute myocardial infarction Peripheral arterial disease Cerebrovascular disease Abdominal aortic aneurysm	Myocardial ischaemia Stroke Heart failure	Coronary revascularisation Stroke Myocardial infarction Congestive heart failure	Arterial hypertension
Results	<5 mg daily did not show a statistically significant increase in the risk of thrombotic stroke or MI compared to RA patients not using GCs (OR 1.05; 95% CI 0.81–1.37).	Increased risk of CV associated with GC dose intake even at low dose (<5 mg daily)	Cumulative dose >8.4 g (equivalent to 5 mg/day for 5 years) significantly raises the incidence of CV diseases to 7.9% compared to 1.4% in non-users.	Initiating prednisone at doses <4 mg daily is not associated with an increased CV risk over one year, but the risk becomes statistically significant (HR 1.47) if the total annual cumulative dose is 1100-2100 mg	No significant association with arterial hypertension
HR adjusted	NA	1.84	NR	1.47	1.10
CI 95% (lower)	NA	1.62	NR	1.06	0.98
CI 95% (upper)	NA	2.1	NR	2.03	1.24
Incidence in GC-free RA patients at 1 year	NA	1.4%	NA	NA	NA
Confounders adjusted	RA duration, cardiovascular history/risks, comorbidities, lifestyle and medications	Demographics, socioeconomics, lifestyle comorbidities, biomarkers, prior hospitalisations, and medication use	NA	Demographics, RA duration/severity CV history/risks, comorbidities, lifestyle and baseline medications	Demographics, lifestyle, Charlson comorbidity index, time-varying synthetic DMARD use, and time-varying NSAID use
Quality, NOS	8/9 (High)	8/9 (High)	8/9 (High)	8/9 (High)	8/9 (High)
Risk of bias, RoB 2	NA	NA	NA	NA	NA

	Boers/Cutolo, 2022	**So, 2023**	**Coburn, 2024**	**Giollo, 2025**	**Sugitani, 2025**
Reference	25	26	27	28	29
Study design	Double blind randomised clinical trial (the only interventional *vs*. placebo)	Retrospective, cohort	Retrospective, cohort	Prospective, cohort	Prospective, cohort
Country	Multicentre, Europe	Hong Kong	USA	Italy	Japan
RA patients, n	449	12,233	174,855	229	10,613
Age, years	72.5 (mean – RA prednisolone group); 72.6 (mean – RA placebo group)	57.7 (mean)	68.4 (mean)	57 (mean)	59 (median)

	Boers/Cutolo, 2022	So, 2023	Coburn, 2024	Giollo, 2025	Sugitani, 2025
Females, n (%)	316 (70.1)	9,953 (81.4)	47,6 (82%)	188 (82.1%)	8,881 (83.7%)
RA patients treated with long-term low-dose GCs, n (%)	224 (50%) *vs*. placebo	750 (6.1%)	57,800 (33.1)	124 (54.1%)	3382 (31.9%)
'Low-dose', mg/day of prednisone-equivalent	5	<5	<5	<5	<5
Period of treatment	24 months (as per study design)	8.7 years (mean)	1 year	36 months	14 years
Reported CV events	Myocardial infarction Cerebrovascular event Peripheral arterial vascular event Arterial hypertension	MACE (myocardial infarction, unstable angina, ischaemic or haemorrhagic cerebrovascular accident, transient ischaemic attack, CV death)	Myocardial infarction Stroke	Myocardial infarction Arterial hypertension	Heart failure Ischaemic heart disease Aortic dissection CV death
Results	Add-on low-dose prednisolone has beneficial long-term effects in senior patients with established RA without increased CV risk over 2 years (RR 1.7 in the prednisolone group *vs*. 2 in the placebo group)	No significant association with increased MACE risk compared to no GC use	Low-dose GCs increase bid (HR 1.23) and high-bid (HR 1.23) and high-risk patients (HR 1.29), but not in younger, healthier patients (HR 1.20).	Low-dose GCs were associated with higher, non-significant CV morbidity *vs*. discontinuation (arterial hypertension 20% *vs*. 11%; myocardial infarction 2.3% *vs*. 0%).	Low dose long term GCs is associated with an increased risk of CV disease (HR 1.69, 95% CI: 1.14–2.51) and CV mortality including sudden death (HR 1.38, 95% CI: 0.99–1.93)
HR adjusted	NA	0.84	1.23	NA	1.69
CI 95% (lower)	NA	0.62	1.11	NA	1.14
CI 95% (upper)	NA	1.15	1.36	NA	2.51
Incidence in GC-free RA patients		0.8%	CDM: 0.67% Medicare: 1.1%		
Confounders adjusted	NA	Demographics, traditional CV risk factors, inflammatory markers and the usage of anti-rheumatic drugs.	Demographics socioeconomics lifestyle, comorbidities, RA severity healthcare utilisation and concomitant medications	NA	Demographics, lifestyle, comorbidities, disease activity, concomitant medications
Quality, NOS	NA	9/9 (High)	9/9 (High)	7/9 (High)	9/9 (High)
Risk of bias, RoB 2	Low	NA	NA	NA	NA

CV: cardiovascular; DMARD: disease modifying anti-rheumatic drug; HR: hazard ratio; CI: confidence interval; GCs: glucocorticoids; IQR: interquartile range; MACE: major adverse cardiovascular events; NA: not applicable; NOS: Newcastle Ottawa Scale; NR: not reported; NSAID: non-steroidal anti-inflammatory drug; OR: odds ratio; RA: rheumatoid arthritis; RoB2: Cochrane Risk of Bias 2; RR: relative risk; SLR: systematic literature review; Medicare: U.S. federal health insurance program for individuals aged ≥65 years or with a disability; CDM: Clinformatics Data Mart, Optum's de-identified U.S. commercial health insurance database.

and CI were not applicable due to the absence of variability between ratings.

Results demographics

The included population comprised a large and heterogeneous sample of patients with RA, with study sizes ranging from 229 to 174,855 individuals. The mean or median age was generally in the late 50s to late 60s, with some studies focusing on older populations (*e.g*. Boers/Cutolo *et al*., 2022, with a mean age >72 years). Females accounted for approximately 70–84% of the study populations, reflecting the known epidemiology of RA. The studies were conducted across diverse geographic regions, including Europe (UK, France, Italy, and multicentre European cohorts), North America (USA), and Asia (Hong Kong and Japan), suggesting a degree of ethnic variability. Regarding GC exposure, most studies specifically evaluated long-term use of low-dose PDN-equivalent therapy, generally defined as <5 mg/day, although one randomised trial used a fixed dose of 5 mg/day. Reported daily doses ranged from approximately 1 to 4.9 mg/day, with some studies providing median values around 1.9 mg/day. Importantly, treatment duration varied substantially across studies, ranging from 1 up to 14 years. Some studies emphasised cumulative dose rather than daily dose alone, demonstrating that prolonged exposure, even at low daily doses, resulted in substantial cumulative intake (*e.g*. equivalent to 5 mg/day over 5 years), which was associated with increased CV risk.

Results of the systematic review

Large retrospective cohort studies consistently indicate that even low daily doses (<5 mg PDN-equivalent) may be associated with an increased CV risk, particularly when cumulative exposure is high or treatment is prolonged. Pujades Rodriguez *et al*. reported a significant increase in CV risk even at low doses (HR 1.84, 95% CI 1.62–2.1) (21), while Sugitani *et al*. found a similar association with long-term exposure (HR 1.69, 95% CI 1.14–2.51), includ-

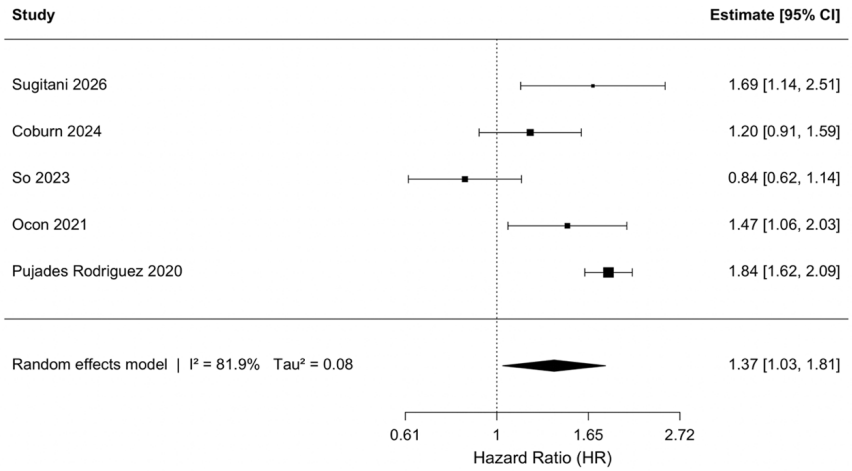

Fig. 2. Forest plot showing hazard ratios (HRs) and 95% confidence intervals (CI) for the association between CV risk and low dose long term GCs therapy in RA in the manuscripts included for meta-analysis. Squares represent study-specific effect estimates (with size proportional to study weight), and horizontal lines indicate 95% CIs. The dashed vertical line marks the null effect (HR=1). The pooled estimate from the random-effects model is shown as a diamond (HR 1.37, 95% CI 1.03–1.81), indicating a statistically significant overall association. Substantial heterogeneity was observed ($I^2 = 81.9\%$, $\tau^2 = 0.08$).

ing increased CV mortality (29). Similarly, Roubille *et al*. demonstrated that a cumulative exposure equivalent to 5 mg/day over five years significantly increased CV disease incidence (7.9% *vs*. 1.4% in non-users) (22).

A smaller prospective study by Giollo *et al*. suggested a trend toward higher CV morbidity with continued low-dose GC use compared to discontinuation, although results did not reach statistical significance (28). Nevertheless, the RCT by Boers/Cutolo *et al*., the only interventional study *versus* placebo in a population at high risk of comorbidities (aged over 65), found no increased CV risk with add-on low-dose prednisolone over two years in patients with established RA, with numerically fewer events in the treatment group compared to placebo (25).

Likewise, So *et al*. reported no significant association between low-dose GC use and MACE (26), and Coburn *et al*. further refined this perspective, showing that increased CV risk was primarily observed in older or comorbid patients (HR 1.23–1.29), whereas younger and healthier individuals did not exhibit a statistically significant increase (27). Interestingly, a nested case-control study reported that doses below 5 mg/die of PDN did not increase the risk of thrombotic stroke or myocardial infarction compared with RA patients not receiving GCs (OR 1.05; 95% CI 0.81–1.37) (20).

Similarly, in a retrospective cohort study no significant association with

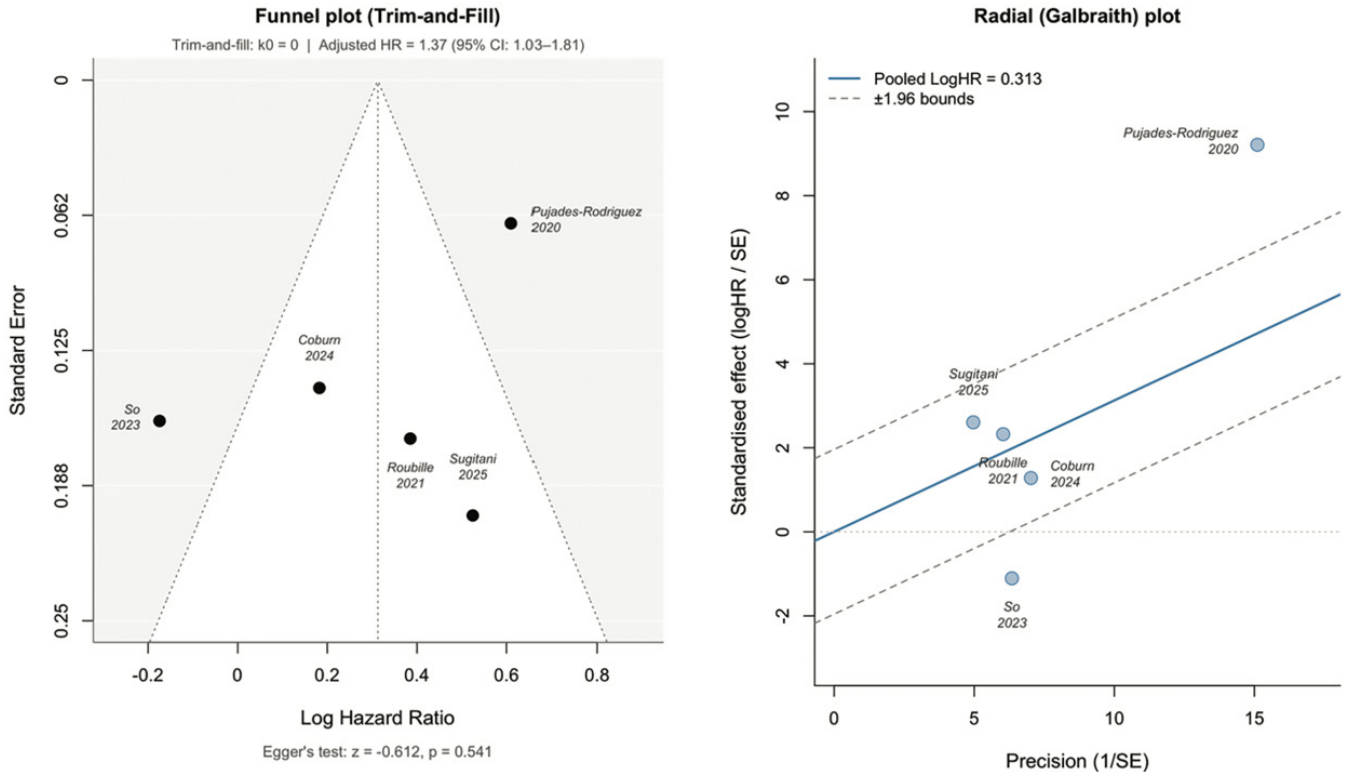

Fig. 3. Funnel plot with trim-and-fill procedure (left panel) and Radial (Galbraith) plot (right panel) for assessment of publication bias and small-study effects in the manuscripts included for meta-analysis. Egger's regression test did not show statistically significant asymmetry (z= -0.612, *p*=0.541; intercept = 0.600, 95% CI: -0.372 to 1.571). The trim-and-fill procedure identified no imputed studies (k0=0), with an adjusted pooled HR of 1.37 (95% CI: 1.03–1.81). Given the limited number of included studies (k=5), these results should be interpreted with caution.

arterial hypertension and low dose GCs was reported (HR 1.10.; 95% CI 0.98–1.24) (24). This finding is noteworthy and warrants consideration, but the data was not included in the meta-analysis to avoid conflating the isolated hypertension outcome with other CV events, such as myocardial infarction and thrombosis.

Interestingly, Ocon *et al*. found that initiating low-dose PDN (<4 mg/day) was not associated with increased CV risk over one year; however, risk became significant (HR 1.47, 95% CI 1.06–2.03) when the annual cumulative dose reached 1100–2100 mg (23).

Results of the meta-analysis

A random-effects meta-analysis was conducted to evaluate the impact of low-dose GCs on CV risk in RA patients, including only studies reporting HRs adjusted for confounders. Ten studies were included, comprising a total of five remaining for the presence of HR adjusted for confounders (Table I). The pooled HR for CV events among patients exposed to GCs was 1.37 (95% CI: 1.03–1.81; p=0.01) (Fig. 2). This indicates that low-dose long-term GC use was significantly associated with a modest increase in the risk of CV events in the included populations.

Considerable heterogeneity was observed across studies (I^2=81.9%, τ^2=0.08, τ=0.283; p<0.01), reflecting substantial variability in effect estimates (Fig. 2). Despite a statistically significant effect, the high heterogeneity, possibly due to the limited number of included studies (n=5), restricts the generalisability of the results.

A mixed-effects meta-regression was performed to investigate whether study quality, assessed using NOS or RoB 2 as appropriate, could explain the observed heterogeneity among studies. The analysis showed a negative, non-significant association between study quality and HR (β=-0,359, SE=0.245, z=-1.465, p=0.143), suggesting a trend toward lower risk estimates in higher-quality studies that did not reach statistical significance. Residual heterogeneity remained moderate (τ^2=0.0526, τ=0.229, I^2=70.5%, QE (df=4)=13.56), indicating that study quality accounted for only a modest portion of the variability (R^2=34.58%).

Egger's regression test was performed to evaluate potential funnel plot asymmetry and small-study effects (Fig. 3). The analysis did not show evidence of significant asymmetry (z=-0.612, p=0.541). The intercept was estimated at b=0.600 (95% CI: -0.372 to 1.571), with the CI including zero, further suggesting the absence of statistically significant publication bias. Of note, given the limited number of included studies (k=5), Egger's test has insufficient statistical power to reliably detect funnel plot asymmetry, and these results should be interpreted with caution. Leave-one-out sensitivity analysis confirmed the robustness of the pooled estimate, with HRs ranging from 1.24 (95% CI: 0.93–1.66) to 1.56 (95% CI: 1.26–1.92) across all combinations. The direction of the association remained consistent in all scenarios. The exclusion of So *et al*. (2023), yielded the strongest and only statistically significant estimate (HR=1.56, 95% CI: 1.26–1.92, p<0.05). These findings suggest that ethnic and demographic differences across study populations may partly account for the observed between-study heterogeneity, while the overall direction and magnitude of the CV risk associated with long-term low-dose GC therapy remained stable regardless of which study was excluded. To contextualise the clinical relevance of the pooled HR, ARD and NNH were calculated applying the baseline CV event incidences from the GC-free arms of Coburn *et al*. (2024), the only included study providing stratified estimates by CV risk profile. Applying the pooled HR of 1.37 (95% CI: 1.03–1.81), the ARD was 0.40% (95% CI: 0.03–0.89%) with a NNH of 248 (95% CI: 112–3,333) in older, more comorbid patients (Medicare cohort, I_0 = 1.1%/year), and 0.25% (95% CI: 0.02–0.54%) with a NNH of 406 (95% CI: 185–5,000) in younger, healthier patients (Optum Clinformatics Data Mart cohort, I_0=0.67%/year). These findings indicate that while the relative risk increase is consistent across populations, the absolute CV risk attributable to long-term low-dose GC therapy is substantially greater in older patients with pre-existing CV comorbidities (Suppl. Fig. S2).

Discussion

The present SLR with meta-analysis summarised the available data on the CV effects of low-dose, long-term GC therapy in different cohorts of patients with RA even in populations at high risk of co-morbidities, and for the first time provided an adjusted HR for CV events, estimated at 1.37 (95% CI: 1.03–1.81). All the studies appear to agree in identifying a slight increase in adjusted HR ranging between 1.23 and 1.84, except for So *et al*. that estimated a decrease in adjusted HR of 0.84 (26). The divergent finding of So *et al*. (HR=0.84), identified as the primary source of heterogeneity by leave-one-out sensitivity analysis, is most plausibly attributed to the exclusively Asian study population, lower baseline CV event rates, and broader MACE definition adopted, rather than a genuine cardioprotective effect of GCs (26).

This finding is highly relevant for assessing the real CV risk of RA patients chronically treated with GCs and suggests that clinicians should consider all the factors that may confound this estimate (older age, male gender, pre-existing co-morbidities, disease activity, and concomitant therapies).

Of note, a prior CV condition remains the main predictor of CV mortality in RA patients assuming GCs (HR 1.89, 95% CI: 1.14–3.14), as claimed by Sugitani *et al* (29).

In 2024, Coburn *et al*. showed how GCs were associated with a dose-dependent increased risk of myocardial infarction and stroke, even at doses ≤5 mg/day in patients with comorbidities and high risk for CV disease, while no association was noted among younger, healthier patients with RA (27). The translation of the pooled HR into absolute risk estimates revealed a clinically meaningful difference between patient profiles: older, more comorbid patients face nearly twice the absolute CV risk compared to younger, healthier individuals (NNH 248 *vs*. 406), underscoring that the CV burden of long-term low-dose GC therapy is not uniform across

RA populations and strongly depends on the patient's baseline risk profile.

Therefore, baseline CV frailty stratification is essential to optimise GCs therapy using appropriate risk assessment tools (*e.g.* QRISK3, SCORE2, Framingham Risk Score) (30).

Although the CV risk appears increased, it is nonetheless more reassuring compared to older studies, particularly those in which daily PDN-equivalent dose >5 mg was systematically used for prolonged periods and in patients with longer-standing joint disease, classified according to the former ARA (American Rheumatism Association) 1987 criteria (31).

For this reason, to ensure data robustness, stringent inclusion criteria were applied to this analysis.

The cumulative dose threshold of GCs beyond which RA patients develop an unacceptable CV risk remains unclear (32). According to the study by Roubille *et al.,* a cumulative dose ≥8.4 g is associated with the highest risk of CV events (p=0.001) (22).

Unfortunately, in this SLR no data is available on the radiographic benefit associated with the initiation of GC therapy. Previous studies had reported a radiologically significant effect of adding GCs to background therapy with cDMARDs in RA patients, even at doses of PDN equivalent <7.5 mg/day (33, 34).

In particular, the administration of 7.5 mg of prednisolone daily in combination with cDMARDs, during the first two years of disease in a cohort of patients with early RA, demonstrated sustained efficacy up to 4 years in slowing radiographic damage and was statistically superior to cDMARD therapy alone (35).

Interestingly, another study showed that the use of GCs at doses of PDN equivalent ≤7.5 mg daily significantly increased the duration during which RA patients remained on cDMARD therapy (methotrexate and sulfasalazine) (36).

These effects on radiographic damage are likely due to the long-term genomic and epigenomic actions of GCs on inflammatory cells, interacting through different mechanisms on target genes (transactivation and transrepression), resulting in a sustained anti-inflammatory response over time (37).

Nonetheless, in our SLR, only Giollo *et al.*, reported conflicting data on radiological outcomes (28). Of note, in their study, baseline use of low-dose GCs appeared to be associated with reduced radiographic damage after 36 months (OR 2.5; 95% CI 1.3–5.0), although this finding did not seem to persist after adjustment for disease activity (28).

It should also be noted that the present SLR does not consider other common comorbidities associated with chronic GCs therapy, such as increased infection risk and bone demineralisation with a rise in fracture risk during the first months of GCs treatment (38, 39).

Conversely, no data is currently available on the long-term use of modified-release PDN formulations, which showed satisfactory results in the 12-week CAPRA-2 trial (40, 41).

Cumulative GC exposure emerged as a key determinant of CV risk across included studies. A total cumulative dose ≥8.4 g and annual cumulative doses of 1,100–2,100 mg (HR 1.47, 95% CI 1.06–2.03) were associated with significantly increased CV risk, whereas daily doses below 4 mg/day and annual cumulative doses below 1,100 mg did not confer additional risk (22,23).

Although all studies fall within the EULAR-defined low-dose range (≤7.5 mg/day), actual daily doses were often lower (median <5 mg/day in most cohorts), reflecting a potential 'within-low-dose' gradient of risk that our pooled estimate cannot fully capture. A formal dose–response meta-analysis was not feasible in the absence of individual patient-level data; however, available evidence suggests that daily doses <4 mg/day and annual cumulative doses <1,100 mg may not confer additional CV risk (14, 23).

Our inclusion of recent data highlights the ongoing debate regarding the "safety floor" of GC therapy (27, 29).

While the pooled estimate remains significant, the shift toward lower HRs in the most recent, high-quality studies suggests that modern management strategies, specifically the use of ultra-low doses may mitigate some of the CV risks associated with prednisone use.

The present analysis has some limitations inherent to the available evidence. The number of studies included in the meta-analysis (k=5) reflects the stringent eligibility criteria applied specifically the requirement for adjusted HRs from long-term low-dose GC exposure rather than a paucity of literature and should be interpreted in this context. The substantial residual heterogeneity observed (I^2=81.9%) reflects the clinical and methodological diversity of the included populations, which span different continents, healthcare systems, and CV risk profiles, and underscores the need for future individual patient data meta-analyses. No data was available on modified-release PDN formulations, and ARD and NNH estimates should be interpreted with caution as approximations derived from a single external reference cohort. Notwithstanding these limitations, the robustness of the pooled estimate across all leave-one-out combinations, the absence of significant publication bias, and the consistency of the direction of effect across geographically and ethnically diverse populations represent meaningful strengths of the present analysis.

Of note, as RA management continues to evolve, there is a clear need for prospective studies specifically targeting 'ultra-low' dosages (1 or 2 mg/day), to establish their long-term safety profile on CV risk. Other topics related to the long-term management of GCs in RA fall outside the scope of this analysis, such as therapy discontinuation and dose timing, which is addressed in other relevant studies (42, 43).

Finally, among the limitations of our manuscript, we underscore the need for cautious interpretation of the findings of the meta-analysis, due to high heterogeneity between-study and further research with larger, more homogenous cohorts is warranted to clarify the CV risk associated with low-dose long-term use of GCs in RA patients.

Conclusions

Overall, the current body of evidence indicates that while short-term low-dose GC therapy may be relatively safe in selected RA populations, prolonged use and mainly higher cumulative ex-

posure are associated with increased CV risk, particularly in patients with pre-existing risk factors or comorbidities. Control of CV risk factors remains essential for overall risk management, together with optimisation of GCs therapy, which continues to represent a relevant option in the therapeutic armamentarium for RA, particularly in the early stages of the disease.

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