Low-dose prednisolone treatment of early rheumatoid arthritis was associated with an increased risk of cerebrovascular events but not with coronary artery complications or overall survival: a ten year follow-up of a randomized trial

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Low-dose prednisolone treatment of early rheumatoid arthritis was associated with an increased risk of cerebrovascular events but not with coronary artery complications or overall survival: a ten year follow-up of a randomized trial

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Abstract

Objective: To examine the long-term effects of low-dose prednisolone use on cardiovascular (CV) morbidity and mortality in patients with early rheumatoid arthritis (RA).

Design: Retrieval of data from a 2-year open randomized trial comparing prednisolone 7.5 mg/day in addition to DMARDs with DMARD therapy alone. Participants were followed for ten years since inclusion into the original prednisolone trial or until occurrence of the studied outcomes.

Setting: Secondary level of care; six participating centres from southern Sweden; both urban and rural populations.

Participants: Overall, 223 patients with early RA were included and followed in the study. The participants had no history of CV events at baseline and incident cases were identified via the Swedish Hospital Discharge and Cause of Death Registries.

Outcomes: Composite CV event i.e. ischemic coronary and cerebrovascular event, components of the composite CV outcome, and death. Relative hazard ratios from Cox proportional-hazards regression models were calculated.

Results: Within 2041 person-years, 17 incident composite CV events occurred in 112 patients (15.2%) randomized to prednisolone, and 15 events out of 111 patients (13.5%) who were assigned not to receive prednisolone. Nine mortalities (8%) were observed in each group.

The age-adjusted hazards for the first composite CV event, first coronary event and death did not differ significantly between the two treatment groups. However, the risk for first cerebrovascular event showed a 3.7-fold hazard (95% CI, 1.2-11.4) among prednisolone treated patients as compared with those not treated with prednisolone, p=0.022. These results persisted in sensitivity analyses restricted to the participants who were adherent to the study protocol.

Conclusion: In this study low-dose prednisolone use during the first two years of RA disease was not associated with long-term coronary artery events or deaths, but with an increased risk of cerebrovascular events.

Article summary

Article focus

- To examine association between exposure to low-dose prednisolone in early rheumatoid arthritis (RA) and long-term cardiovascular (CV) outcomes and all-cause mortality.
- To study these associations separately for ischemic coronary artery events, ischemic cerebrovascular events and all-cause mortality.

Key messages

- Low-dose prednisolone exposure in early RA may influence cerebrovascular risk.
- Neither ischemic coronary artery events nor all-cause death was associated with low-dose prednisolone treatment in our study.

Strengths and limitations of this study

- Randomized allocation to therapy within the setting of prospective follow-up in the incident cohort of RA patients with diagnose validated by the ACR criteria.
- The treatment protocol was highly compliant with few patients who were lost to follow-up or discontinued the allocated therapy.
- Data on outcomes were derived from the reliable nationwide registry system and sampled during a long observation period sufficient for development of studied complications.
- The original prednisolone trial was not primarily designed to examine the risk of CV events and mortality; and the population studied was relatively young with low burden of traditional CV risk factors at inclusion.

Introduction

Glucocorticoids (GCs) are powerful anti-inflammatory agents which have been used since the 1950s, first, as symptomatic treatment of rheumatoid arthritis (RA), but in the last years, as disease modifying therapy. Thus, inhibition of the progression of radiological damage in RA has been documented for GCs given in addition to disease-modifying anti-rheumatic drugs (DMARDs).[1-3] However, the relationship between short-, and long-term GC exposure and cardiovascular (CV) events and mortality in RA is still controversial.

The discussion on the side effects of GC use is still far from settled. Whereas adverse effects of long-term GCs use, at least at high dose, are well recognized in the general population and include effects on blood pressure, insulin resistance, lipid profile, homeostasis, body weight and fat distribution,[4-10] the nature of unfavourable CV effects and possible modulation of effects of GCs by other processes in RA are less known.[11-13] Some data are available which imply that chronic GC-using has no additive pro-atherogenic effects in the inflammatory milieu.[14, 15] A systematic literature review has shown poor association between low-dose GC exposure and CV risk factors, and probably no effect on atherosclerosis in RA patients.[16] GCs may have anti-atherogenic effects mediated by their anti-inflammatory and anti-proliferative actions in the vessel wall, and modify the recovery from occlusive vascular events and intravascular injury.[17-19]

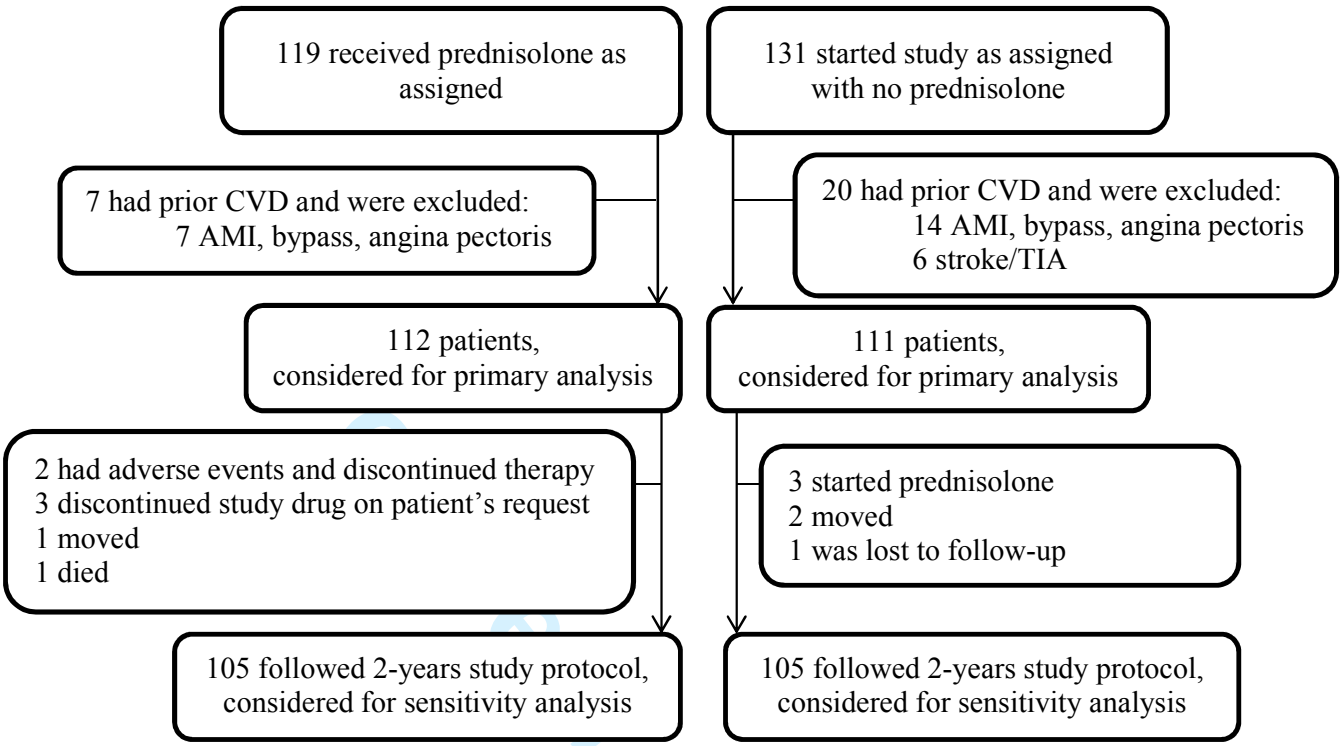
However, in the scientific literature, the potential risks and benefits of GC exposure in RA have shown disparate results. Increased CV and/or mortality risk associated with the use of GCs, particularly with increasing doses, has been found in several studies,[20-25] while other studies have found GCs use to improve CV/mortality prognosis,[26] or to have no or uncertain effect.[27, 28] Diversity of outcomes definitions, different stages of RA disease, GC exposure in various dosages at any time during follow-up, and the potential for confounding by indication in observational cohorts make the results of the studies not fairly conclusive.

In an attempt to shed some light on the CV risk of exposure to low-dose prednisolone in early RA, we performed this study with retrospective retrieval of data from the previously conducted randomized prednisolone trial, a BARFOT (Better Anti-Rheumatic PharmacOTherapy) study.[3]

Patients and Methods

Adults with a diagnosis of RA according to ACR classification criteria 1987[29] and symptom duration ≤ 12 months were eligible for the BARFOT programme.[30] The design of the 2-year low-dose prednisolone multicenter open-label randomized study, nested in the BARFOT cohort, has been described in detail previously.[3] Of 250 patients who entered the study with the treatments as assigned, 27 patients with a history of prior CV events were excluded for the purpose of the current study. The final study population, thus, included 112 patients of the prednisolone randomization arm, P-group, and 111 patients of the no prednisolone arm, NoP-group. Figure 1 shows the flow of participation in the study.

Figure 1. Flow diagram for the enrollment, randomization and participation in the study



After randomization, the patients received 7.5 mg oral prednisolone daily in addition to their initial DMARD therapy, or DMARD therapy alone during 2 years. Violation of the 2-years protocol-specified therapy was uncommon, a total of 8 cases. DMARDs were prescribed at the discretion of the treating rheumatologists who were encouraged to adhere to clinical-practice guidelines.

Patients underwent standard laboratory testing for erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and assessment of RA disease at inclusion and after 3, 6, 12, 18 and 24 months, which included the Disease Activity Score for 28 joints (DAS28)[31] and the Swedish version of the Stanford Health Assessment Questionnaire (HAQ).[32]

Sera from study enrollment was analyzed for IgM rheumatoid factor (RF), using the Serodia agglutination test, (Fujirebio, Tokyo, Japan), positive RF defines as a titer of >20 IU/ml. Anti-citrullinated peptide antibody (anti-CCP) was analysed using the ELISA CCP2 test, (Euro-Diagnostica, Malmö, Sweden), positive anti-CCP defined as a titer >25 U/ml.

Information on smoking status, hypertension, diabetes mellitus, hyperlipidaemia and body mass index (BMI) from first visit, and use of biological agents during follow-up was drawn from the BARFOT registry.

All study participants provided written informed consent. The study was approved by the Regional Ethic committee, and was performed in accordance with the Declaration of Helsinki.

Outcome Assessment

The CV events considered were acute myocardial infarction (AMI), hospitalization for angina pectoris, coronary-artery bypass grafting or percutaneous coronary intervention, ischemic stroke, and transient ischemic attack (TIA).

The end points of the study were the time to the first CV event: the first composite event (i.e. the first coronary artery or cerebrovascular event), the components of the composite event or death from all causes. CV events were defined after ICD-9 and ICD-10 codes: AMI (ICD-9 410, ICD-10 I21), angina pectoris (411, 413, I20), or coronary intervention (3066-3067, 3080, 3092, 3105, 3127, 3141, 3158, Y832); ischemic stroke and TIA (433-436, I63-I66, G45).

The observation period started between September 1995 and December 1999, i.e. when the patients were included in the main BARFOT cohort. Each patient was followed for ten years or until the occurrence of the first-ever incident CV event or death.

All subjects could be followed through record linkage to the nationwide Causes of Death Registry, and the Swedish Hospital Discharge Registry, between January, 1987, and December, 2009. The registers used for this study have nationwide coverage and are complete, and their diagnostic validity is estimated to be high.[33]

Statistical Analysis

The demographic and clinical features were compared using the t-test, the Mann-Whitney U-test, the chi-square or Fisher's exact tests, as suitable. Area under the curve (AUC) was calculated using the trapezoidal rule for the RA disease measures assessed at all time points.

If outcomes were considered to be randomly distributed in time, incidence rates (with the 95% confidence interval (CI) for a Poisson count) were presented as events per 100 person-years at risk.

For primary analysis we collected and analysed end-point data on all participants. For the time to the end point, we computed Kaplan-Meier product-limit estimates of the event-free survival time and compared the randomized groups using a two-sided log-rank test. We calculated relative hazard ratios (HR) and 95% confidence intervals (CI) from Cox proportional-hazards regression models. Covariates for adjusted Cox analyses were pre-specified as variables which were imbalanced in the randomization arms. Finally, we analysed all end-points restricted to the participants who were adherent to the allocated intervention and clinical trial instructions as stipulated in the protocol.

A 2-tailed value of $p<0.05$ was considered significant. Statistical analyses were performed using IBM SPSS, version 20 (SPSS Inc., Chicago, IL).

Results

As shown in Table 1, the study groups differed in age but not sex or traditional CV risk factors, except for hypertension which was less common in the P-group (p=0.049). Disease characteristics and anti-rheumatic medications at baseline were well balanced between the study groups, but the cumulative burden of disease within two years after inclusion was lower in patients treated with prednisolone, as compared with those who were randomized not to receive prednisolone, $p<0.05$. Ever usage of a biological agent throughout 10 years of observation was evenly distributed in the treatment arms.

Table 1. Clinical characteristics and cardiovascular outcomes for patients randomized to prednisolone or no prednisolone treatment

	Groups by randomization		
	Prednisolone n=112	No-prednisolone n=111	p-value
Age at inclusion, years	50.6 ± 14.1	56.9 ± 13.0	0.001
Female, n (%)	77 (69)	76 (69)	0.96
Traditional CV risk factors at baseline:			
BMI, kg/m^2	25.2 ± 4.3	26.4 ± 4.2	0.87
Smoking ever, n (%)	73 (65)	64 (58)	0.25
Hypertension, n (%)	14 (12.5)	25 (22.5)	0.049
Diabetes mellitus, n (%)	0	4 (4)	0.060
Hyperlipidaemia, n (%)	1 (1)	1 (1)	1.0
Baseline RA characteristics:			

Disease duration, months	6.5 ± 3.5	5.8 ± 2.8	0.12
RF positive, n (%)	72 (65)	72 (65)	1.0
anti-CCP positive, n (%)	58 (64)	50 (59)	0.50
DAS28	5.3 ± 1.1	5.4 ± 1.1	0.34
ESR, mm/hour	38 ± 26	37 ± 25	0.83
CRP, mg/l	22 (8-51)	21 (8-53)	0.96
HAQ	1.0 ± 0.6	1.0 ± 0.7	0.58
Started DMARDs at baseline:			
MTX, n (%)	57 (51)	61 (55)	0.54
SSZ, n (%)	36 (32)	38 (34)	0.74
AMA, n (%)	9 (8)	4 (4)	0.25
Gold, n (%)	9 (8)	8 (7)	0.82
Ever use of biological agents during the study, n (%)	17 (15)	17 (15)	1.0
Cumulative RA disease burden the first 2 years:			
AUC-DAS28	71.2 (28.1)	89.3 (28.4)	0.000
AUC-ESR, mm/hour	386 ± 254	504 ± 348	0.011
AUC-CRP, mg/l	253 (189-364)	296 (162-480)	0.37
AUC-HAQ	11.5 ± 10.9	17.6 ± 12.7	0.001
Outcomes:			
Incident CV event, total, n (%)	17 (15.2)	15 (13.5)	0.72
Incident ischemic coronary event, n (%)	7 (6.2)	10 (9.0)	0.44
Incident ischemic cerebrovascular event, n (%)	10 (8.9)	5 (4.5)	0.19
Death, n (%)	9 (8)	9 (8)	0.98

Values are means ±SD or medians (IQR) depending on values distribution. P-values indicate between-group differences. CV = cardiovascular; BMI = body mass index; RF = rheumatoid factor; anti-CCP = anti-citrullinated peptide antibody; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; HAQ = Health Assessment Questionnaire; DMARD = disease modifying anti-rheumatic drugs; MTX = methotrexate; SSZ = sulfasalazine; AMA = antimalarials; AUC = area under the curve calculated on measurements at baseline, after 3, 6, 12, 18 and 24 months.

Study Outcomes

During ten years of observation, the total number of incident CV events, was 17 of 112 patients (15.2%) in the P-group (7 cases of AMI, hospitalization for angina pectoris and coronary interventions; 7 cases of ischemic stroke and 3 of TIA), as compared with 15 of 111 patients (13.5%) in the NoP-group (corresponding events in 10, 3 and 2 cases), p=0.72. None of the events was fatal. Incident CV events occurred after a median of 5.4 years (range 3 – 114 months) in the P-group and 4.9 years (range 2 - 120 months) in the NoP-group, p=0.66.

For the entire cohort, the total follow-up time was 2041 person-years. The cumulative incidence of CV events was 1.7 per 100 person-years (95% CI, 0.9-2.5) in the P-group, and 1.5 per 100 person-years (95% CI, 0.7-2.3) in the NoP-group. The rate of the first ever observed ischemic coronary event was 0.7 per 100 person-years (95% CI, 0.2-1.2) in the P-group; and 1.0 per 100 person-years (95% CI, 0.4-1.6) in the NoP-group. Occurrence of the first ever cerebrovascular event was nominally 2-fold higher in the P-group, 10 cases (8.9%), rates of 1.0 per 100 person-years (95% CI, 0.4-1.6), as compared with the NoP-group, 5 cases

(4.5%), rates of 0.5 per 100 person-years (95% CI, 0.1-0.9). The pattern of distribution of the CV outcomes over time was even in the groups.

Nine mortalities (8%) were observed in each group during the 10-years period.

Primary analyses of outcomes

In the univariate Cox proportional hazard models, age at the study inclusion was found to be associated with the incident composite CV event, hazard ratio (HR), 1.08 (95% CI, 1.05-1.12, p=0.000), but not hypertension at inclusion, or AUCs of DAS28, ESR, and HAQ during the first two years of RA disease. Similar results were obtained in the univariate analyses of the CV subgroups and death, data not shown.

After adjustment for age, the relative hazards for the composite CV event end-point and death did not differ statistically significantly between the treatment groups (Figure 2, panels A and D). When analysing the components of the composite CV event end-point, the hazard for the first coronary event was much the same in the two groups, while the hazard for the first cerebrovascular event among prednisolone treated patients was 3.7 times higher than that among those who did not receive prednisolone, p=0.022 (Figure 2, panels B and C).

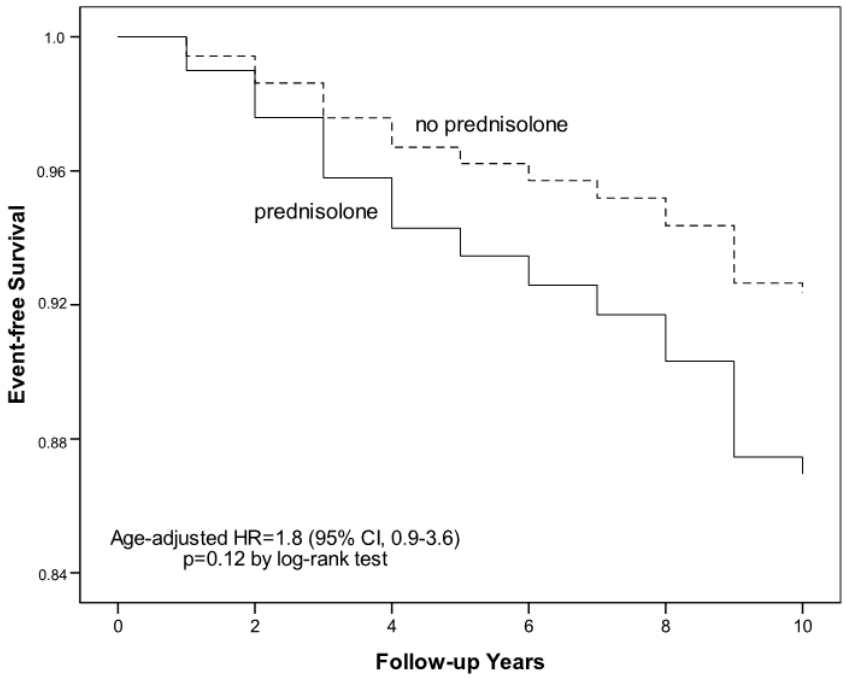
Sensitivity analyses of outcomes

When we considered data for the patients who followed the assigned treatment, 105 participants in each randomization arm, the results were not changed. Given the decreasing survival trend 5 years after the study commencement, we recalculated estimates for the time to death between 5 and 10 years after enrollment. The additional analysis for this time period comparing the relative age-adjusted hazards for death in the P-group with the NoP-group yielded stable findings similar that for the whole 10-year follow-up, 1.4 (95% CI, 0.5-3.9, p=0.47).

Figure 2. Primary analysis of the study outcomes.

Shown are Kaplan-Meier curves comparing the prednisolone group (P-group) with the no-prednisolone group (NoP-group) for the time to the first composite cardiovascular event (panel A), the first ever ischemic coronary artery event (panel B), the first ever cerebrovascular event (panel C), and death (panel D). The relative age-adjusted hazard ratios (HR) were calculated with the use of a Cox proportional-hazards model.

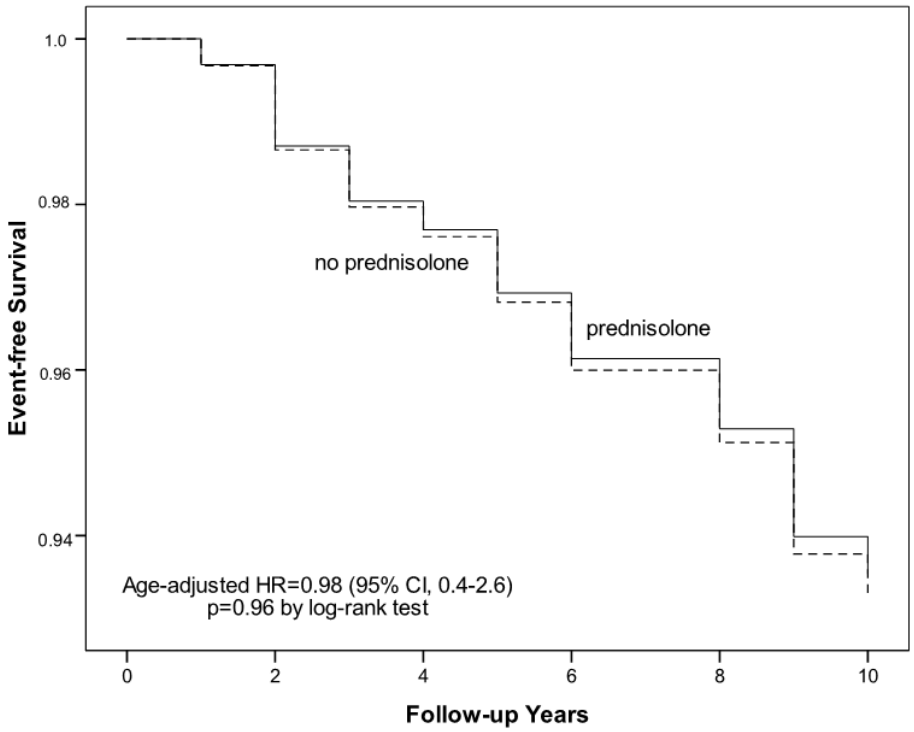
A. Incident Composite Cardiovascular Event End Point



No. At Risk

NoP-group	111 (1)	110 (5)	104 (3)	98 (2)	94 (3)	46 (1)
P-group	112 (2)	109 (4)	104 (3)	100 (2)	96 (6)	44 (0)

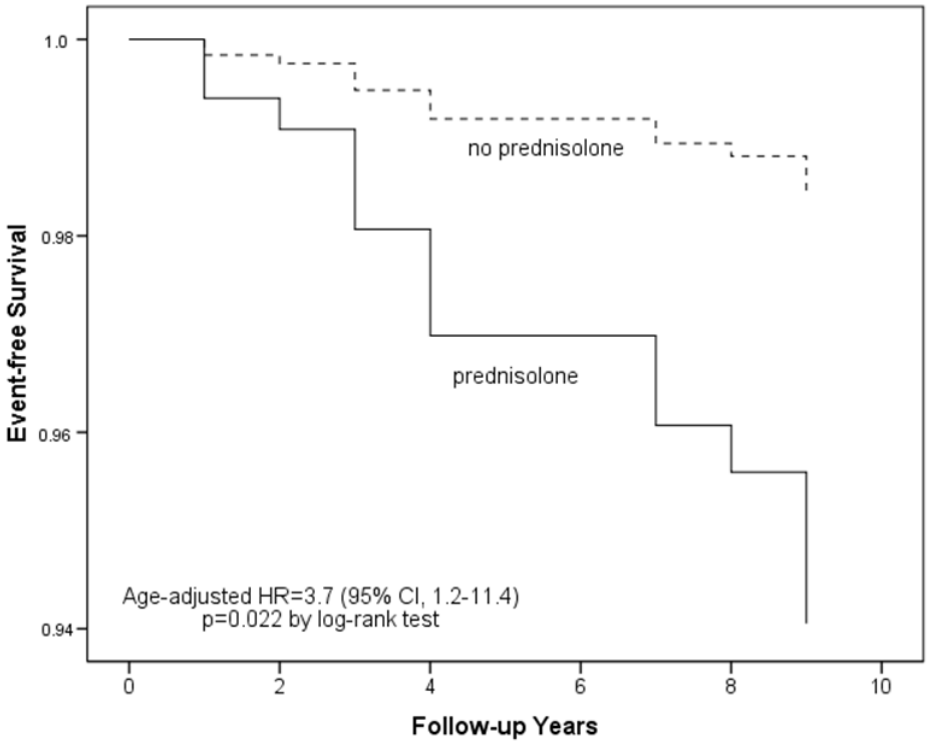
B. Incident Ischemic Coronary Artery Event End Point



No. At Risk

NoP-group	111 (0)	109 (3)	103 (1)	98 (2)	94 (3)	46 (1)
P-group	112 (1)	108 (2)	104 (2)	99 (0)	94 (2)	44 (0)

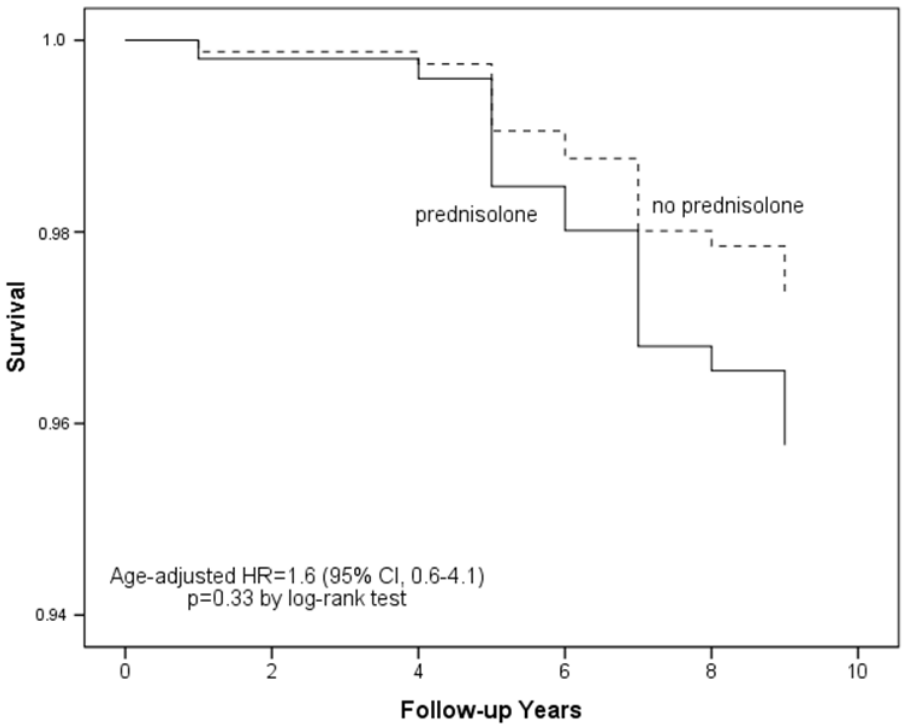
C. Incident Cerebrovascular Event End Point



No. At Risk

NoP-group	111 (1)	109 (2)	103 (2)	97 (0)	93 (0)	46 (0)
P-group	112 (1)	108 (2)	103 (1)	100 (2)	95 (4)	44 (0)

D. Death



No. At Risk

NoP-group	111 (0)	111 (0)	111 (4)	107 (5)	102 (0)	51 (0)
P-group	112 (1)	111 (0)	111 (2)	109 (2)	107 (4)	52 (0)

Discussion

We presented herein the results of the 10-year follow-up of cardiovascular events and deaths in a large, multicenter, prospective, open-label, randomized clinical trial of low-dose prednisolone 7.5 mg per day over the first 2 years of early RA disease in patients with no previous glucocorticoid or DMARD therapy. The risk for a composite CV event, a first coronary artery event and death did not differ between patients assigned to receive prednisolone or not. However, the relative age-adjusted risk for a first cerebrovascular event among prednisolone-treated patients was increased by about 4-folds as compared with those not treated with prednisolone.

To the best of our knowledge, this is the first study which examined the CV and survival consequences of exposure to low-dose prednisolone, cumulative dose up to 5,500 mg, in addition to DMARDs compared in a randomized design with exposure only to conventional DMARDs in patients with early RA. Our study is different in several important ways to previous studies as to the relationship between glucocorticoid exposure and CV in RA and these differences make a broad comparison of the results difficult.

Based on prescription databases from the general population, Wei *et al.*[34] reported an increased risk for CV disease in GC users only in doses > or =7.5 mg of prednisolone or equivalent, the relative risk being 2.56 (CI, 2.18 to 2.99). Aviña-Zubieta *et al.*[22] determined that that the current dose (13% risk increase per additional 5 mg/day), cumulative duration of past GC use (10% risk increase for every additional year), and total cumulative dose (6% per each gram accumulated in the past) were independently associated with an increased risk of first myocardial infarction (MI) in RA cases identified through administrative data sources. In that study, GC exposure, again, included GCs dispensed by pharmacists at some time over the entire disease course. It should also be noted, that participants using GC had a high absolute risk of the CV outcomes, and due to lack of direct information on individual patient's characteristics, surrogate indices were applied to control for confounding by indication. In a population-based incidence RA cohort, Davis *et al.*[25] reported that overall, a higher risk of the initial combined CV outcome was associated with recent exposure to GC, adjusted HR 1.66 (95% CI,1.14–2.41), and the highest tertile of cumulative exposure (>7,000 mg of prednisone equivalents), HR 2.11 (95% CI, 1.47–3.04); whereas there was no association with past GC exposure > 3 months, or mid tertile cumulative exposure (>1,500 to ≤7,000 mg).

Conversely, a lower prevalence for lifetime CV morbidity among patients with prolonged exposure to GCs, similar to conventional DMARDs and anti-TNF blockers, has been shown by Naranjo *et al.*[35] in the cross-sectional study in non-selected outpatients with RA, HR 0.95 (95% CI 0.92-0.98). In a prospective RA cohort, Gonzalez-Gay *et al,*[36] could not confirm an excess risk of incident CV events or CV mortality induced by median dose of prednisone 5 mg/day for at least 1 year, and the mean ± SD cumulative dose of prednisone of 13.5 ± 9.0 gram at the end of the study. Interestingly, risk of hospitalization for MI and stroke, which was assessed in the nested case-control study reported by Solomon *et al,*[24] was significantly increased only if GC were used in monotherapy (MTX monotherapy used as the reference group), but not in combination with another DMARDs.

Our results suggest that it may be possible to avoid potential negative effects of GC on future ischemic coronary artery complications and survival prognosis if GCs are used in low-dose, over limited time, in conjunction with DMARDs in patients with a low baseline rate of traditional CV risk factors. This is in line with the encouraging reports about association between effective anti-rheumatic therapy and favourable overall CV and survival prognosis,[37-40] which formed the basis for the hypothesis that dampening of systemic inflammation by GC may halt development of atherosclerotic disease. Using the present knowledge, it seems fair to say that even if the possibility of an excess CV risk associated with GC exposure cannot be excluded, negative effects of GC may be counteracted by positive impact of suppression of chronic inflammation. Thus, the significant benefits of the low-dose GC therapy, both in terms of disease activity and radiographic progression in the present trial,[2, 3] as compared with therapy not including GC, could likely have overcome adverse coronary events and overall survival. In support of this hypothesis, the previous subgroup analysis has shown that low-dose of prednisolone in early RA was not pro-atherogenic, considering carotid artery intima-media measures, presence of atherosclerotic plaques, and endothelial function after five years of follow-up.[41]

When it comes to the potential cerebrovascular risk of GC use, the evidence is limited. There are studies showing an excess risk when using GC,[28, 34] while several others have failed to find any excess risk.[42, 43] Notably, few studies have divided CV events into subtypes. Such a subdivision could be of importance, considering the possibility of different etiologies of coronary and cerebrovascular events. The results of our study indicate that even low-dose mid-term GC exposure could be associated with long-term cerebrovascular safety issues in patients with RA. What pathways of the GC would be involved in occurrence of cerebrovascular events but not coronary events are unclear. About 14-30% of all strokes in the general population are of cardio-embolic origin, and atrial fibrillation is a risk factor for this type of ischemic stroke.[44] An almost 2-fold increased risk of atrial fibrillation or flutter has been reported in current and long-term users of GC in a population-based case-control study.[45] As we found differences in the risk of ischemic coronary and cerebrovascular complications, we cannot exclude that the excess cerebrovascular risk in our study was essentially confined to participants with other specific underlying risk factors, e.g. atrial fibrillation. Such a possibility though could not be tested here through hospitalization registries.

Our study has several important strengths such as an incidence cohort of RA patients with the diagnose validated by the ACR criteria, randomized allocation to therapy within the setting of prospective follow-up, long observation period sufficient for development of studied complications, high compliance with the treatment protocol, few losses to follow-up or therapy discontinuation. Furthermore, the reliable nationwide registry system ascertains the outcomes.

However, these data should be interpreted with caution because it is not clear to what extent a more prolonged therapy with oral glucocorticoids may affect the risk of CV-related adverse clinical events. Further, the population of this study was relatively young and had a low frequency of baseline traditional CV risk factors. Then, we could not have anticipated the

observed baseline imbalance between the treatment groups, but the age difference was adjusted for in the analyses. It should be also acknowledged that the prednisolone trial was not primarily designed to examine the risk of incident CV events.

Conclusion

This study has focused on the long-term cardiovascular and mortality risks of low-dose glucocorticoid therapy in RA and adds further weight to the arguments for appropriate use of glucocorticoids in early disease. Our data suggest that the 2-year low-dose GC exposure in patients with early RA may affect the risk of cerebrovascular events. On the other side, the results of this study would argue against GC-induced risk of ischemic coronary artery complications and death in a population with low frequency of background traditional CV risk factors. Further studies addressing CV effects, especially risk for stroke in relation to GC use are needed.

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Competing interest

The authors have declared no relevant conflicts of interest.

Contributor statement

IH and BS designed the original low-dose prednisolone study and were involved in acquisition of data. SA was responsible for the current study concept, data acquisition, statistical analyses and drafting of the manuscript. IH participated in the interpretation of data and manuscript preparation. All authors have critically revised and approved the final version of the manuscript to be published, and contributed to the study with regard to important intellectual content.

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Low-dose prednisolone treatment of early rheumatoid arthritis and late cardiovascular outcome and survival: ten year follow-up of a two year randomized trial

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Low-dose prednisolone treatment of early rheumatoid arthritis and late cardiovascular outcome and survival: ten year follow-up of a two year randomized trial

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Abstract

Objective: To examine the long-term effects of early low-dose prednisolone use in patients with rheumatoid arthritis (RA) on cardiovascular (CV) morbidity and mortality.

Design: Retrieval of data from a 2-year open randomized trial comparing prednisolone 7.5 mg/day in addition to disease-modifying anti-rheumatic drugs (DMARDs) with DMARD therapy alone. Participants were followed for ten years since inclusion into the original prednisolone trial or until occurrence of the studied outcomes.

Setting: Secondary level of care; six participating centres from southern Sweden; both urban and rural populations.

Participants: Overall, 223 patients with early RA were included. The participants had no history of CV events at baseline and incident cases were identified via the Swedish Hospital Discharge and Cause of Death Registries.

Outcomes: Composite CV events i.e. ischemic coronary and cerebrovascular events, components of the composite CV outcome, and death. Relative hazard ratios from Cox proportional-hazards regression models were calculated.

Results: Within 2041 person-years, 17 incident composite CV events occurred in 112 patients (15 %) randomized to prednisolone, and 15 events out of 111 patients (14%) who were assigned not to receive prednisolone. Nine mortalities (8%) were observed in each group.

The age-adjusted relative hazards (HRs) (95% CI) for the first composite CV event, first coronary event and death in the prednisolone group vs. the group not treated with prednisolone were 1.8 (0.9-3.6), 0.98 (0.4-2.6), and 1.6 (0.6-4.1), respectively. The risk for the first cerebrovascular event showed a 3.7-fold increased relative hazard (95% CI, 1.2-11.4) among prednisolone treated patients. These results persisted in sensitivity analyses restricted to the participants who were adherent to the study treatment protocol.

Conclusion: In this study low-dose prednisolone use during the first two years of RA disease ~~was not associated with long-term coronary artery events or deaths, but with an~~ increased long-term risk of ischemic cerebrovascular events, but not risk of death.

Trial registration: ISRCTN20612367

Article summary

Article focus

- To examine associations between exposure to low-dose prednisolone in early rheumatoid arthritis (RA) and long-term cardiovascular (CV) outcomes and all-cause mortality.
- To study these associations separately for ischemic coronary artery events and ischemic cerebrovascular events.

Key messages

- Low-dose prednisolone exposure for two years in this early RA study showed increased cerebrovascular but not mortality risk.
- The results are inconclusive regarding clinically important long-term overall cardiovascular risk in an individual patient.
- ~~Neither ischemic coronary artery events nor all-cause death was associated with low-dose prednisolone treatment in our study.~~

Strengths and limitations of this study

- Randomized allocation to prednisolone therapy to patients with early RA diagnosed according to the American College of Rheumatology (ACR) criteria.
- The treatment protocol was highly compliant with only a few patients who were lost to follow-up or discontinued the allocated therapy.
- Data on outcomes were derived from the reliable nationwide registry system and sampled during a long observation period sufficient for development of studied complications.
- The original prednisolone trial was not primarily designed to examine the risk of CV events and mortality; and the population studied was relatively young with low burden of traditional CV risk factors at inclusion.

Introduction

Glucocorticoids (GCs) are powerful anti-inflammatory agents which have been used since the 1950s, first, as symptomatic treatment of rheumatoid arthritis (RA), but in the last years, as disease modifying therapy. Thus, inhibition of the progression of radiological damage in RA has been documented for GCs given in addition to disease-modifying anti-rheumatic drugs (DMARDs).[1-3] However, the relationship between short-, and long-term GC exposure and cardiovascular (CV) events and mortality in RA is still controversial.

The discussion on the side effects of GC use is still far from settled. Whereas adverse effects of long-term GCs use, at least at high dose, are well recognized in the general population and include effects on blood pressure, insulin resistance, lipid profile, homeostasis, body weight and fat distribution,[4-10] the nature of unfavourable CV effects and possible modulation of effects of GCs by other processes in RA are less known.[11-13] Some data are available which imply that chronic GC-using has no additive pro-atherogenic effects in the inflammatory milieu.[14, 15] A systematic literature review has shown poor association between low-dose GC exposure and CV risk factors, and probably no effect on atherosclerosis in RA patients.[16] GCs may have anti-atherogenic effects mediated by their anti-inflammatory and anti-proliferative actions in the vessel wall, and modify the recovery from occlusive vascular events and intravascular injury.[17-19]

However, in the scientific literature, the potential risks and benefits of GC exposure in RA have shown disparate results. Increased CV and/or mortality risk associated with the use of GCs, particularly with increasing doses, has been found in several studies,[20-25] while other studies have found GCs use to improve CV/mortality prognosis,[26] or to have no or uncertain effect.[27, 28] Diversity of outcomes definitions, different stages of RA disease, GC exposure in various dosages at any time during follow-up, and the potential for confounding by indication in observational cohorts make the results of the studies not fairly conclusive.

In an attempt to shed some light on the CV risk of exposure to low-dose prednisolone in early RA, we performed this study with retrieval of data from the previously conducted randomized prednisolone trial, a BARFOT (Better Anti-Rheumatic PharmacOTherapy) study.[3] In that trial, prednisolone 7.5 mg per day added to the initial DMARD retarded the progression of radiographic damage after 2 years, provided a high remission rate and was well tolerated.

Patients and Methods

Adults with a diagnosis of RA according to American College of Rheumatology (ACR) classification criteria 1987 [29] and symptom duration ≤ 12 months were eligible for the BARFOT inception cohort study.[30] The design of the 2-year low-dose prednisolone multicenter open-label randomized study, nested in the BARFOT cohort, has been described in detail previously.[3] This trial is registered with ISRCTN www.isrctn.org, number 20612367. Of 250 patients who entered the study with the treatments as assigned, 27 patients with a history of prior CV events were excluded for the purpose of the current study. The final study population, thus, included 112 patients of the prednisolone randomization arm, P-group,

and 111 patients of the no prednisolone arm, NoP-group. Figure 1 shows the flow of participation in the study.

Figure 1. Flow diagram for the randomization and participation in the two-year randomized part of the study

After randomization, the patients received 7.5 mg oral prednisolone daily in addition to their initial DMARD therapy, or DMARD therapy alone during 2 years. Violation of the 2-years protocol-specified therapy was uncommon, a total of 8 cases. DMARDs were prescribed at the discretion of the treating rheumatologists who were encouraged to adhere to clinical-practice guidelines.

Patients underwent standard laboratory testing for erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and assessment of RA disease at inclusion and after 3, 6, 12, 18 and 24 months, which included the Disease Activity Score for 28 joints (DAS28)[31] and the Swedish version of the Stanford Health Assessment Questionnaire (HAQ).[32] *Remission* was defined according to the DAS28 remission criterion, DAS28<2.6,[31] and *good response* according to European League Against Rheumatism (EULAR) response criteria as improvement in DAS28 of at least 1.2 units and achievement of an absolute score of < 3.2.[33]

Sera from study enrollment was analyzed for IgM rheumatoid factor (RF), using the Serodia agglutination test, (Fujirebio, Tokyo, Japan), positive RF defines as a titer of >20 IU/ml. Anti-citrullinated peptide antibody (anti-CCP) was analysed using the ELISA CCP2 test, (Euro-Diagnostica, Malmö, Sweden), positive anti-CCP defined as a titer >25 U/ml.

Information on smoking status (ever or never), hypertension, diabetes mellitus, hyperlipidaemia, body mass index (BMI), use of prednisolone, DMARDs and biological agents from the first visit and during follow-up was obtained from the BARFOT data base and from medical records.

All study participants provided written informed consent. The study was approved by the Regional Ethic committee, and was performed in accordance with the Declaration of Helsinki.

Outcome Assessment

The CV events considered were acute myocardial infarction (AMI), hospitalization for angina pectoris, coronary-artery bypass grafting or percutaneous coronary intervention, ischemic stroke, and transient ischemic attack (TIA).

The end points of the study were the time to the first CV event: the first composite event (i.e. the first coronary artery or cerebrovascular event), the components of the composite event or death from all causes. CV events were defined after ICD-9 and ICD-10 codes: AMI (ICD-9 410, ICD-10 I21), angina pectoris (411, 413, I20), or coronary intervention (3066-3067, 3080, 3092, 3105, 3127, 3141, 3158, Y832); ischemic stroke and TIA (433-436, I63-I66, G45).

The observation period started between September 1995 and December 1999, i.e. when the patients were included in the main BARFOT cohort. Each patient was followed for ten years or until the occurrence of the first-ever incident CV event or death.

All subjects could be followed through record linkage to the nationwide Causes of Death Registry, and the Swedish Hospital Discharge Registry, between January, 1987, and December, 2009. The registers used for this study have nationwide coverage and are complete, and their diagnostic validity is estimated to be high.[34]

Statistical Analysis

The demographic and clinical features were compared using the t-test, the Mann-Whitney U-test, the chi-square or Fisher's exact tests, as suitable. Area under the curve (AUC) was calculated using the trapezoidal rule for the RA disease measures assessed at all time points.

If outcomes were considered to be randomly distributed in time, incidence rates (with the 95% confidence interval (CI) for a Poisson count) were presented as events per 100 person-years at risk.

For primary analysis we collected and analysed end-point data on all participants. For the time to the end point, we computed Kaplan-Meier product-limit estimates of the event-free survival time and compared the randomized groups using a two-sided log-rank test. We calculated relative hazard ratios (HRs) and 95% confidence intervals (CI) from Cox proportional-hazards regression models. Covariates for adjusted Cox analyses were pre-specified as variables which were imbalanced in the randomization arms, and adjusted for in multivariate analyses if univariate tests showed significant association with the outcomes. Finally, we analysed all end-points restricted to the participants who were adherent to the allocated intervention and clinical trial instructions as stipulated in the protocol (Figure 1).

All significance tests were two tailed and conducted at the 0.05 level of significance. Statistical analyses were performed using IBM SPSS, version 20 (SPSS Inc., Chicago, IL).

Results

As shown in Table 1, the treatment groups differed in age but not sex or traditional CV risk factors, except for hypertension which was less common in the P-group (p=0.049). Disease characteristics and anti-rheumatic medications at baseline were well balanced between the study groups, but the cumulative burden of disease within two years after inclusion was lower in patients treated with prednisolone except for AUC-CRP, as compared with those who not received prednisolone~~, p<0.05~~.

Table 1. Clinical characteristics and cardiovascular outcomes for patients randomized to prednisolone or no prednisolone treatment

	Groups by randomization		
	Prednisolone n=112	No-prednisolone n=111	p-value

Age at inclusion, years	50.6 (14.1)	56.9 (13.0)	0.001
Female, n (%)	77 (69)	76 (69)	0.96
Traditional CV risk factors at baseline:			
BMI, kg/m^2	25.2 (4.3)	26.4 (4.2)	0.87
Smoking ever, n (%)	73 (65)	64 (58)	0.25
Hypertension, n (%)	14 (12.5)	25 (22.5)	0.049
Diabetes mellitus, n (%)	0	4 (4)	0.06
Hyperlipidaemia, n (%)	1 (1)	1 (1)	1.00
Baseline RA characteristics:			
Disease duration, months	6.5 (3.5)	5.8 (2.8)	0.12
RF positive, n (%)	72 (65)	72 (65)	1.00
anti-CCP positive, n (%)	58 (64)	50 (59)	0.50
DAS28	5.3 (1.1)	5.4 (1.1)	0.34
ESR, mm/hour	38 (26)	37 (25)	0.83
CRP, mg/l	22 (8-51)	21 (8-53)	0.96
HAQ	1.0 (0.6)	1.0 (0.7)	0.58
Started DMARDs at baseline:			
MTX, n (%)	57 (51)	61 (55)	0.54
SSZ, n (%)	36 (32)	38 (34)	0.74
AMA, n (%)	9 (8)	4 (4)	0.25
Gold, n (%)	9 (8)	8 (7)	0.82
Ever use of biological agents during the study, n (%)	17 (15)	17 (15)	1.00
Cumulative RA disease burden the first 2 years:			
AUC-DAS28	71.2 (28.1)	89.3 (28.4)	<0.001
AUC-ESR, mm/hour	386 (254)	504 (348)	0.011
AUC-CRP, mg/l	253 (189-364)	296 (162-480)	0.37
AUC-HAQ	11.5 (10.9)	17.6 (12.7)	0.001
Outcomes:			
Incident CV event, total, n (%)	17 (15.2)	15 (13.5)	0.72
Incident ischemic coronary event, n (%)	7 (6.2)	10 (9.0)	0.44
Incident ischemic cerebrovascular event, n (%)	10 (8.9)	5 (4.5)	0.19
Death, n (%)	9 (8)	9 (8)	0.98

Values are means (SD) or medians (IQR) depending on values distribution. P-values indicate between-group differences. CV = cardiovascular; BMI = body mass index; RF = rheumatoid factor; anti-CCP = anti-citrullinated peptide antibody; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; HAQ = Health Assessment Questionnaire; DMARD = disease modifying anti-rheumatic drugs; MTX = methotrexate; SSZ = sulfasalazine; AMA = antimalarials; AUC = area under the curve calculated on measurements at baseline, after 3, 6, 12, 18 and 24 months.

Treatments and traditional cardiovascular risk factors during follow-up

The prednisolone therapy was assessed during follow-up to the last visit in the two study groups.

In the P-group, 59/111 patients (53%) stopped prednisolone treatment after the first two study years, 30/109 patients (28%) stopped after a total of 4-5 years and 23/106 patients (22%) continued for more than 8 years. The mean (SD) daily dose of prednisolone decreased from 7.2 (1.1) mg at the 2-year follow-up to 6.5 (3.6) mg at the 4-year and 4.9 (3.3) mg at the 8-year assessment.

In the NoP-group, most patients (94%) continued without prednisolone after the two study years, albeit prednisolone therapy was initiated and maintained over a period of more than 6 months during the follow-up in 7/111 patients (6%), with a mean average dose (SD) of 5.2 (1.4) mg daily.

Ever usage of a biological agent throughout 10 years of observation was evenly distributed in the treatment arms (15% of the patients in each group).

The mean (SD) BMI at the two-year visit was similar in the two study groups, 26.2 (4.8) and 27.1 (4.4) in the P-group and the NoP-group respectively, p=0.21. None of the enrolled patients became a smoker during the observation period. Thus, the never-smoking status throughout the study was not changed. During follow-up, the number of patients registered with hypertension increased to 33 (30%) in the P-group and to 41 patients (37%) in the NoP-group, p=0.24. Diabetes mellitus was recorded in 2 patients (2%) in the P-group vs. 10 patients (9%) in the NoP-group, p=0.017, and hyperlipidaemia in 6 (5%) vs. 3 patients (3%) in the respective groups, p=0.50.

Study Outcomes

During ten years of observation, the total number of incident CV events, was 17 of 112 patients (15%) in the P-group (7 cases of AMI, hospitalization for angina pectoris and coronary interventions; 7 cases of ischemic stroke and 3 of TIA), as compared with 15 of 111 patients (14%) in the NoP-group (corresponding events in 10, 3 and 2 cases), p=0.72. None of the events was fatal. Incident CV events occurred after a median of 5.4 years (range 3 – 114 months) in the P-group and 4.9 years (range 2 - 120 months) in the NoP-group, p=0.66.

For the entire cohort, the total follow-up time was 2041 person-years. The cumulative incidence of CV events was 1.7 per 100 person-years (95% CI, 0.9-2.5) in the P-group, and 1.5 per 100 person-years (95% CI, 0.7-2.3) in the NoP-group. The rate of the first ever observed ischemic coronary event was 0.7 per 100 person-years (95% CI, 0.2-1.2) in the P-group; and 1.0 per 100 person-years (95% CI, 0.4-1.6) in the NoP-group. Occurrence of the first ever cerebrovascular event was nominally 2-fold higher in the P-group, 10 cases (8.9%), rates of 1.0 per 100 person-years (95% CI, 0.4-1.6), as compared with the NoP-group, 5 cases (4.5%), rates of 0.5 per 100 person-years (95% CI, 0.1-0.9). The pattern of distribution of the CV outcomes over time was even in the groups.

Nine mortalities (8%) were observed in each group during the 10-year period.

Primary analyses of outcomes

In the univariate Cox proportional hazard models, age at the study inclusion was found to be associated with the incident composite CV event, hazard ratio (HR), 1.08 (95% CI, 1.05-1.12), but not hypertension at inclusion, or AUCs of DAS28, ESR, and HAQ during the first two years of RA disease. Similar results were obtained in the univariate analyses of the CV subgroups and death, data not shown.

After adjustment for age, the relative hazards for the composite CV event end-point and death did not differ statistically significantly between the P-group and the NoP-group, HRs (95% CI) 1.8 (0.9-3.6), and 1.6 (0.6-4.1), respectively (Figure 2, panels A and D). When analysing the components of the composite CV event end-point, the hazard for the first coronary event was much the same in the two groups, HR 0.98 (0.4-2.6), while the hazard for the first cerebrovascular event among prednisolone treated patients was 3.7 times (95% CI, 1.2-11.4) higher than that among those who did not receive prednisolone (Figure 2, panels B and C).

Figure 2. Primary analysis of the study outcomes.

Shown are Kaplan-Meier curves comparing the prednisolone group (P-group) with the no-prednisolone group (NoP-group) for the time to the first composite cardiovascular event (panel A), the first ever ischemic coronary artery event (panel B), the first ever cerebrovascular event (panel C), and death (panel D). The relative age-adjusted hazard ratios (HR) were calculated with the use of a Cox proportional-hazards model. The tables below the panels represent the number of subjects at risk for the end points (number of the end points) at 2-year intervals throughout the 10-year observation.

Sensitivity analyses of outcomes

When we considered data for the patients who followed the assigned treatment, 105 participants in each randomization arm, the results were not changed. Given the decreasing survival trend 5 years after the study commencement, we recalculated estimates for the time to death between 5 and 10 years after enrollment. The additional analysis for this time period comparing the relative age-adjusted hazards for death in the P-group with the NoP-group yielded stable findings similar that for the whole 10-year follow-up, 1.4 (95% CI, 0.5-3.9, p=0.47).

Further analyses of outcomes in relation to therapy response

We performed analyses in order to investigate whether the effect of prednisolone was mediated through reduced inflammation. The cohort was stratified by therapy response at the 2-year visit according to DAS28 remission criteria and EULAR response criteria.

Relative age-adjusted hazards for death among subjects with DAS28 remission tended to be lower than those among patients who did not achieve DAS28 remission, The HRs were 0.41 (95% CI, 0.15-1.15), p=0.089 in the whole cohort, 0.30 (0.07-1.19), p=0.087 in the P-group, and 0.42 (0.09-2.03), p=0.28 in the NoP-group.

A similar tendency to decreased estimated relative mortality risks was observed among good EULAR responders compared with those not achieving good response. The age-adjusted

relative hazards were 0.37 (0.15-0.95), p=0.038 in the whole cohort, 0.45 (0.12-1.70), p=0.24 in the P-group and 0.28 (0.07-1.13) and p=0.074 in the NoP-group.

These relative differences were sustained over time. As to the composite CV event end-point, stratifying by therapy efficacy did not show differences, or trends to differences in the risks for the outcome, data not shown.

Discussion

We presented herein the results of the 10-year follow-up of cardiovascular events and deaths in a large, multicenter, prospective, open-label, randomized clinical trial of low-dose prednisolone, 7.5 mg per day, over the first two years of early RA disease in patients with no previous glucocorticoid or DMARD therapy. The estimated risk for a composite CV event, a first coronary artery event and death did not differ between patients assigned to receive prednisolone or not. However, the observed age-adjusted relative risk for a first cerebrovascular event among prednisolone-treated patients was increased by about 4 times that not treated with prednisolone. It should though be noticed that due to the low number of events and the wide estimated rates, a clinically important cardiovascular risk in the long-term in an individual patient treated with prednisolone is uncertain.

To the best of our knowledge, this is the first study addressing cardiovascular and survival consequences of exposure to low-dose prednisolone during two years in early RA in a randomized design. It should be mentioned that a good half of those randomized to prednisolone stopped that treatment after two years from baseline and that a further fourth quarter stopped after 4-5 years. In contrast, only a few patients who were randomized not to take prednisolone initiated prednisolone therapy during follow-up. Still, the distribution of traditional risk factors during the study period (body mass index, hypertension and hyperlipidaemia) was similar in the treatment groups, which strengthens the present findings and also challenges the idea of a negative impact of prednisolone on traditional CV risk factors in patients with an inflammatory condition.

Our study is different in several important ways to previous studies as to the relationship between glucocorticoid exposure and CV in RA and these differences make a broad comparison of the results difficult.

Based on prescription databases from the general population, Wei *et al.*[35] reported an increased risk for CV disease in GC users only in doses > or =7.5 mg of prednisolone or equivalent, the relative risk being 2.56 (CI, 2.18 to 2.99). Aviňa-Zubieta *et al.*[22] determined that that the current dose (13% risk increase per additional 5 mg/day), cumulative duration of past GC use (10% risk increase for every additional year), and total cumulative dose (6% per each gram accumulated in the past) were independently associated with an increased risk of first myocardial infarction (MI) in RA cases identified through administrative data sources. In that study, GC exposure, again, included GCs dispensed by pharmacists at some time over the entire disease course. It should also be noted, that participants using GC had a high absolute risk of the CV outcomes, and due to lack of direct information on individual patient's characteristics, surrogate indices were applied to control for confounding by indication. In a

population-based incidence RA cohort, Davis *et al*.[25] reported that overall, a higher risk of the initial combined CV outcome was associated with recent exposure to GC, adjusted HR 1.66 (95% CI,1.14–2.41), and the highest tertile of cumulative exposure (>7,000 mg of prednisone equivalents), HR 2.11 (95% CI, 1.47–3.04); whereas there was no association with past GC exposure > 3 months, or mid tertile cumulative exposure (>1,500 to ≤7,000 mg).

Conversely, a lower prevalence for lifetime CV morbidity among patients with prolonged exposure to GCs, similar to conventional DMARDs and anti-TNF blockers, has been shown by Naranjo *et al.*[36] in the cross-sectional study in non-selected outpatients with RA, HR 0.95 (95% CI 0.92-0.98). In a prospective RA cohort, Gonzalez-Gay *et al,*[37] could not confirm an excess risk of incident CV events or CV mortality induced by median dose of prednisone 5 mg/day for at least 1 year, and the mean (SD) cumulative dose of prednisone of 13.5 (9.0) gram at the end of the study. Interestingly, risk of hospitalization for MI and stroke, which was assessed in the nested case-control study reported by Solomon *et al,*[24] was significantly increased only if GC were used in monotherapy (MTX monotherapy used as the reference group), but not in combination with another DMARDs.

Our results further suggest that it may be possible to avoid potential negative effects of GC on future ischemic coronary artery complications and survival prognosis if GCs are used in low-dose, over limited time, in conjunction with DMARDs in patients with a low baseline rate of traditional CV risk factors. This is in line with the encouraging reports about associations between effective anti-rheumatic therapy and favourable overall CV and survival prognosis,[38-41] which formed the basis for the hypothesis that dampening of systemic inflammation by GC may halt development of atherosclerotic disease.

Using the present knowledge, it seems fair to say that even if the possibility of an excess CV risk associated with GC exposure cannot be excluded, negative effects of GC may be counteracted by positive impact of suppression of chronic inflammation. Thus, the significant benefits of the low-dose GC therapy, both in terms of disease activity and radiographic progression in the present trial,[2, 3] as compared with therapy not including GC, could likely have overcome adverse coronary events and overall survival. In support of this hypothesis, the previous subgroup analysis has shown that low-dose of prednisolone in early RA was not pro-atherogenic, considering carotid artery intima-media measures, presence of atherosclerotic plaques, and endothelial function after five years of follow-up.[42] Accordingly, we observed a tendency towards reduction in mortality for patients with a better therapy response, possibly due to an overall decrease in inflammation related to the anti-rheumatic therapy.

When it comes to the potential cerebrovascular risk of GC use, the evidence is limited. There are studies showing an excess risk when using GC,[28, 35] while several others have failed to find any excess risk.[43, 44] Notably, few studies have divided CV events into subtypes. Such a subdivision could be of importance, considering the possibility of different etiologies of coronary and cerebrovascular events. The results of our study indicate that even low-dose GC exposure could be associated with long-term cerebrovascular safety issues in patients with RA. What pathways of the GC would be involved in occurrence of cerebrovascular events but not coronary events are unclear. About 14-30% of all strokes in the general population are of

cardio-embolic origin, and atrial fibrillation is a risk factor for this type of ischemic stroke.[45] An almost 2-fold increased risk of atrial fibrillation or flutter has been reported in current and long-term users of GC in a population-based case-control study.[46] As we found differences in the risk of ischemic coronary and cerebrovascular complications, we cannot exclude that the excess cerebrovascular risk in our study was essentially confined to participants with other specific underlying risk factors, e.g. atrial fibrillation. Such a possibility though could not be tested here through hospitalization registries.

Our study has several important strengths such as an incidence cohort of RA patients with the diagnose validated by the ACR criteria, randomized allocation to therapy within the setting of prospective follow-up, long observation period sufficient for development of studied complications, high compliance with the treatment protocol, few losses to follow-up or therapy discontinuation. Furthermore, the reliable nationwide registry system ascertains the outcomes.

However, these data should be interpreted with caution because it is not clear to what extent a more prolonged therapy with oral glucocorticoids may affect the risk of CV-related adverse clinical events. Further, the population of this study was relatively young and had a low frequency of baseline traditional CV risk factors. Then, we could not have anticipated the observed baseline imbalance between the treatment groups, but the age difference was adjusted for in the analyses. It should be also acknowledged that the prednisolone trial was not primarily designed to examine the risk of incident CV events. Given the low precision of estimated hazards, the results should be interpreted as non-definitive regarding possible long-term risks of CV events in patients treated with low dose prednisolone.

Conclusion

This study has focused on the long-term cardiovascular and mortality risks of low-dose glucocorticoid therapy in RA and adds further weight to the arguments for appropriate use of glucocorticoids in early disease. Our data suggest that the 2-year low-dose GC exposure in patients with early RA may have affected the risk of cerebrovascular events. On the other side, the results of this study would argue against GC-induced risk of ischemic coronary artery complications and death in a population with low frequency of background traditional CV risk factors. ~~Further studies addressing CV effects, especially risk for stroke in relation to GC use are needed.~~

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Competing interest

The authors have declared no relevant conflicts of interest.

Contributor statement

IH and BS designed the original low-dose prednisolone study and were involved in acquisition of data. SA was responsible for the current study concept, data acquisition, statistical analyses and drafting of the manuscript. IH participated in the interpretation of data and manuscript preparation. All authors have critically revised and approved the final version of the manuscript to be published, and contributed to the study with regard to important intellectual content.

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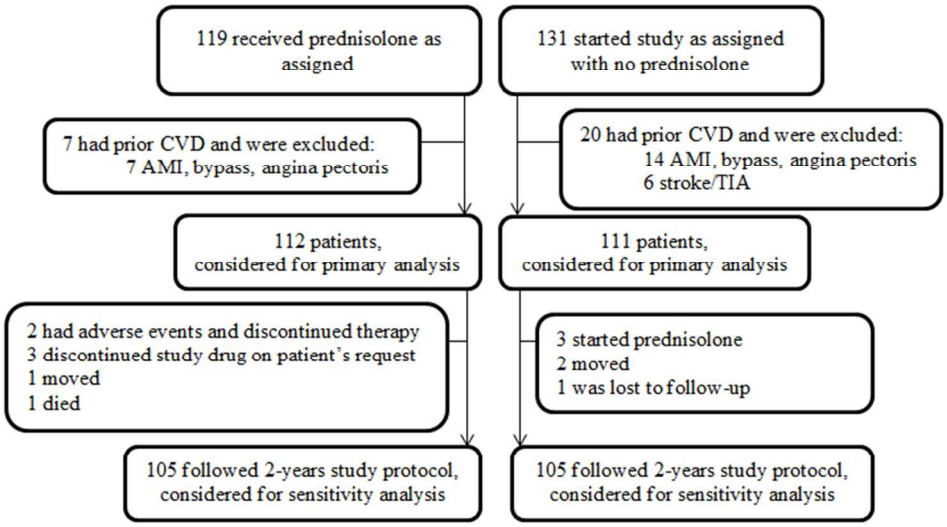

Flow diagram for the randomization and participation in the two-year randomized part of the study
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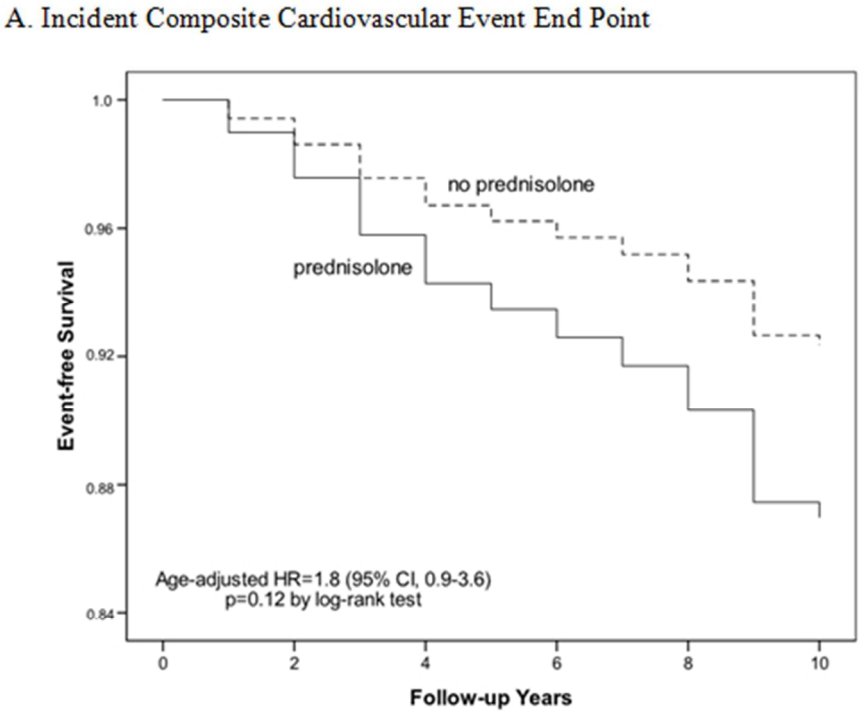
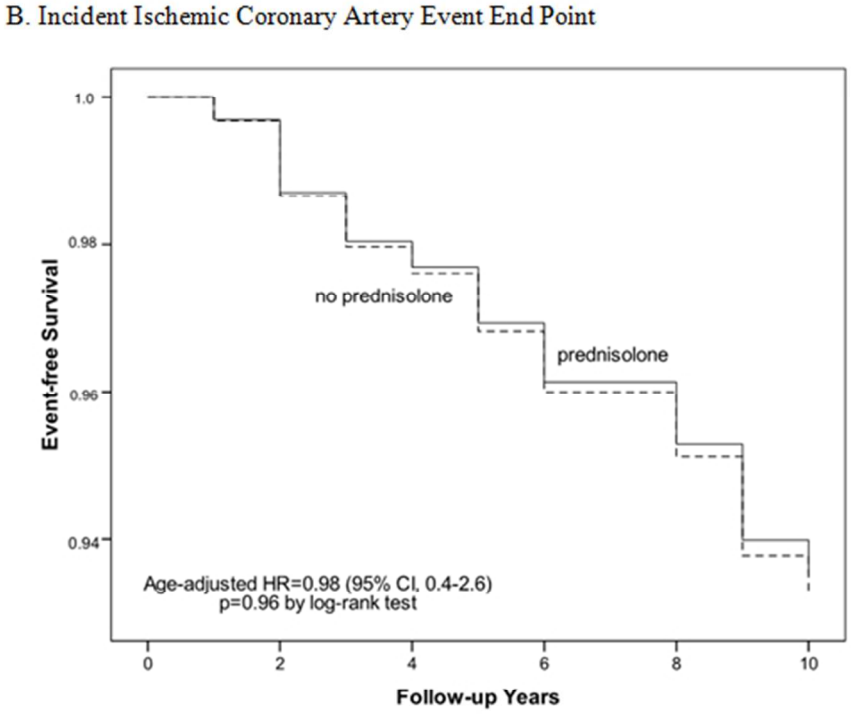


No. At Risk						
NoP-group	111 (1)	110 (5)	104 (3)	98 (2)	94 (3)	46 (1)
P-group	112 (2)	109 (4)	104 (3)	100 (2)	96 (6)	44 (0)

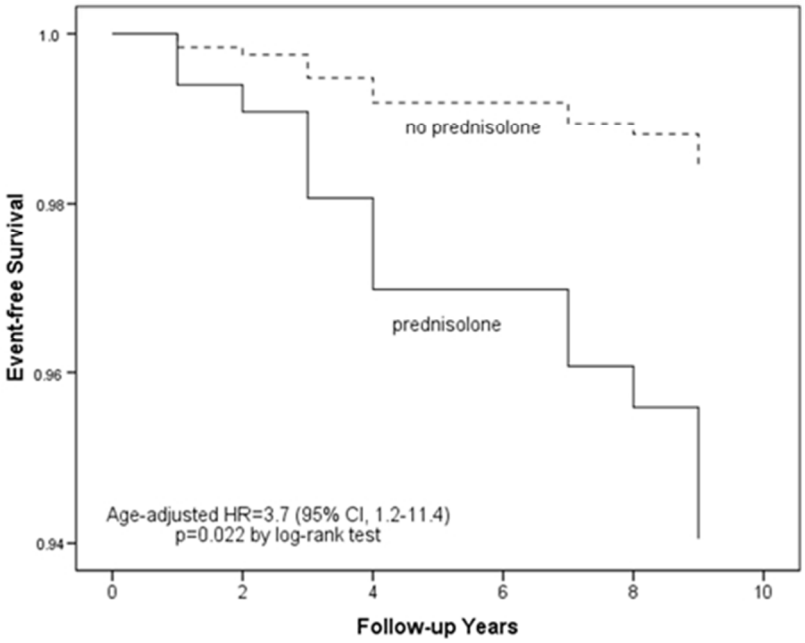
Incident Composite Cardiovascular Event End Point
46x44mm (300 x 300 DPI)



No. At Risk						
NoP-group	111 (0)	109 (3)	103 (1)	98 (2)	94 (3)	46 (1)
P-group	112 (1)	108 (2)	104 (2)	99 (0)	94 (2)	44 (0)

Incident Ischemic Coronary Artery Event End Point
50x44mm (300 x 300 DPI)

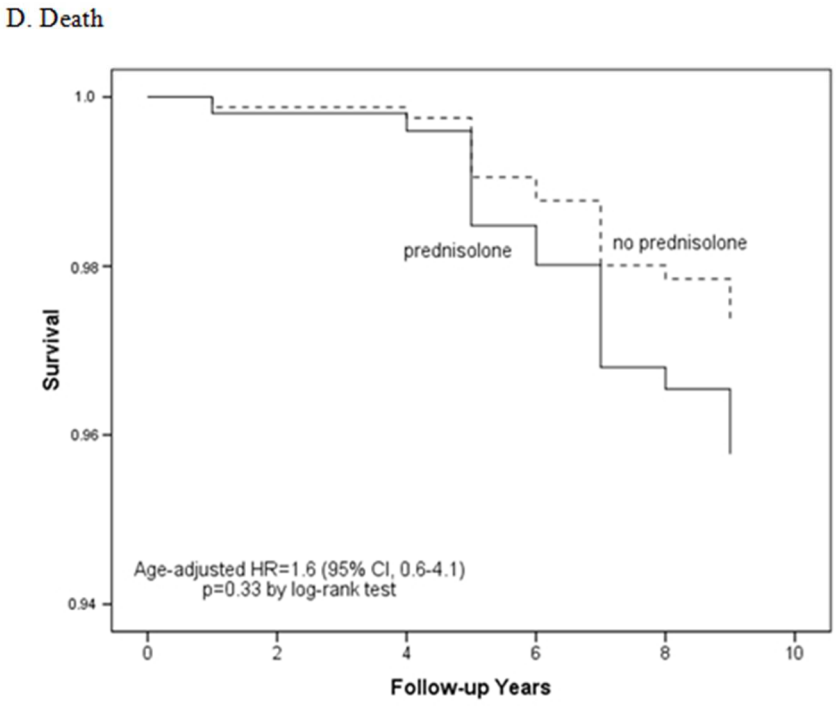
C. Incident Cerebrovascular Event End Point



No. At Risk

NoP-group	111 (1)	109 (2)	103 (2)	97 (0)	93 (0)	46 (0)
P-group	112 (1)	108 (2)	103 (1)	100 (2)	95 (4)	44 (0)

Incident Cerebrovascular Event End Point
52x49mm (300 x 300 DPI)



No. At Risk						
NoP-group	111 (0)	111 (0)	111 (4)	107 (5)	102 (0)	51 (0)
P-group	112 (1)	111 (0)	111 (2)	109 (2)	107 (4)	52 (0)

Death
51x48mm (300 x 300 DPI)

Low-dose prednisolone treatment of early rheumatoid arthritis and late cardiovascular outcome and survival: ten year follow-up of a two year randomized trial

Sofia Ajeganova, Björn Svensson, and Ingiäld Hafström, on behalf of the BARFOT Study Group

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Keywords: rheumatoid arthritis, prednisolone, cardiovascular event, mortality, risk

Word count: 3594

Abstract

Objective: To examine the long-term effects of early low-dose prednisolone use in patients with rheumatoid arthritis (RA) on cardiovascular (CV) morbidity and mortality.

Design: Retrieval of data from a 2-year open randomized trial comparing prednisolone 7.5 mg/day in addition to disease-modifying anti-rheumatic drugs (DMARDs) with DMARD therapy alone. Participants were followed for ten years since inclusion into the original prednisolone trial or until occurrence of the studied outcomes.

Setting: Secondary level of care; six participating centres from southern Sweden; both urban and rural populations.

Participants: Overall, 223 patients with early RA were included. The participants had no history of CV events at baseline and incident cases were identified via the Swedish Hospital Discharge and Cause of Death Registries.

Outcomes: Composite CV events i.e. ischemic coronary and cerebrovascular events, components of the composite CV outcome, and death. Relative hazard ratios from Cox proportional-hazards regression models were calculated.

Results: Within 2041 person-years, 17 incident composite CV events occurred in 112 patients (15 %) randomized to prednisolone, and 15 events out of 111 patients (14%) who were assigned not to receive prednisolone. Nine mortalities (8%) were observed in each group.

The age-adjusted relative hazards (HRs) (95% CI) for the first composite CV event, first coronary event and death in the prednisolone group vs. the group not treated with prednisolone were 1.8 (0.9-3.6), 0.98 (0.4-2.6), and 1.6 (0.6-4.1), respectively. The risk for the first cerebrovascular event showed a 3.7-fold increased relative hazard (95% CI, 1.2-11.4) among prednisolone treated patients. These results persisted in sensitivity analyses restricted to the participants who were adherent to the study treatment protocol.

Conclusion: In this study low-dose prednisolone use during the first two years of RA disease ~~was not associated with long-term coronary artery events or deaths, but with an~~ increased long-term risk of ischemic cerebrovascular events, but not risk of death.

Trial registration: ISRCTN20612367

Article summary

Article focus

- To examine associations between exposure to low-dose prednisolone in early rheumatoid arthritis (RA) and long-term cardiovascular (CV) outcomes and all-cause mortality.
- To study these associations separately for ischemic coronary artery events and ischemic cerebrovascular events.

Key messages

- Low-dose prednisolone exposure for two years in this early RA study showed increased cerebrovascular but not mortality risk.
- The results are inconclusive regarding clinically important long-term overall cardiovascular risk in an individual patient.
- ~~Neither ischemic coronary artery events nor all-cause death was associated with low-dose prednisolone treatment in our study.~~

Strengths and limitations of this study

- Randomized allocation to prednisolone therapy to patients with early RA diagnosed according to the American College of Rheumatology (ACR) criteria.
- The treatment protocol was highly compliant with only a few patients who were lost to follow-up or discontinued the allocated therapy.
- Data on outcomes were derived from the reliable nationwide registry system and sampled during a long observation period sufficient for development of studied complications.
- The original prednisolone trial was not primarily designed to examine the risk of CV events and mortality; and the population studied was relatively young with low burden of traditional CV risk factors at inclusion.

Introduction

Glucocorticoids (GCs) are powerful anti-inflammatory agents which have been used since the 1950s, first, as symptomatic treatment of rheumatoid arthritis (RA), but in the last years, as disease modifying therapy. Thus, inhibition of the progression of radiological damage in RA has been documented for GCs given in addition to disease-modifying anti-rheumatic drugs (DMARDs).[1-3] However, the relationship between short-, and long-term GC exposure and cardiovascular (CV) events and mortality in RA is still controversial.

The discussion on the side effects of GC use is still far from settled. Whereas adverse effects of long-term GCs use, at least at high dose, are well recognized in the general population and include effects on blood pressure, insulin resistance, lipid profile, homeostasis, body weight and fat distribution,[4-10] the nature of unfavourable CV effects and possible modulation of effects of GCs by other processes in RA are less known.[11-13] Some data are available which imply that chronic GC-using has no additive pro-atherogenic effects in the inflammatory milieu.[14, 15] A systematic literature review has shown poor association between low-dose GC exposure and CV risk factors, and probably no effect on atherosclerosis in RA patients.[16] GCs may have anti-atherogenic effects mediated by their anti-inflammatory and anti-proliferative actions in the vessel wall, and modify the recovery from occlusive vascular events and intravascular injury.[17-19]

However, in the scientific literature, the potential risks and benefits of GC exposure in RA have shown disparate results. Increased CV and/or mortality risk associated with the use of GCs, particularly with increasing doses, has been found in several studies,[20-25] while other studies have found GCs use to improve CV/mortality prognosis,[26] or to have no or uncertain effect.[27, 28] Diversity of outcomes definitions, different stages of RA disease, GC exposure in various dosages at any time during follow-up, and the potential for confounding by indication in observational cohorts make the results of the studies not fairly conclusive.

In an attempt to shed some light on the CV risk of exposure to low-dose prednisolone in early RA, we performed this study with retrieval of data from the previously conducted randomized prednisolone trial, a BARFOT (Better Anti-Rheumatic PharmacOTherapy) study.[3] In that trial, prednisolone 7.5 mg per day added to the initial DMARD retarded the progression of radiographic damage after 2 years, provided a high remission rate and was well tolerated.

Patients and Methods

Adults with a diagnosis of RA according to American College of Rheumatology (ACR) classification criteria 1987 [29] and symptom duration ≤ 12 months were eligible for the BARFOT inception cohort study.[30] The design of the 2-year low-dose prednisolone multicenter open-label randomized study, nested in the BARFOT cohort, has been described in detail previously.[3] This trial is registered with ISRCTN www.isrctn.org, number 20612367. Of 250 patients who entered the study with the treatments as assigned, 27 patients with a history of prior CV events were excluded for the purpose of the current study. The final study population, thus, included 112 patients of the prednisolone randomization arm, P-group,

and 111 patients of the no prednisolone arm, NoP-group. Figure 1 shows the flow of participation in the study.

Figure 1. Flow diagram for the randomization and participation in the two-year randomized part of the study

After randomization, the patients received 7.5 mg oral prednisolone daily in addition to their initial DMARD therapy, or DMARD therapy alone during 2 years. Violation of the 2-years protocol-specified therapy was uncommon, a total of 8 cases. DMARDs were prescribed at the discretion of the treating rheumatologists who were encouraged to adhere to clinical-practice guidelines.

Patients underwent standard laboratory testing for erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and assessment of RA disease at inclusion and after 3, 6, 12, 18 and 24 months, which included the Disease Activity Score for 28 joints (DAS28)[31] and the Swedish version of the Stanford Health Assessment Questionnaire (HAQ).[32] *Remission* was defined according to the DAS28 remission criterion, DAS28<2.6,[31] and *good response* according to European League Against Rheumatism (EULAR) response criteria as improvement in DAS28 of at least 1.2 units and achievement of an absolute score of < 3.2.[33]

Sera from study enrollment was analyzed for IgM rheumatoid factor (RF), using the Serodia agglutination test, (Fujirebio, Tokyo, Japan), positive RF defines as a titer of >20 IU/ml. Anti-citrullinated peptide antibody (anti-CCP) was analysed using the ELISA CCP2 test, (Euro-Diagnostica, Malmö, Sweden), positive anti-CCP defined as a titer >25 U/ml.

Information on smoking status (ever or never), hypertension, diabetes mellitus, hyperlipidaemia, body mass index (BMI), use of prednisolone, DMARDs and biological agents from the first visit and during follow-up was obtained from the BARFOT data base and from medical records.

All study participants provided written informed consent. The study was approved by the Regional Ethic committee, and was performed in accordance with the Declaration of Helsinki.

Outcome Assessment

The CV events considered were acute myocardial infarction (AMI), hospitalization for angina pectoris, coronary-artery bypass grafting or percutaneous coronary intervention, ischemic stroke, and transient ischemic attack (TIA).

The end points of the study were the time to the first CV event: the first composite event (i.e. the first coronary artery or cerebrovascular event), the components of the composite event or death from all causes. CV events were defined after ICD-9 and ICD-10 codes: AMI (ICD-9 410, ICD-10 I21), angina pectoris (411, 413, I20), or coronary intervention (3066-3067, 3080, 3092, 3105, 3127, 3141, 3158, Y832); ischemic stroke and TIA (433-436, I63-I66, G45).

The observation period started between September 1995 and December 1999, i.e. when the patients were included in the main BARFOT cohort. Each patient was followed for ten years or until the occurrence of the first-ever incident CV event or death.

All subjects could be followed through record linkage to the nationwide Causes of Death Registry, and the Swedish Hospital Discharge Registry, between January, 1987, and December, 2009. The registers used for this study have nationwide coverage and are complete, and their diagnostic validity is estimated to be high.[34]

Statistical Analysis

The demographic and clinical features were compared using the t-test, the Mann-Whitney U-test, the chi-square or Fisher's exact tests, as suitable. Area under the curve (AUC) was calculated using the trapezoidal rule for the RA disease measures assessed at all time points.

If outcomes were considered to be randomly distributed in time, incidence rates (with the 95% confidence interval (CI) for a Poisson count) were presented as events per 100 person-years at risk.

For primary analysis we collected and analysed end-point data on all participants. For the time to the end point, we computed Kaplan-Meier product-limit estimates of the event-free survival time and compared the randomized groups using a two-sided log-rank test. We calculated relative hazard ratios (HRs) and 95% confidence intervals (CI) from Cox proportional-hazards regression models. Covariates for adjusted Cox analyses were pre-specified as variables which were imbalanced in the randomization arms, and adjusted for in multivariate analyses if univariate tests showed significant association with the outcomes. Finally, we analysed all end-points restricted to the participants who were adherent to the allocated intervention and clinical trial instructions as stipulated in the protocol (Figure 1).

All significance tests were two tailed and conducted at the 0.05 level of significance. Statistical analyses were performed using IBM SPSS, version 20 (SPSS Inc., Chicago, IL).

Results

As shown in Table 1, the treatment groups differed in age but not sex or traditional CV risk factors, except for hypertension which was less common in the P-group (p=0.049). Disease characteristics and anti-rheumatic medications at baseline were well balanced between the study groups, but the cumulative burden of disease within two years after inclusion was lower in patients treated with prednisolone except for AUC-CRP, as compared with those who not received prednisolone~~, p<0.05~~.

Table 1. Clinical characteristics and cardiovascular outcomes for patients randomized to prednisolone or no prednisolone treatment

	Groups by randomization		
	Prednisolone n=112	No-prednisolone n=111	p-value

Age at inclusion, years	50.6 (14.1)	56.9 (13.0)	0.001
Female, n (%)	77 (69)	76 (69)	0.96
Traditional CV risk factors at baseline:			
BMI, kg/m^2	25.2 (4.3)	26.4 (4.2)	0.87
Smoking ever, n (%)	73 (65)	64 (58)	0.25
Hypertension, n (%)	14 (12.5)	25 (22.5)	0.049
Diabetes mellitus, n (%)	0	4 (4)	0.06
Hyperlipidaemia, n (%)	1 (1)	1 (1)	1.00
Baseline RA characteristics:			
Disease duration, months	6.5 (3.5)	5.8 (2.8)	0.12
RF positive, n (%)	72 (65)	72 (65)	1.00
anti-CCP positive, n (%)	58 (64)	50 (59)	0.50
DAS28	5.3 (1.1)	5.4 (1.1)	0.34
ESR, mm/hour	38 (26)	37 (25)	0.83
CRP, mg/l	22 (8-51)	21 (8-53)	0.96
HAQ	1.0 (0.6)	1.0 (0.7)	0.58
Started DMARDs at baseline:			
MTX, n (%)	57 (51)	61 (55)	0.54
SSZ, n (%)	36 (32)	38 (34)	0.74
AMA, n (%)	9 (8)	4 (4)	0.25
Gold, n (%)	9 (8)	8 (7)	0.82
Ever use of biological agents during the study, n (%)	17 (15)	17 (15)	1.00
Cumulative RA disease burden the first 2 years:			
AUC-DAS28	71.2 (28.1)	89.3 (28.4)	<0.001
AUC-ESR, mm/hour	386 (254)	504 (348)	0.011
AUC-CRP, mg/l	253 (189-364)	296 (162-480)	0.37
AUC-HAQ	11.5 (10.9)	17.6 (12.7)	0.001
Outcomes:			
Incident CV event, total, n (%)	17 (15.2)	15 (13.5)	0.72
Incident ischemic coronary event, n (%)	7 (6.2)	10 (9.0)	0.44
Incident ischemic cerebrovascular event, n (%)	10 (8.9)	5 (4.5)	0.19
Death, n (%)	9 (8)	9 (8)	0.98

Values are means (SD) or medians (IQR) depending on values distribution. P-values indicate between-group differences. CV = cardiovascular; BMI = body mass index; RF = rheumatoid factor; anti-CCP = anti-citrullinated peptide antibody; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; HAQ = Health Assessment Questionnaire; DMARD = disease modifying anti-rheumatic drugs; MTX = methotrexate; SSZ = sulfasalazine; AMA = antimalarials; AUC = area under the curve calculated on measurements at baseline, after 3, 6, 12, 18 and 24 months.

Treatments and traditional cardiovascular risk factors during follow-up

The prednisolone therapy was assessed during follow-up to the last visit in the two study groups.

In the P-group, 59/111 patients (53%) stopped prednisolone treatment after the first two study years, 30/109 patients (28%) stopped after a total of 4-5 years and 23/106 patients (22%) continued for more than 8 years. The mean (SD) daily dose of prednisolone decreased from 7.2 (1.1) mg at the 2-year follow-up to 6.5 (3.6) mg at the 4-year and 4.9 (3.3) mg at the 8-year assessment.

In the NoP-group, most patients (94%) continued without prednisolone after the two study years, albeit prednisolone therapy was initiated and maintained over a period of more than 6 months during the follow-up in 7/111 patients (6%), with a mean average dose (SD) of 5.2 (1.4) mg daily.

Ever usage of a biological agent throughout 10 years of observation was evenly distributed in the treatment arms (15% of the patients in each group).

The mean (SD) BMI at the two-year visit was similar in the two study groups, 26.2 (4.8) and 27.1 (4.4) in the P-group and the NoP-group respectively, p=0.21. None of the enrolled patients became a smoker during the observation period. Thus, the never-smoking status throughout the study was not changed. During follow-up, the number of patients registered with hypertension increased to 33 (30%) in the P-group and to 41 patients (37%) in the NoP-group, p=0.24. Diabetes mellitus was recorded in 2 patients (2%) in the P-group vs. 10 patients (9%) in the NoP-group, p=0.017, and hyperlipidaemia in 6 (5%) vs. 3 patients (3%) in the respective groups, p=0.50.

Study Outcomes

During ten years of observation, the total number of incident CV events, was 17 of 112 patients (15%) in the P-group (7 cases of AMI, hospitalization for angina pectoris and coronary interventions; 7 cases of ischemic stroke and 3 of TIA), as compared with 15 of 111 patients (14%) in the NoP-group (corresponding events in 10, 3 and 2 cases), p=0.72. None of the events was fatal. Incident CV events occurred after a median of 5.4 years (range 3 – 114 months) in the P-group and 4.9 years (range 2 - 120 months) in the NoP-group, p=0.66.

For the entire cohort, the total follow-up time was 2041 person-years. The cumulative incidence of CV events was 1.7 per 100 person-years (95% CI, 0.9-2.5) in the P-group, and 1.5 per 100 person-years (95% CI, 0.7-2.3) in the NoP-group. The rate of the first ever observed ischemic coronary event was 0.7 per 100 person-years (95% CI, 0.2-1.2) in the P-group; and 1.0 per 100 person-years (95% CI, 0.4-1.6) in the NoP-group. Occurrence of the first ever cerebrovascular event was nominally 2-fold higher in the P-group, 10 cases (8.9%), rates of 1.0 per 100 person-years (95% CI, 0.4-1.6), as compared with the NoP-group, 5 cases (4.5%), rates of 0.5 per 100 person-years (95% CI, 0.1-0.9). The pattern of distribution of the CV outcomes over time was even in the groups.

Nine mortalities (8%) were observed in each group during the 10-year period.

Primary analyses of outcomes

In the univariate Cox proportional hazard models, age at the study inclusion was found to be associated with the incident composite CV event, hazard ratio (HR), 1.08 (95% CI, 1.05-1.12), but not hypertension at inclusion, or AUCs of DAS28, ESR, and HAQ during the first two years of RA disease. Similar results were obtained in the univariate analyses of the CV subgroups and death, data not shown.

After adjustment for age, the relative hazards for the composite CV event end-point and death did not differ statistically significantly between the P-group and the NoP-group, HRs (95% CI) 1.8 (0.9-3.6), and 1.6 (0.6-4.1), respectively (Figure 2, panels A and D). When analysing the components of the composite CV event end-point, the hazard for the first coronary event was much the same in the two groups, HR 0.98 (0.4-2.6), while the hazard for the first cerebrovascular event among prednisolone treated patients was 3.7 times (95% CI, 1.2-11.4) higher than that among those who did not receive prednisolone (Figure 2, panels B and C).

Figure 2. Primary analysis of the study outcomes.

Shown are Kaplan-Meier curves comparing the prednisolone group (P-group) with the no-prednisolone group (NoP-group) for the time to the first composite cardiovascular event (panel A), the first ever ischemic coronary artery event (panel B), the first ever cerebrovascular event (panel C), and death (panel D). The relative age-adjusted hazard ratios (HR) were calculated with the use of a Cox proportional-hazards model. The tables below the panels represent the number of subjects at risk for the end points (number of the end points) at 2-year intervals throughout the 10-year observation.

Sensitivity analyses of outcomes

When we considered data for the patients who followed the assigned treatment, 105 participants in each randomization arm, the results were not changed. Given the decreasing survival trend 5 years after the study commencement, we recalculated estimates for the time to death between 5 and 10 years after enrollment. The additional analysis for this time period comparing the relative age-adjusted hazards for death in the P-group with the NoP-group yielded stable findings similar that for the whole 10-year follow-up, 1.4 (95% CI, 0.5-3.9, p=0.47).

Further analyses of outcomes in relation to therapy response

We performed analyses in order to investigate whether the effect of prednisolone was mediated through reduced inflammation. The cohort was stratified by therapy response at the 2-year visit according to DAS28 remission criteria and EULAR response criteria.

Relative age-adjusted hazards for death among subjects with DAS28 remission tended to be lower than those among patients who did not achieve DAS28 remission, The HRs were 0.41 (95% CI, 0.15-1.15), p=0.089 in the whole cohort, 0.30 (0.07-1.19), p=0.087 in the P-group, and 0.42 (0.09-2.03), p=0.28 in the NoP-group.

A similar tendency to decreased estimated relative mortality risks was observed among good EULAR responders compared with those not achieving good response. The age-adjusted

relative hazards were 0.37 (0.15-0.95), p=0.038 in the whole cohort, 0.45 (0.12-1.70), p=0.24 in the P-group and 0.28 (0.07-1.13) and p=0.074 in the NoP-group.

These relative differences were sustained over time. As to the composite CV event end-point, stratifying by therapy efficacy did not show differences, or trends to differences in the risks for the outcome, data not shown.

Discussion

We presented herein the results of the 10-year follow-up of cardiovascular events and deaths in a large, multicenter, prospective, open-label, randomized clinical trial of low-dose prednisolone, 7.5 mg per day, over the first two years of early RA disease in patients with no previous glucocorticoid or DMARD therapy. The estimated risk for a composite CV event, a first coronary artery event and death did not differ between patients assigned to receive prednisolone or not. However, the observed age-adjusted relative risk for a first cerebrovascular event among prednisolone-treated patients was increased by about 4 times that not treated with prednisolone. It should though be noticed that due to the low number of events and the wide estimated rates, a clinically important cardiovascular risk in the long-term in an individual patient treated with prednisolone is uncertain.

To the best of our knowledge, this is the first study addressing cardiovascular and survival consequences of exposure to low-dose prednisolone during two years in early RA in a randomized design. It should be mentioned that a good half of those randomized to prednisolone stopped that treatment after two years from baseline and that a further fourth quarter stopped after 4-5 years. In contrast, only a few patients who were randomized not to take prednisolone initiated prednisolone therapy during follow-up. Still, the distribution of traditional risk factors during the study period (body mass index, hypertension and hyperlipidaemia) was similar in the treatment groups, which strengthens the present findings and also challenges the idea of a negative impact of prednisolone on traditional CV risk factors in patients with an inflammatory condition.

Our study is different in several important ways to previous studies as to the relationship between glucocorticoid exposure and CV in RA and these differences make a broad comparison of the results difficult.

Based on prescription databases from the general population, Wei *et al.*[35] reported an increased risk for CV disease in GC users only in doses > or =7.5 mg of prednisolone or equivalent, the relative risk being 2.56 (CI, 2.18 to 2.99). Aviña-Zubieta *et al.*[22] determined that that the current dose (13% risk increase per additional 5 mg/day), cumulative duration of past GC use (10% risk increase for every additional year), and total cumulative dose (6% per each gram accumulated in the past) were independently associated with an increased risk of first myocardial infarction (MI) in RA cases identified through administrative data sources. In that study, GC exposure, again, included GCs dispensed by pharmacists at some time over the entire disease course. It should also be noted, that participants using GC had a high absolute risk of the CV outcomes, and due to lack of direct information on individual patient's characteristics, surrogate indices were applied to control for confounding by indication. In a

population-based incidence RA cohort, Davis *et al*.[25] reported that overall, a higher risk of the initial combined CV outcome was associated with recent exposure to GC, adjusted HR 1.66 (95% CI,1.14–2.41), and the highest tertile of cumulative exposure (>7,000 mg of prednisone equivalents), HR 2.11 (95% CI, 1.47–3.04); whereas there was no association with past GC exposure > 3 months, or mid tertile cumulative exposure (>1,500 to ≤7,000 mg).

Conversely, a lower prevalence for lifetime CV morbidity among patients with prolonged exposure to GCs, similar to conventional DMARDs and anti-TNF blockers, has been shown by Naranjo *et al.*[36] in the cross-sectional study in non-selected outpatients with RA, HR 0.95 (95% CI 0.92-0.98). In a prospective RA cohort, Gonzalez-Gay *et al,*[37] could not confirm an excess risk of incident CV events or CV mortality induced by median dose of prednisone 5 mg/day for at least 1 year, and the mean (SD) cumulative dose of prednisone of 13.5 (9.0) gram at the end of the study. Interestingly, risk of hospitalization for MI and stroke, which was assessed in the nested case-control study reported by Solomon *et al,*[24] was significantly increased only if GC were used in monotherapy (MTX monotherapy used as the reference group), but not in combination with another DMARDs.

Our results further suggest that it may be possible to avoid potential negative effects of GC on future ischemic coronary artery complications and survival prognosis if GCs are used in low-dose, over limited time, in conjunction with DMARDs in patients with a low baseline rate of traditional CV risk factors. This is in line with the encouraging reports about associations between effective anti-rheumatic therapy and favourable overall CV and survival prognosis,[38-41] which formed the basis for the hypothesis that dampening of systemic inflammation by GC may halt development of atherosclerotic disease.

Using the present knowledge, it seems fair to say that even if the possibility of an excess CV risk associated with GC exposure cannot be excluded, negative effects of GC may be counteracted by positive impact of suppression of chronic inflammation. Thus, the significant benefits of the low-dose GC therapy, both in terms of disease activity and radiographic progression in the present trial,[2, 3] as compared with therapy not including GC, could likely have overcome adverse coronary events and overall survival. In support of this hypothesis, the previous subgroup analysis has shown that low-dose of prednisolone in early RA was not pro-atherogenic, considering carotid artery intima-media measures, presence of atherosclerotic plaques, and endothelial function after five years of follow-up.[42] Accordingly, we observed a tendency towards reduction in mortality for patients with a better therapy response, possibly due to an overall decrease in inflammation related to the anti-rheumatic therapy.

When it comes to the potential cerebrovascular risk of GC use, the evidence is limited. There are studies showing an excess risk when using GC,[28, 35] while several others have failed to find any excess risk.[43, 44] Notably, few studies have divided CV events into subtypes. Such a subdivision could be of importance, considering the possibility of different etiologies of coronary and cerebrovascular events. The results of our study indicate that even low-dose GC exposure could be associated with long-term cerebrovascular safety issues in patients with RA. What pathways of the GC would be involved in occurrence of cerebrovascular events but not coronary events are unclear. About 14-30% of all strokes in the general population are of

cardio-embolic origin, and atrial fibrillation is a risk factor for this type of ischemic stroke.[45] An almost 2-fold increased risk of atrial fibrillation or flutter has been reported in current and long-term users of GC in a population-based case-control study.[46] As we found differences in the risk of ischemic coronary and cerebrovascular complications, we cannot exclude that the excess cerebrovascular risk in our study was essentially confined to participants with other specific underlying risk factors, e.g. atrial fibrillation. Such a possibility though could not be tested here through hospitalization registries.

Our study has several important strengths such as an incidence cohort of RA patients with the diagnose validated by the ACR criteria, randomized allocation to therapy within the setting of prospective follow-up, long observation period sufficient for development of studied complications, high compliance with the treatment protocol, few losses to follow-up or therapy discontinuation. Furthermore, the reliable nationwide registry system ascertains the outcomes.

However, these data should be interpreted with caution because it is not clear to what extent a more prolonged therapy with oral glucocorticoids may affect the risk of CV-related adverse clinical events. Further, the population of this study was relatively young and had a low frequency of baseline traditional CV risk factors. Then, we could not have anticipated the observed baseline imbalance between the treatment groups, but the age difference was adjusted for in the analyses. It should be also acknowledged that the prednisolone trial was not primarily designed to examine the risk of incident CV events. Given the low precision of estimated hazards, the results should be interpreted as non-definitive regarding possible long-term risks of CV events in patients treated with low dose prednisolone.

Conclusion

This study has focused on the long-term cardiovascular and mortality risks of low-dose glucocorticoid therapy in RA and adds further weight to the arguments for appropriate use of glucocorticoids in early disease. Our data suggest that the 2-year low-dose GC exposure in patients with early RA may have affected the risk of cerebrovascular events. On the other side, the results of this study would argue against GC-induced risk of ischemic coronary artery complications and death in a population with low frequency of background traditional CV risk factors. ~~Further studies addressing CV effects, especially risk for stroke in relation to GC use are needed.~~

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Competing interest

The authors have declared no relevant conflicts of interest.

Contributor statement

IH and BS designed the original low-dose prednisolone study and were involved in acquisition of data. SA was responsible for the current study concept, data acquisition, statistical analyses and drafting of the manuscript. IH participated in the interpretation of data and manuscript preparation. All authors have critically revised and approved the final version of the manuscript to be published, and contributed to the study with regard to important intellectual content.

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Low-dose prednisolone treatment of early rheumatoid arthritis and late cardiovascular outcome and survival: ten year follow-up of a two year randomized trial

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Low-dose prednisolone treatment of early rheumatoid arthritis and late cardiovascular outcome and survival: ten year follow-up of a two year randomized trial

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Abstract

Objective: To examine the long-term effects of early low-dose prednisolone use in patients with rheumatoid arthritis (RA) on cardiovascular (CV) morbidity and mortality.

Design: Retrieval of data from a 2-year open randomized trial comparing prednisolone 7.5 mg/day in addition to disease-modifying anti-rheumatic drugs (DMARDs) with DMARD therapy alone. Participants were followed for ten years since inclusion into the original prednisolone trial or until occurrence of the studied outcomes.

Setting: Secondary level of care; six participating centres from southern Sweden; both urban and rural populations.

Participants: Overall, 223 patients with early RA were included. The participants had no history of CV events at baseline and incident cases were identified via the Swedish Hospital Discharge and Cause of Death Registries.

Outcomes: Composite CV events i.e. ischemic coronary and cerebrovascular events, components of the composite CV outcome, and death. Relative hazard ratios from Cox proportional-hazards regression models were calculated.

Results: Within 2041 person-years, 17 incident composite CV events occurred in 112 patients (15%) randomized to prednisolone, and 15 events out of 111 patients (14%) who were assigned not to receive prednisolone. Nine deaths (8%) were in each group.

The age-adjusted relative hazards (HRs) (95% CI) for the first composite CV event, first coronary event and death in the prednisolone group vs. the group not treated with prednisolone were 1.8 (0.9-3.6), 0.98 (0.4-2.6), and 1.6 (0.6-4.1), respectively. The risk for the first cerebrovascular event showed a 3.7-fold increased relative hazard (95% CI, 1.2-11.4) among prednisolone treated patients.

Conclusion: In this inception cohort study of low-dose prednisolone use during the first two years of RA disease, the incidence of ischemic coronary artery events was similar in the two treatment groups, whereas the long-term risk of ischemic cerebrovascular events was higher in the prednisolone group. There was a trend to reduced survival in the prednisolone group.

Trial registration: ISRCTN20612367

Article summary

Article focus

- To examine associations between exposure to low-dose prednisolone in early rheumatoid arthritis (RA) and long-term cardiovascular (CV) outcomes and all-cause mortality.
- To study these associations separately for ischemic coronary artery events and ischemic cerebrovascular events.

Key messages

- Low-dose prednisolone exposure for two years in this early RA study showed increased cerebrovascular risk.
- This study showed similar incidence of ischemic coronary events in the prednisolone group and the group not treated with prednisolone.
- The results are inconclusive regarding clinically important long-term overall cardiovascular morbidity.
- A trend towards reduced survival was observed in the prednisolone group.

Strengths and limitations of this study

- Randomized allocation to prednisolone therapy to patients with early RA diagnosed according to the American College of Rheumatology (ACR) criteria.
- The treatment protocol was highly compliant with only a few patients who were lost to follow-up or discontinued the allocated therapy.
- Data on outcomes were derived from the reliable nationwide registry system and sampled during a long observation period sufficient for development of studied complications.
- The original prednisolone trial was not primarily designed to examine the risk of CV events and mortality; and the population studied was relatively young with low burden of traditional CV risk factors at inclusion.

Introduction

Glucocorticoids (GCs) are powerful anti-inflammatory agents which have been used since the 1950s, first, as symptomatic treatment of rheumatoid arthritis (RA), but in the last years, as disease modifying therapy. Thus, inhibition of the progression of radiological damage in RA has been documented for GCs given in addition to disease-modifying anti-rheumatic drugs (DMARDs).[1-3] However, the relationship between short-, and long-term GC exposure and cardiovascular (CV) events and mortality in RA is still controversial.

The discussion on the side effects of GC use is still far from settled. Whereas adverse effects of long-term GCs use, at least at high dose, are well recognized in the general population and include effects on blood pressure, insulin resistance, lipid profile, homeostasis, body weight and fat distribution,[4-10] the nature of unfavourable CV effects and possible modulation of effects of GCs by other processes in RA are less known.[11-13] Some data are available which imply that chronic GC-using has no additive pro-atherogenic effects in the inflammatory milieu.[14, 15] A systematic literature review has shown poor association between low-dose GC exposure and CV risk factors, and probably no effect on atherosclerosis in RA patients.[16] GCs may have anti-atherogenic effects mediated by their anti-inflammatory and anti-proliferative actions in the vessel wall, and modify the recovery from occlusive vascular events and intravascular injury.[17-19]

However, in the scientific literature, the potential risks and benefits of GC exposure in RA have shown disparate results. Increased CV and/or mortality risk associated with the use of GCs, particularly with increasing doses, has been found in several studies,[20-25] while other studies have found GCs use to improve CV/mortality prognosis,[26] or to have no or uncertain effect.[27, 28] Diversity of outcomes definitions, different stages of RA disease, GC exposure in various dosages at any time during follow-up, and the potential for confounding by indication in observational cohorts make the results of the studies not fairly conclusive.

In an attempt to shed some light on the CV risk of exposure to low-dose prednisolone in early RA, we performed this study with retrieval of data from the previously conducted randomized prednisolone trial, a BARFOT (Better Anti-Rheumatic PharmacOTherapy) study.[3] In that trial, prednisolone 7.5 mg per day added to the initial DMARD retarded the progression of radiographic damage after 2 years, provided a high remission rate and was well tolerated.

Patients and Methods

Adults with a diagnosis of RA according to American College of Rheumatology (ACR) classification criteria 1987 [29] and symptom duration ≤ 12 months were eligible for the BARFOT inception cohort study.[30] The design of the 2-year low-dose prednisolone multicenter open-label randomized study, nested in the BARFOT cohort, has been described in detail previously.[3] This trial is registered with ISRCTN www.isrctn.org, number 20612367. Of 250 patients who entered the study with the treatments as assigned, 27 patients with a history of prior CV events were excluded for the purpose of the current study. The final study population, thus, included 112 patients of the prednisolone randomization arm, P-group,

and 111 patients of the no prednisolone arm, NoP-group. Figure 1 shows the flow of participation in the study.

Figure 1. Flow diagram for the randomization and participation in the two-year randomized part of the study

After randomization, the patients received 7.5 mg oral prednisolone daily in addition to their initial DMARD therapy, or DMARD therapy alone during 2 years. Violation of the 2-years protocol-specified therapy was uncommon, a total of 8 cases. DMARDs were prescribed at the discretion of the treating rheumatologists who were encouraged to adhere to clinical-practice guidelines.

Patients underwent standard laboratory testing for erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and assessment of RA disease at inclusion and after 3, 6, 12, 18 and 24 months, which included the Disease Activity Score for 28 joints (DAS28)[31] and the Swedish version of the Stanford Health Assessment Questionnaire (HAQ).[32] *Remission* was defined according to the DAS28 remission criterion, DAS28<2.6,[31] and *good response* according to European League Against Rheumatism (EULAR) response criteria as improvement in DAS28 of at least 1.2 units and achievement of an absolute score of < 3.2.[33]

Sera from study enrollment was analyzed for IgM rheumatoid factor (RF), using the Serodia agglutination test, (Fujirebio, Tokyo, Japan), positive RF defines as a titer of >20 IU/ml. Anti-citrullinated peptide antibody (anti-CCP) was analysed using the ELISA CCP2 test, (Euro-Diagnostica, Malmö, Sweden), positive anti-CCP defined as a titer >25 U/ml.

Information on smoking status (ever or never), hypertension, diabetes mellitus, hyperlipidaemia, body mass index (BMI), use of prednisolone, DMARDs and biological agents from the first visit and during follow-up was obtained from the BARFOT data base and from medical records.

All study participants provided written informed consent. The study was approved by the Regional Ethic committee, and was performed in accordance with the Declaration of Helsinki.

Outcome Assessment

The CV events considered were acute myocardial infarction (AMI), hospitalization for angina pectoris, coronary-artery bypass grafting or percutaneous coronary intervention, ischemic stroke, and transient ischemic attack (TIA).

The end points of the study were the time to the first CV event: the first composite event (i.e. the first coronary artery or cerebrovascular event), the components of the composite event or death from all causes. CV events were defined after ICD-9 and ICD-10 codes: AMI (ICD-9 410, ICD-10 I21), angina pectoris (411, 413, I20), or coronary intervention (3066-3067, 3080, 3092, 3105, 3127, 3141, 3158, Y832); ischemic stroke and TIA (433-436, I63-I66, G45).

The observation period started between September 1995 and December 1999, i.e. when the patients were included in the main BARFOT cohort. Each patient was followed for ten years or until the occurrence of the first-ever incident CV event or death.

All subjects could be followed through record linkage to the nationwide Causes of Death Registry, and the Swedish Hospital Discharge Registry, between January, 1987, and December, 2009. The registers used for this study have nationwide coverage and are complete, and their diagnostic validity is estimated to be high.[34]

Statistical Analysis

The demographic and clinical features were compared using the t-test, the Mann-Whitney U-test, the chi-square or Fisher's exact tests, as suitable. Area under the curve (AUC) was calculated using the trapezoidal rule for the RA disease measures assessed at all time points.

If outcomes were considered to be randomly distributed in time, incidence rates (with the 95% confidence interval (CI) for a Poisson count) were presented as events per 100 person-years at risk.

For primary analysis we collected and analysed end-point data on all participants. For the time to the end point, we computed Kaplan-Meier product-limit estimates of the event-free survival time and compared the randomized groups using a two-sided log-rank test. We calculated relative hazard ratios (HRs) and 95% confidence intervals (CI) from Cox proportional-hazards regression models. Covariates for adjusted Cox analyses were pre-specified as variables which were imbalanced in the randomization arms, and adjusted for in multivariate analyses if univariate tests showed significant association with the outcomes. Finally, we analysed all end-points restricted to the participants who were adherent to the allocated intervention and clinical trial instructions as stipulated in the protocol (Figure 1).

All significance tests were two tailed and conducted at the 0.05 level of significance. Statistical analyses were performed using IBM SPSS, version 20 (SPSS Inc., Chicago, IL).

Results

As shown in Table 1, the treatment groups differed in age but not sex or traditional CV risk factors, except for hypertension which was less common in the P-group (p=0.049). Disease characteristics and anti-rheumatic medications at baseline were well balanced between the study groups, but the cumulative burden of disease within two years after inclusion was lower in patients treated with prednisolone except for AUC-CRP, as compared with those who not received prednisolone.

Table 1. Clinical characteristics and cardiovascular outcomes for patients randomized to prednisolone or no prednisolone treatment

	Groups by randomization		
	Prednisolone n=112	No-prednisolone n=111	p-value

Age at inclusion, years	50.6 (14.1)	56.9 (13.0)	0.001
Female, n (%)	77 (69)	76 (69)	0.96
Traditional CV risk factors at baseline:			
BMI, kg/m^2	25.2 (4.3)	26.4 (4.2)	0.87
Smoking ever, n (%)	73 (65)	64 (58)	0.25
Hypertension, n (%)	14 (12.5)	25 (22.5)	0.049
Diabetes mellitus, n (%)	0	4 (4)	0.06
Hyperlipidaemia, n (%)	1 (1)	1 (1)	1.00
Baseline RA characteristics:			
Disease duration, months	6.5 (3.5)	5.8 (2.8)	0.12
RF positive, n (%)	72 (65)	72 (65)	1.00
anti-CCP positive, n (%)	58 (64)	50 (59)	0.50
DAS28	5.3 (1.1)	5.4 (1.1)	0.34
ESR, mm/hour	38 (26)	37 (25)	0.83
CRP, mg/l	22 (8-51)	21 (8-53)	0.96
HAQ	1.0 (0.6)	1.0 (0.7)	0.58
Started DMARDs at baseline:			
MTX, n (%)	57 (51)	61 (55)	0.54
SSZ, n (%)	36 (32)	38 (34)	0.74
AMA, n (%)	9 (8)	4 (4)	0.25
Gold, n (%)	9 (8)	8 (7)	0.82
Ever use of biological agents during the study, n (%)	17 (15)	17 (15)	1.00
Cumulative RA disease burden the first 2 years:			
AUC-DAS28	71.2 (28.1)	89.3 (28.4)	<0.001
AUC-ESR, mm/hour	386 (254)	504 (348)	0.011
AUC-CRP, mg/l	253 (189-364)	296 (162-480)	0.37
AUC-HAQ	11.5 (10.9)	17.6 (12.7)	0.001
Outcomes:			
Incident CV event, total, n (%)	17 (15.2)	15 (13.5)	0.72
Incident ischemic coronary event, n (%)	7 (6.2)	10 (9.0)	0.44
Incident ischemic cerebrovascular event, n (%)	10 (8.9)	5 (4.5)	0.19
Death, n (%)	9 (8)	9 (8)	0.98

Values are means (SD) or medians (IQR) depending on values distribution. P-values indicate between-group differences. CV = cardiovascular; BMI = body mass index; RF = rheumatoid factor; anti-CCP = anti-citrullinated peptide antibody; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; HAQ = Health Assessment Questionnaire; DMARD = disease modifying anti-rheumatic drugs; MTX = methotrexate; SSZ = sulfasalazine; AMA = antimalarials; AUC = area under the curve calculated on measurements at baseline, after 3, 6, 12, 18 and 24 months.

Treatments and traditional cardiovascular risk factors during follow-up

The prednisolone therapy was assessed during follow-up to the last visit in the two study groups.

In the P-group, 59/111 patients (53%) stopped prednisolone treatment after the first two study years. A further 30/109 patients (28%) had stopped prednisolone after a total of 4-5 years. Twenty-three of the remaining 106 patients (22%) continued prednisolone for more than 8

years. The mean (SD) daily dose of prednisolone, in those taking prednisolone, decreased from 7.2 (1.1) mg at the 2-year follow-up to 6.5 (3.6) mg at the 4-year and 4.9 (3.3) mg at the 8-year assessment.

In the NoP-group, most patients (94%) continued without prednisolone after the two study years, albeit prednisolone therapy was initiated and maintained over a period of more than 6 months during the follow-up in 7/111 patients (6%), with a mean average dose (SD) of 5.2 (1.4) mg daily.

Ever usage of a biological agent throughout 10 years of observation was evenly distributed in the treatment arms (15% of the patients in each group).

The mean (SD) BMI at the two-year visit was similar in the two study groups, 26.2 (4.8) and 27.1 (4.4) in the P-group and the NoP-group respectively, p=0.21. None of the enrolled patients became a smoker during the observation period. Thus, the never-smoking status throughout the study was not changed. During follow-up, the number of patients registered with hypertension increased to 33 (30%) in the P-group and to 41 patients (37%) in the NoP-group, p=0.24. Diabetes mellitus was recorded in 2 patients (2%) in the P-group vs. 10 patients (9%) in the NoP-group, p=0.017, and hyperlipidaemia in 6 (5%) vs. 3 patients (3%) in the respective groups, p=0.50.

Study Outcomes

During ten years of observation, the total number of incident CV events, was 17 of 112 patients (15%) in the P-group (7 cases of AMI, hospitalization for angina pectoris and coronary interventions; 7 cases of ischemic stroke and 3 of TIA), as compared with 15 of 111 patients (14%) in the NoP-group (corresponding events in 10, 3 and 2 cases), p=0.72. None of the events was fatal. Incident CV events occurred after a median of 5.4 years (range 3 – 114 months) in the P-group and 4.9 years (range 2 - 120 months) in the NoP-group, p=0.66.

For the entire cohort, the total follow-up time was 2041 person-years. The cumulative incidence of CV events was 1.7 per 100 person-years (95% CI, 0.9-2.5) in the P-group, and 1.5 per 100 person-years (95% CI, 0.7-2.3) in the NoP-group. The rate of the first ever observed ischemic coronary event was 0.7 per 100 person-years (95% CI, 0.2-1.2) in the P-group; and 1.0 per 100 person-years (95% CI, 0.4-1.6) in the NoP-group. Occurrence of the first ever cerebrovascular event was nominally 2-fold higher in the P-group, 10 cases (8.9%), rates of 1.0 per 100 person-years (95% CI, 0.4-1.6), as compared with the NoP-group, 5 cases (4.5%), rates of 0.5 per 100 person-years (95% CI, 0.1-0.9). The pattern of distribution of the CV outcomes over time was even in the groups.

Nine mortalities (8%) were observed in each group during the 10-year period.

Primary analyses of outcomes

In the univariate Cox proportional hazard models, age at the study inclusion was found to be associated with the incident composite CV event, hazard ratio (HR), 1.08 (95% CI, 1.05-1.12), but not hypertension at inclusion, or AUCs of DAS28, ESR, and HAQ during the first

two years of RA disease. Similar results were obtained in the univariate analyses of the CV subgroups and death, data not shown.

After adjustment for age, the relative hazards for the composite CV event end-point and death did not differ statistically significantly between the P-group and the NoP-group, HRs (95% CI) 1.8 (0.9-3.6), and 1.6 (0.6-4.1), respectively (Figure 2, panels A and D). When analysing the components of the composite CV event end-point, the hazard for the first coronary event was much the same in the two groups, HR 0.98 (0.4-2.6), while the hazard for the first cerebrovascular event among prednisolone treated patients was 3.7 times (95% CI, 1.2-11.4) higher than that among those who did not receive prednisolone (Figure 2, panels B and C).

Figure 2. Primary analysis of the study outcomes.

Shown are Kaplan-Meier curves comparing the prednisolone group (P-group) with the no-prednisolone group (NoP-group) for the time to the first composite cardiovascular event (panel A), the first ever ischemic coronary artery event (panel B), the first ever cerebrovascular event (panel C), and death (panel D). The relative age-adjusted hazard ratios (HR) were calculated with the use of a Cox proportional-hazards model. The tables below the panels represent the number of subjects at risk for the end points (number of the end points) at 2-year intervals throughout the 10-year observation.

Sensitivity analyses of outcomes

When we considered data for the patients who followed the assigned treatment, 105 participants in each randomization arm, the results were not changed. Given the decreasing survival trend 5 years after the study commencement, we recalculated estimates for the time to death between 5 and 10 years after enrollment. The additional analysis for this time period comparing the relative age-adjusted hazards for death in the P-group with the NoP-group yielded stable findings similar that for the whole 10-year follow-up, 1.4 (95% CI, 0.5-3.9, p=0.47).

Further analyses of outcomes in relation to therapy response

We performed analyses in order to investigate whether the effect of prednisolone was mediated through reduced inflammation. The cohort was stratified by therapy response at the 2-year visit according to DAS28 remission criteria and EULAR response criteria.

Relative age-adjusted hazards for death among subjects with DAS28 remission tended to be lower than those among patients who did not achieve DAS28 remission, The HRs were 0.41 (95% CI, 0.15-1.15), p=0.089 in the whole cohort, 0.30 (0.07-1.19), p=0.087 in the P-group, and 0.42 (0.09-2.03), p=0.28 in the NoP-group.

A similar tendency to decreased estimated relative mortality risks was observed among good EULAR responders compared with those not achieving good response. The age-adjusted relative hazards were 0.37 (0.15-0.95), p=0.038 in the whole cohort, 0.45 (0.12-1.70), p=0.24 in the P-group and 0.28 (0.07-1.13) and p=0.074 in the NoP-group.

These relative differences were sustained over time. As to the composite CV event end-point, stratifying by therapy efficacy did not show differences, or trends to differences in the risks for the outcome, data not shown.

Discussion

We presented herein the results of the 10-year follow-up of cardiovascular events and deaths in a large, multicenter, prospective, open-label, randomized clinical trial of low-dose prednisolone, 7.5 mg per day, over the first two years of early RA disease in patients with no previous glucocorticoid or DMARD therapy. The estimated risk for a composite CV event, a first coronary artery event and death did not differ between patients assigned to receive prednisolone or not. However, the observed age-adjusted relative risk for a first cerebrovascular event among prednisolone-treated patients was increased by about 4 times that not treated with prednisolone. It should though be noticed that due to the low number of events and the wide estimated rates, a clinically important cardiovascular risk in the long-term in an individual patient treated with prednisolone is uncertain.

To the best of our knowledge, this is the first study addressing cardiovascular and survival consequences of exposure to low-dose prednisolone during two years in early RA in a randomized design. It should be mentioned that a good half of those randomized to prednisolone stopped that treatment after two years from baseline and that a further fourth quarter stopped after 4-5 years. In contrast, only a few patients who were randomized not to take prednisolone initiated prednisolone therapy during follow-up. Still, the distribution of traditional risk factors during the study period (body mass index, hypertension and hyperlipidaemia) was similar in the treatment groups, which strengthens the present findings and also challenges the idea of a negative impact of prednisolone on traditional CV risk factors in patients with an inflammatory condition.

Our study is different in several important ways to previous studies as to the relationship between glucocorticoid exposure and CV in RA and these differences make a broad comparison of the results difficult.

Based on prescription databases from the general population, Wei *et al.*[35] reported an increased risk for CV disease in GC users only in doses > or =7.5 mg of prednisolone or equivalent, the relative risk being 2.56 (CI, 2.18 to 2.99). Aviña-Zubieta *et al.*[22] determined that that the current dose (13% risk increase per additional 5 mg/day), cumulative duration of past GC use (10% risk increase for every additional year), and total cumulative dose (6% per each gram accumulated in the past) were independently associated with an increased risk of first myocardial infarction (MI) in RA cases identified through administrative data sources. In that study, GC exposure, again, included GCs dispensed by pharmacists at some time over the entire disease course. It should also be noted, that participants using GC had a high absolute risk of the CV outcomes, and due to lack of direct information on individual patient's characteristics, surrogate indices were applied to control for confounding by indication. In a population-based incidence RA cohort, Davis *et al.*[25] reported that overall, a higher risk of the initial combined CV outcome was associated with recent exposure to GC, adjusted HR

1.66 (95% CI,1.14–2.41), and the highest tertile of cumulative exposure (>7,000 mg of prednisone equivalents), HR 2.11 (95% CI, 1.47–3.04); whereas there was no association with past GC exposure > 3 months, or mid tertile cumulative exposure (>1,500 to ≤7,000 mg).

Conversely, a lower prevalence for lifetime CV morbidity among patients with prolonged exposure to GCs, similar to conventional DMARDs and anti-TNF blockers, has been shown by Naranjo *et al.*[36] in the cross-sectional study in non-selected outpatients with RA, HR 0.95 (95% CI 0.92-0.98). In a prospective RA cohort, Gonzalez-Gay *et al,*[37] could not confirm an excess risk of incident CV events or CV mortality induced by median dose of prednisone 5 mg/day for at least 1 year, and the mean (SD) cumulative dose of prednisone of 13.5 (9.0) gram at the end of the study. Interestingly, risk of hospitalization for MI and stroke, which was assessed in the nested case-control study reported by Solomon *et al,*[24] was significantly increased only if GC were used in monotherapy (MTX monotherapy used as the reference group), but not in combination with another DMARDs.

Our results further suggest that it may be possible to avoid potential negative effects of GC on future ischemic coronary artery complications and survival prognosis if GCs are used in low-dose, over limited time, in conjunction with DMARDs in patients with a low baseline rate of traditional CV risk factors. This is in line with the encouraging reports about associations between effective anti-rheumatic therapy and favourable overall CV and survival prognosis,[38-41] which formed the basis for the hypothesis that dampening of systemic inflammation by GC may halt development of atherosclerotic disease.

Using the present knowledge, it seems fair to say that even if the possibility of an excess CV risk associated with GC exposure cannot be excluded, negative effects of GC may be counteracted by positive impact of suppression of chronic inflammation. Thus, the significant benefits of the low-dose GC therapy, both in terms of disease activity and radiographic progression in the present trial,[2, 3] as compared with therapy not including GC, could likely have overcome adverse coronary events and overall survival. In support of this hypothesis, the previous subgroup analysis has shown that low-dose of prednisolone in early RA was not pro-atherogenic, considering carotid artery intima-media measures, presence of atherosclerotic plaques, and endothelial function after five years of follow-up.[42] Accordingly, we observed a tendency towards reduction in mortality for patients with a better therapy response, possibly due to an overall decrease in inflammation related to the anti-rheumatic therapy.

When it comes to the potential cerebrovascular risk of GC use, the evidence is limited. There are studies showing an excess risk when using GC,[28, 35] while several others have failed to find any excess risk.[43, 44] Notably, few studies have divided CV events into subtypes. Such a subdivision could be of importance, considering the possibility of different etiologies of coronary and cerebrovascular events. The results of our study indicate that even low-dose GC exposure could be associated with long-term cerebrovascular safety issues in patients with RA. What pathways of the GC would be involved in occurrence of cerebrovascular events but not coronary events are unclear. About 14-30% of all strokes in the general population are of cardio-embolic origin, and atrial fibrillation is a risk factor for this type of ischemic stroke.[45] An almost 2-fold increased risk of atrial fibrillation or flutter has been reported in

current and long-term users of GC in a population-based case-control study.[46] As we found differences in the risk of ischemic coronary and cerebrovascular complications, we cannot exclude that the excess cerebrovascular risk in our study was essentially confined to participants with other specific underlying risk factors, e.g. atrial fibrillation. Such a possibility though could not be tested here through hospitalization registries.

Our study has several important strengths such as an incidence cohort of RA patients with the diagnose validated by the ACR criteria, randomized allocation to therapy within the setting of prospective follow-up, long observation period sufficient for development of studied complications, high compliance with the treatment protocol, few losses to follow-up or therapy discontinuation. Furthermore, the reliable nationwide registry system ascertains the outcomes.

However, these data should be interpreted with caution because it is not clear to what extent a more prolonged therapy with oral glucocorticoids may affect the risk of CV-related adverse clinical events and survival. Further, the population of this study was relatively young and had a low frequency of baseline traditional CV risk factors. Then, we could not have anticipated the observed baseline imbalance between the treatment groups, but the age difference was adjusted for in the analyses. It should be also acknowledged that the prednisolone trial was not primarily designed to examine the risk of incident CV events. Given the low precision of estimated hazards and restriction of measurements to prednisolone exposure only in the first two years, regardless of subsequent prednisolone use, the results should be interpreted as non-definitive regarding possible long-term risks.

Conclusion

This study has focused on the long-term cardiovascular and mortality risks of low-dose glucocorticoid therapy in RA and adds further weight to the arguments for appropriate use of glucocorticoids in early disease. Our data suggest that the 2-year low-dose GC exposure in patients with early RA may have affected the risk of cerebrovascular events. On the other side, the results of this study would argue against GC-induced risk of ischemic coronary artery complications in a population with low frequency of background traditional CV risk factors.

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Contributor statement

IH and BS designed the original low-dose prednisolone study and were involved in acquisition of data. SA was responsible for the current study concept, data acquisition, statistical analyses and drafting of the manuscript. IH participated in the interpretation of data and manuscript preparation. All authors have critically revised and approved the final version of the manuscript to be published, and contributed to the study with regard to important intellectual content.

Competing interest

The authors have declared no relevant conflicts of interest.

Data Sharing Statement

No additional data available.

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Figure legends

Figure 1.Flow diagram for the randomization and participation in the two-year randomized part of the study

Figure 2. Primary analysis of the study outcomes.

Low-dose prednisolone treatment of early rheumatoid arthritis and late cardiovascular outcome and survival: ten year follow-up of a two year randomized trial

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Abstract

Objective: To examine the long-term effects of early low-dose prednisolone use in patients with rheumatoid arthritis (RA) on cardiovascular (CV) morbidity and mortality.

Design: Retrieval of data from a 2-year open randomized trial comparing prednisolone 7.5 mg/day in addition to disease-modifying anti-rheumatic drugs (DMARDs) with DMARD therapy alone. Participants were followed for ten years since inclusion into the original prednisolone trial or until occurrence of the studied outcomes.

Setting: Secondary level of care; six participating centres from southern Sweden; both urban and rural populations.

Participants: Overall, 223 patients with early RA were included. The participants had no history of CV events at baseline and incident cases were identified via the Swedish Hospital Discharge and Cause of Death Registries.

Outcomes: Composite CV events i.e. ischemic coronary and cerebrovascular events, components of the composite CV outcome, and death. Relative hazard ratios from Cox proportional-hazards regression models were calculated.

Results: Within 2041 person-years, 17 incident composite CV events occurred in 112 patients (15%) randomized to prednisolone, and 15 events out of 111 patients (14%) who were assigned not to receive prednisolone. Nine deaths (8%) were ~~observed~~ in each group.

The age-adjusted relative hazards (HRs) (95% CI) for the first composite CV event, first coronary event and death in the prednisolone group vs. the group not treated with prednisolone were 1.8 (0.9-3.6), 0.98 (0.4-2.6), and 1.6 (0.6-4.1), respectively. The risk for the first cerebrovascular event showed a 3.7-fold increased relative hazard (95% CI, 1.2-11.4) among prednisolone treated patients. ~~These results persisted in sensitivity analyses restricted to the participants who were adherent to the study treatment protocol.~~

Conclusion: In this inception cohort study of low-dose prednisolone use during the first two years of RA disease, the incidence of ischaemic coronary artery events was similar in the two treatment groups, whereas the long-term risk of ischemic cerebrovascular events was higher in the prednisolone group. There was a trend to reduced survival in the prednisolone group.

Trial registration: ISRCTN20612367

Article summary

Article focus

- To examine associations between exposure to low-dose prednisolone in early rheumatoid arthritis (RA) and long-term cardiovascular (CV) outcomes and all-cause mortality.
- To study these associations separately for ischemic coronary artery events and ischemic cerebrovascular events.

Key messages

- Low-dose prednisolone exposure for two years in this early RA study showed increased cerebrovascular ~~but not mortality~~ risk.
- This study showed similar incidence of ischemic coronary events in the prednisolone group and the group not treated with prednisolone.
- The results are inconclusive regarding clinically important long-term overall cardiovascular morbidity.
- A trend towards reduced survival was observed in the prednisolone group.

Strengths and limitations of this study

- Randomized allocation to prednisolone therapy to patients with early RA diagnosed according to the American College of Rheumatology (ACR) criteria.
- The treatment protocol was highly compliant with only a few patients who were lost to follow-up or discontinued the allocated therapy.
- Data on outcomes were derived from the reliable nationwide registry system and sampled during a long observation period sufficient for development of studied complications.
- The original prednisolone trial was not primarily designed to examine the risk of CV events and mortality; and the population studied was relatively young with low burden of traditional CV risk factors at inclusion.

Introduction

Glucocorticoids (GCs) are powerful anti-inflammatory agents which have been used since the 1950s, first, as symptomatic treatment of rheumatoid arthritis (RA), but in the last years, as disease modifying therapy. Thus, inhibition of the progression of radiological damage in RA has been documented for GCs given in addition to disease-modifying anti-rheumatic drugs (DMARDs).[1-3] However, the relationship between short-, and long-term GC exposure and cardiovascular (CV) events and mortality in RA is still controversial.

The discussion on the side effects of GC use is still far from settled. Whereas adverse effects of long-term GCs use, at least at high dose, are well recognized in the general population and include effects on blood pressure, insulin resistance, lipid profile, homeostasis, body weight and fat distribution,[4-10] the nature of unfavourable CV effects and possible modulation of effects of GCs by other processes in RA are less known.[11-13] Some data are available which imply that chronic GC-using has no additive pro-atherogenic effects in the inflammatory milieu.[14, 15] A systematic literature review has shown poor association between low-dose GC exposure and CV risk factors, and probably no effect on atherosclerosis in RA patients.[16] GCs may have anti-atherogenic effects mediated by their anti-inflammatory and anti-proliferative actions in the vessel wall, and modify the recovery from occlusive vascular events and intravascular injury.[17-19]

However, in the scientific literature, the potential risks and benefits of GC exposure in RA have shown disparate results. Increased CV and/or mortality risk associated with the use of GCs, particularly with increasing doses, has been found in several studies,[20-25] while other studies have found GCs use to improve CV/mortality prognosis,[26] or to have no or uncertain effect.[27, 28] Diversity of outcomes definitions, different stages of RA disease, GC exposure in various dosages at any time during follow-up, and the potential for confounding by indication in observational cohorts make the results of the studies not fairly conclusive.

In an attempt to shed some light on the CV risk of exposure to low-dose prednisolone in early RA, we performed this study with retrieval of data from the previously conducted randomized prednisolone trial, a BARFOT (Better Anti-Rheumatic PharmacOTherapy) study.[3] In that trial, prednisolone 7.5 mg per day added to the initial DMARD retarded the progression of radiographic damage after 2 years, provided a high remission rate and was well tolerated.

Patients and Methods

Adults with a diagnosis of RA according to American College of Rheumatology (ACR) classification criteria 1987 [29] and symptom duration ≤ 12 months were eligible for the BARFOT inception cohort study.[30] The design of the 2-year low-dose prednisolone multicenter open-label randomized study, nested in the BARFOT cohort, has been described in detail previously.[3] This trial is registered with ISRCTN www.isrctn.org, number 20612367. Of 250 patients who entered the study with the treatments as assigned, 27 patients with a history of prior CV events were excluded for the purpose of the current study. The final study population, thus, included 112 patients of the prednisolone randomization arm, P-group,

and 111 patients of the no prednisolone arm, NoP-group. Figure 1 shows the flow of participation in the study.

Figure 1. Flow diagram for the randomization and participation in the two-year randomized part of the study

After randomization, the patients received 7.5 mg oral prednisolone daily in addition to their initial DMARD therapy, or DMARD therapy alone during 2 years. Violation of the 2-years protocol-specified therapy was uncommon, a total of 8 cases. DMARDs were prescribed at the discretion of the treating rheumatologists who were encouraged to adhere to clinical-practice guidelines.

Patients underwent standard laboratory testing for erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and assessment of RA disease at inclusion and after 3, 6, 12, 18 and 24 months, which included the Disease Activity Score for 28 joints (DAS28)[31] and the Swedish version of the Stanford Health Assessment Questionnaire (HAQ).[32] *Remission* was defined according to the DAS28 remission criterion, DAS28<2.6,[31] and *good response* according to European League Against Rheumatism (EULAR) response criteria as improvement in DAS28 of at least 1.2 units and achievement of an absolute score of < 3.2.[33]

Sera from study enrollment was analyzed for IgM rheumatoid factor (RF), using the Serodia agglutination test, (Fujirebio, Tokyo, Japan), positive RF defines as a titer of >20 IU/ml. Anti-citrullinated peptide antibody (anti-CCP) was analysed using the ELISA CCP2 test, (Euro-Diagnostica, Malmö, Sweden), positive anti-CCP defined as a titer >25 U/ml.

Information on smoking status (ever or never), hypertension, diabetes mellitus, hyperlipidaemia, body mass index (BMI), use of prednisolone, DMARDs and biological agents from the first visit and during follow-up was obtained from the BARFOT data base and from medical records.

All study participants provided written informed consent. The study was approved by the Regional Ethic committee, and was performed in accordance with the Declaration of Helsinki.

Outcome Assessment

The CV events considered were acute myocardial infarction (AMI), hospitalization for angina pectoris, coronary-artery bypass grafting or percutaneous coronary intervention, ischemic stroke, and transient ischemic attack (TIA).

The end points of the study were the time to the first CV event: the first composite event (i.e. the first coronary artery or cerebrovascular event), the components of the composite event or death from all causes. CV events were defined after ICD-9 and ICD-10 codes: AMI (ICD-9 410, ICD-10 I21), angina pectoris (411, 413, I20), or coronary intervention (3066-3067, 3080, 3092, 3105, 3127, 3141, 3158, Y832); ischemic stroke and TIA (433-436, I63-I66, G45).

The observation period started between September 1995 and December 1999, i.e. when the patients were included in the main BARFOT cohort. Each patient was followed for ten years or until the occurrence of the first-ever incident CV event or death.

All subjects could be followed through record linkage to the nationwide Causes of Death Registry, and the Swedish Hospital Discharge Registry, between January, 1987, and December, 2009. The registers used for this study have nationwide coverage and are complete, and their diagnostic validity is estimated to be high.[34]

Statistical Analysis

The demographic and clinical features were compared using the t-test, the Mann-Whitney U-test, the chi-square or Fisher's exact tests, as suitable. Area under the curve (AUC) was calculated using the trapezoidal rule for the RA disease measures assessed at all time points.

If outcomes were considered to be randomly distributed in time, incidence rates (with the 95% confidence interval (CI) for a Poisson count) were presented as events per 100 person-years at risk.

For primary analysis we collected and analysed end-point data on all participants. For the time to the end point, we computed Kaplan-Meier product-limit estimates of the event-free survival time and compared the randomized groups using a two-sided log-rank test. We calculated relative hazard ratios (HRs) and 95% confidence intervals (CI) from Cox proportional-hazards regression models. Covariates for adjusted Cox analyses were pre-specified as variables which were imbalanced in the randomization arms, and adjusted for in multivariate analyses if univariate tests showed significant association with the outcomes. Finally, we analysed all end-points restricted to the participants who were adherent to the allocated intervention and clinical trial instructions as stipulated in the protocol (Figure 1).

All significance tests were two tailed and conducted at the 0.05 level of significance. Statistical analyses were performed using IBM SPSS, version 20 (SPSS Inc., Chicago, IL).

Results

As shown in Table 1, the treatment groups differed in age but not sex or traditional CV risk factors, except for hypertension which was less common in the P-group (p=0.049). Disease characteristics and anti-rheumatic medications at baseline were well balanced between the study groups, but the cumulative burden of disease within two years after inclusion was lower in patients treated with prednisolone except for AUC-CRP, as compared with those who not received prednisolone.

Table 1. Clinical characteristics and cardiovascular outcomes for patients randomized to prednisolone or no prednisolone treatment

	Groups by randomization		
	Prednisolone n=112	No-prednisolone n=111	p-value

Age at inclusion, years	50.6 (14.1)	56.9 (13.0)	0.001
Female, n (%)	77 (69)	76 (69)	0.96
Traditional CV risk factors at baseline:			
BMI, kg/m^2	25.2 (4.3)	26.4 (4.2)	0.87
Smoking ever, n (%)	73 (65)	64 (58)	0.25
Hypertension, n (%)	14 (12.5)	25 (22.5)	0.049
Diabetes mellitus, n (%)	0	4 (4)	0.06
Hyperlipidaemia, n (%)	1 (1)	1 (1)	1.00
Baseline RA characteristics:			
Disease duration, months	6.5 (3.5)	5.8 (2.8)	0.12
RF positive, n (%)	72 (65)	72 (65)	1.00
anti-CCP positive, n (%)	58 (64)	50 (59)	0.50
DAS28	5.3 (1.1)	5.4 (1.1)	0.34
ESR, mm/hour	38 (26)	37 (25)	0.83
CRP, mg/l	22 (8-51)	21 (8-53)	0.96
HAQ	1.0 (0.6)	1.0 (0.7)	0.58
Started DMARDs at baseline:			
MTX, n (%)	57 (51)	61 (55)	0.54
SSZ, n (%)	36 (32)	38 (34)	0.74
AMA, n (%)	9 (8)	4 (4)	0.25
Gold, n (%)	9 (8)	8 (7)	0.82
Ever use of biological agents during the study, n (%)	17 (15)	17 (15)	1.00
Cumulative RA disease burden the first 2 years:			
AUC-DAS28	71.2 (28.1)	89.3 (28.4)	<0.001
AUC-ESR, mm/hour	386 (254)	504 (348)	0.011
AUC-CRP, mg/l	253 (189-364)	296 (162-480)	0.37
AUC-HAQ	11.5 (10.9)	17.6 (12.7)	0.001
Outcomes:			
Incident CV event, total, n (%)	17 (15.2)	15 (13.5)	0.72
Incident ischemic coronary event, n (%)	7 (6.2)	10 (9.0)	0.44
Incident ischemic cerebrovascular event, n (%)	10 (8.9)	5 (4.5)	0.19
Death, n (%)	9 (8)	9 (8)	0.98

Values are means (SD) or medians (IQR) depending on values distribution. P-values indicate between-group differences. CV = cardiovascular; BMI = body mass index; RF = rheumatoid factor; anti-CCP = anti-citrullinated peptide antibody; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; HAQ = Health Assessment Questionnaire; DMARD = disease modifying anti-rheumatic drugs; MTX = methotrexate; SSZ = sulfasalazine; AMA = antimalarials; AUC = area under the curve calculated on measurements at baseline, after 3, 6, 12, 18 and 24 months.

Treatments and traditional cardiovascular risk factors during follow-up

The prednisolone therapy was assessed during follow-up to the last visit in the two study groups.

In the P-group, 59/111 patients (53%) stopped prednisolone treatment after the first two study years. A further 30/109 patients (28%) had stopped prednisolone after a total of 4-5 years. Twenty-three of the remaining 106 patients (22%) continued prednisolone for more than 8

years. The mean (SD) daily dose of prednisolone, in those taking prednisolone, decreased from 7.2 (1.1) mg at the 2-year follow-up to 6.5 (3.6) mg at the 4-year and 4.9 (3.3) mg at the 8-year assessment.

In the NoP-group, most patients (94%) continued without prednisolone after the two study years, albeit prednisolone therapy was initiated and maintained over a period of more than 6 months during the follow-up in 7/111 patients (6%), with a mean average dose (SD) of 5.2 (1.4) mg daily.

Ever usage of a biological agent throughout 10 years of observation was evenly distributed in the treatment arms (15% of the patients in each group).

The mean (SD) BMI at the two-year visit was similar in the two study groups, 26.2 (4.8) and 27.1 (4.4) in the P-group and the NoP-group respectively, p=0.21. None of the enrolled patients became a smoker during the observation period. Thus, the never-smoking status throughout the study was not changed. During follow-up, the number of patients registered with hypertension increased to 33 (30%) in the P-group and to 41 patients (37%) in the NoP-group, p=0.24. Diabetes mellitus was recorded in 2 patients (2%) in the P-group vs. 10 patients (9%) in the NoP-group, p=0.017, and hyperlipidaemia in 6 (5%) vs. 3 patients (3%) in the respective groups, p=0.50.

Study Outcomes

During ten years of observation, the total number of incident CV events, was 17 of 112 patients (15%) in the P-group (7 cases of AMI, hospitalization for angina pectoris and coronary interventions; 7 cases of ischemic stroke and 3 of TIA), as compared with 15 of 111 patients (14%) in the NoP-group (corresponding events in 10, 3 and 2 cases), p=0.72. None of the events was fatal. Incident CV events occurred after a median of 5.4 years (range 3 – 114 months) in the P-group and 4.9 years (range 2 - 120 months) in the NoP-group, p=0.66.

For the entire cohort, the total follow-up time was 2041 person-years. The cumulative incidence of CV events was 1.7 per 100 person-years (95% CI, 0.9-2.5) in the P-group, and 1.5 per 100 person-years (95% CI, 0.7-2.3) in the NoP-group. The rate of the first ever observed ischemic coronary event was 0.7 per 100 person-years (95% CI, 0.2-1.2) in the P-group; and 1.0 per 100 person-years (95% CI, 0.4-1.6) in the NoP-group. Occurrence of the first ever cerebrovascular event was nominally 2-fold higher in the P-group, 10 cases (8.9%), rates of 1.0 per 100 person-years (95% CI, 0.4-1.6), as compared with the NoP-group, 5 cases (4.5%), rates of 0.5 per 100 person-years (95% CI, 0.1-0.9). The pattern of distribution of the CV outcomes over time was even in the groups.

Nine mortalities (8%) were observed in each group during the 10-year period.

Primary analyses of outcomes

In the univariate Cox proportional hazard models, age at the study inclusion was found to be associated with the incident composite CV event, hazard ratio (HR), 1.08 (95% CI, 1.05-1.12), but not hypertension at inclusion, or AUCs of DAS28, ESR, and HAQ during the first

two years of RA disease. Similar results were obtained in the univariate analyses of the CV subgroups and death, data not shown.

After adjustment for age, the relative hazards for the composite CV event end-point and death did not differ statistically significantly between the P-group and the NoP-group, HRs (95% CI) 1.8 (0.9-3.6), and 1.6 (0.6-4.1), respectively (Figure 2, panels A and D). When analysing the components of the composite CV event end-point, the hazard for the first coronary event was much the same in the two groups, HR 0.98 (0.4-2.6), while the hazard for the first cerebrovascular event among prednisolone treated patients was 3.7 times (95% CI, 1.2-11.4) higher than that among those who did not receive prednisolone (Figure 2, panels B and C).

Figure 2. Primary analysis of the study outcomes.

Shown are Kaplan-Meier curves comparing the prednisolone group (P-group) with the no-prednisolone group (NoP-group) for the time to the first composite cardiovascular event (panel A), the first ever ischemic coronary artery event (panel B), the first ever cerebrovascular event (panel C), and death (panel D). The relative age-adjusted hazard ratios (HR) were calculated with the use of a Cox proportional-hazards model. The tables below the panels represent the number of subjects at risk for the end points (number of the end points) at 2-year intervals throughout the 10-year observation.

Sensitivity analyses of outcomes

When we considered data for the patients who followed the assigned treatment, 105 participants in each randomization arm, the results were not changed. Given the decreasing survival trend 5 years after the study commencement, we recalculated estimates for the time to death between 5 and 10 years after enrollment. The additional analysis for this time period comparing the relative age-adjusted hazards for death in the P-group with the NoP-group yielded stable findings similar that for the whole 10-year follow-up, 1.4 (95% CI, 0.5-3.9, p=0.47).

Further analyses of outcomes in relation to therapy response

We performed analyses in order to investigate whether the effect of prednisolone was mediated through reduced inflammation. The cohort was stratified by therapy response at the 2-year visit according to DAS28 remission criteria and EULAR response criteria.

Relative age-adjusted hazards for death among subjects with DAS28 remission tended to be lower than those among patients who did not achieve DAS28 remission, The HRs were 0.41 (95% CI, 0.15-1.15), p=0.089 in the whole cohort, 0.30 (0.07-1.19), p=0.087 in the P-group, and 0.42 (0.09-2.03), p=0.28 in the NoP-group.

A similar tendency to decreased estimated relative mortality risks was observed among good EULAR responders compared with those not achieving good response. The age-adjusted relative hazards were 0.37 (0.15-0.95), p=0.038 in the whole cohort, 0.45 (0.12-1.70), p=0.24 in the P-group and 0.28 (0.07-1.13) and p=0.074 in the NoP-group.

These relative differences were sustained over time. As to the composite CV event end-point, stratifying by therapy efficacy did not show differences, or trends to differences in the risks for the outcome, data not shown.

Discussion

We presented herein the results of the 10-year follow-up of cardiovascular events and deaths in a large, multicenter, prospective, open-label, randomized clinical trial of low-dose prednisolone, 7.5 mg per day, over the first two years of early RA disease in patients with no previous glucocorticoid or DMARD therapy. The estimated risk for a composite CV event, a first coronary artery event and death did not differ between patients assigned to receive prednisolone or not. However, the observed age-adjusted relative risk for a first cerebrovascular event among prednisolone-treated patients was increased by about 4 times that not treated with prednisolone. It should though be noticed that due to the low number of events and the wide estimated rates, a clinically important cardiovascular risk in the long-term in an individual patient treated with prednisolone is uncertain.

To the best of our knowledge, this is the first study addressing cardiovascular and survival consequences of exposure to low-dose prednisolone during two years in early RA in a randomized design. It should be mentioned that a good half of those randomized to prednisolone stopped that treatment after two years from baseline and that a further fourth quarter stopped after 4-5 years. In contrast, only a few patients who were randomized not to take prednisolone initiated prednisolone therapy during follow-up. Still, the distribution of traditional risk factors during the study period (body mass index, hypertension and hyperlipidaemia) was similar in the treatment groups, which strengthens the present findings and also challenges the idea of a negative impact of prednisolone on traditional CV risk factors in patients with an inflammatory condition.

Our study is different in several important ways to previous studies as to the relationship between glucocorticoid exposure and CV in RA and these differences make a broad comparison of the results difficult.

Based on prescription databases from the general population, Wei *et al.*[35] reported an increased risk for CV disease in GC users only in doses > or =7.5 mg of prednisolone or equivalent, the relative risk being 2.56 (CI, 2.18 to 2.99). Aviña-Zubieta *et al.*[22] determined that that the current dose (13% risk increase per additional 5 mg/day), cumulative duration of past GC use (10% risk increase for every additional year), and total cumulative dose (6% per each gram accumulated in the past) were independently associated with an increased risk of first myocardial infarction (MI) in RA cases identified through administrative data sources. In that study, GC exposure, again, included GCs dispensed by pharmacists at some time over the entire disease course. It should also be noted, that participants using GC had a high absolute risk of the CV outcomes, and due to lack of direct information on individual patient's characteristics, surrogate indices were applied to control for confounding by indication. In a population-based incidence RA cohort, Davis *et al.*[25] reported that overall, a higher risk of the initial combined CV outcome was associated with recent exposure to GC, adjusted HR

1.66 (95% CI,1.14–2.41), and the highest tertile of cumulative exposure (>7,000 mg of prednisone equivalents), HR 2.11 (95% CI, 1.47–3.04); whereas there was no association with past GC exposure > 3 months, or mid tertile cumulative exposure (>1,500 to ≤7,000 mg).

Conversely, a lower prevalence for lifetime CV morbidity among patients with prolonged exposure to GCs, similar to conventional DMARDs and anti-TNF blockers, has been shown by Naranjo *et al.*[36] in the cross-sectional study in non-selected outpatients with RA, HR 0.95 (95% CI 0.92-0.98). In a prospective RA cohort, Gonzalez-Gay *et al,*[37] could not confirm an excess risk of incident CV events or CV mortality induced by median dose of prednisone 5 mg/day for at least 1 year, and the mean (SD) cumulative dose of prednisone of 13.5 (9.0) gram at the end of the study. Interestingly, risk of hospitalization for MI and stroke, which was assessed in the nested case-control study reported by Solomon *et al,*[24] was significantly increased only if GC were used in monotherapy (MTX monotherapy used as the reference group), but not in combination with another DMARDs.

Our results further suggest that it may be possible to avoid potential negative effects of GC on future ischemic coronary artery complications and survival prognosis if GCs are used in low-dose, over limited time, in conjunction with DMARDs in patients with a low baseline rate of traditional CV risk factors. This is in line with the encouraging reports about associations between effective anti-rheumatic therapy and favourable overall CV and survival prognosis,[38-41] which formed the basis for the hypothesis that dampening of systemic inflammation by GC may halt development of atherosclerotic disease.

Using the present knowledge, it seems fair to say that even if the possibility of an excess CV risk associated with GC exposure cannot be excluded, negative effects of GC may be counteracted by positive impact of suppression of chronic inflammation. Thus, the significant benefits of the low-dose GC therapy, both in terms of disease activity and radiographic progression in the present trial,[2, 3] as compared with therapy not including GC, could likely have overcome adverse coronary events and overall survival. In support of this hypothesis, the previous subgroup analysis has shown that low-dose of prednisolone in early RA was not pro-atherogenic, considering carotid artery intima-media measures, presence of atherosclerotic plaques, and endothelial function after five years of follow-up.[42] Accordingly, we observed a tendency towards reduction in mortality for patients with a better therapy response, possibly due to an overall decrease in inflammation related to the anti-rheumatic therapy.

When it comes to the potential cerebrovascular risk of GC use, the evidence is limited. There are studies showing an excess risk when using GC,[28, 35] while several others have failed to find any excess risk.[43, 44] Notably, few studies have divided CV events into subtypes. Such a subdivision could be of importance, considering the possibility of different etiologies of coronary and cerebrovascular events. The results of our study indicate that even low-dose GC exposure could be associated with long-term cerebrovascular safety issues in patients with RA. What pathways of the GC would be involved in occurrence of cerebrovascular events but not coronary events are unclear. About 14-30% of all strokes in the general population are of cardio-embolic origin, and atrial fibrillation is a risk factor for this type of ischemic stroke.[45] An almost 2-fold increased risk of atrial fibrillation or flutter has been reported in

current and long-term users of GC in a population-based case-control study.[46] As we found differences in the risk of ischemic coronary and cerebrovascular complications, we cannot exclude that the excess cerebrovascular risk in our study was essentially confined to participants with other specific underlying risk factors, e.g. atrial fibrillation. Such a possibility though could not be tested here through hospitalization registries.

Our study has several important strengths such as an incidence cohort of RA patients with the diagnose validated by the ACR criteria, randomized allocation to therapy within the setting of prospective follow-up, long observation period sufficient for development of studied complications, high compliance with the treatment protocol, few losses to follow-up or therapy discontinuation. Furthermore, the reliable nationwide registry system ascertains the outcomes.

However, these data should be interpreted with caution because it is not clear to what extent a more prolonged therapy with oral glucocorticoids may affect the risk of CV-related adverse clinical events and survival. Further, the population of this study was relatively young and had a low frequency of baseline traditional CV risk factors. Then, we could not have anticipated the observed baseline imbalance between the treatment groups, but the age difference was adjusted for in the analyses. It should be also acknowledged that the prednisolone trial was not primarily designed to examine the risk of incident CV events. Given the low precision of estimated hazards and restriction of measurements to prednisolone exposure only in the first two years, regardless of subsequent prednisolone use, the results should be interpreted as non-definitive regarding possible long-term risks. ~~of CV events in patients treated with low dose prednisolone.~~

Conclusion

This study has focused on the long-term cardiovascular and mortality risks of low-dose glucocorticoid therapy in RA and adds further weight to the arguments for appropriate use of glucocorticoids in early disease. Our data suggest that the 2-year low-dose GC exposure in patients with early RA may have affected the risk of cerebrovascular events. On the other side, the results of this study would argue against GC-induced risk of ischemic coronary artery complications ~~and death~~ in a population with low frequency of background traditional CV risk factors.

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Competing interest

The authors have declared no relevant conflicts of interest.

Contributor statement

IH and BS designed the original low-dose prednisolone study and were involved in acquisition of data. SA was responsible for the current study concept, data acquisition, statistical analyses and drafting of the manuscript. IH participated in the interpretation of data and manuscript preparation. All authors have critically revised and approved the final version of the manuscript to be published, and contributed to the study with regard to important intellectual content.

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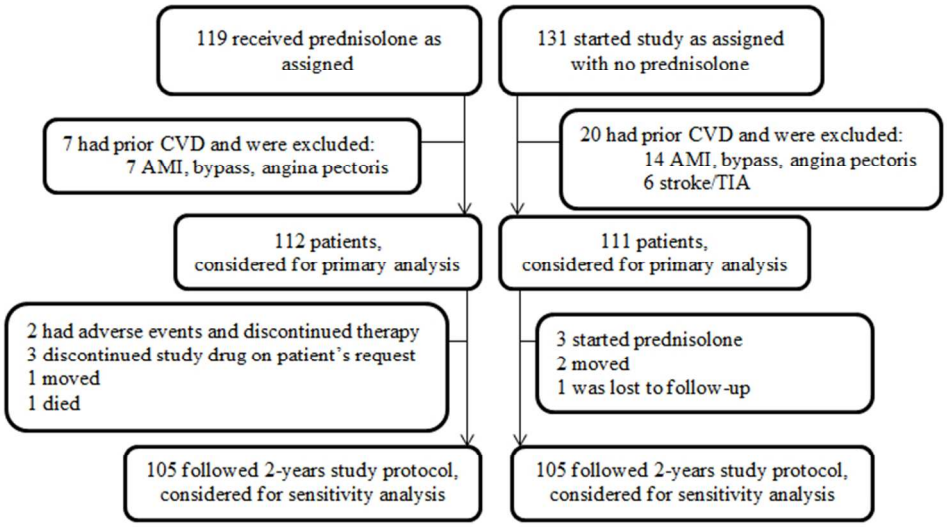
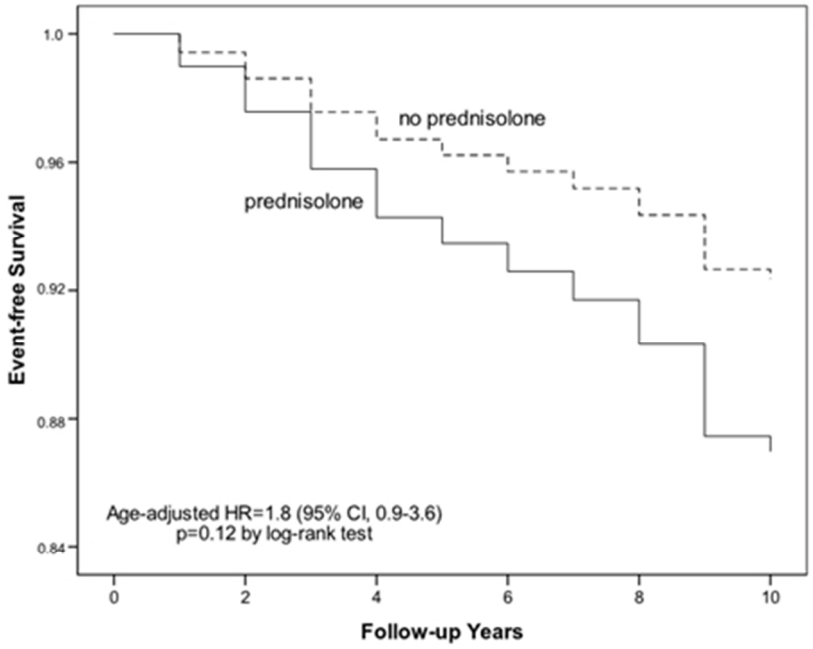


Flow diagram for the randomization and participation in the two-year randomized part of the study
64x36mm (300 x 300 DPI)

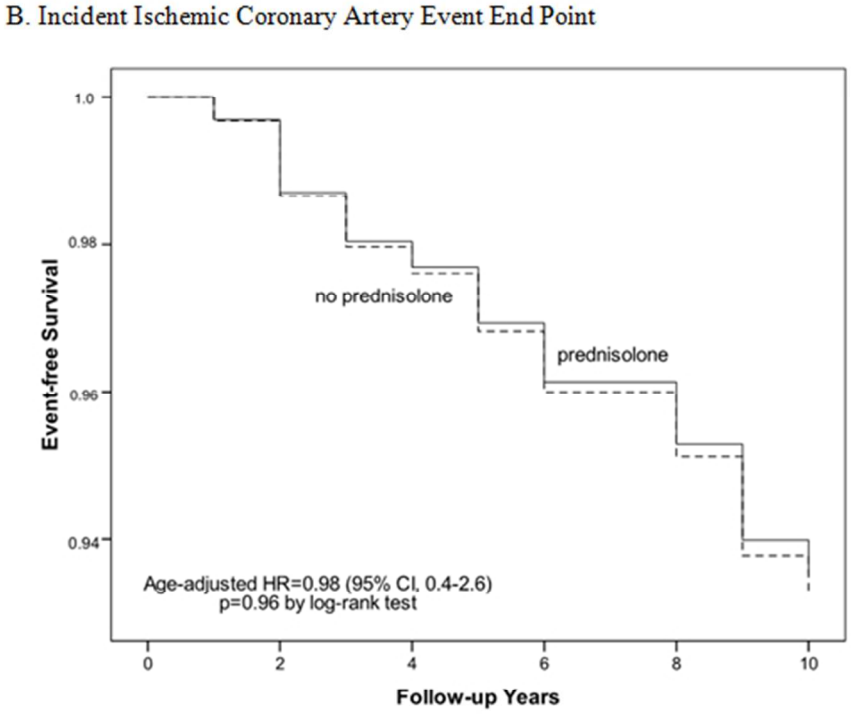
A. Incident Composite Cardiovascular Event End Point



No. At Risk

NoP-group	111 (1)	110 (5)	104 (3)	98 (2)	94 (3)	46 (1)
P-group	112 (2)	109 (4)	104 (3)	100 (2)	96 (6)	44 (0)

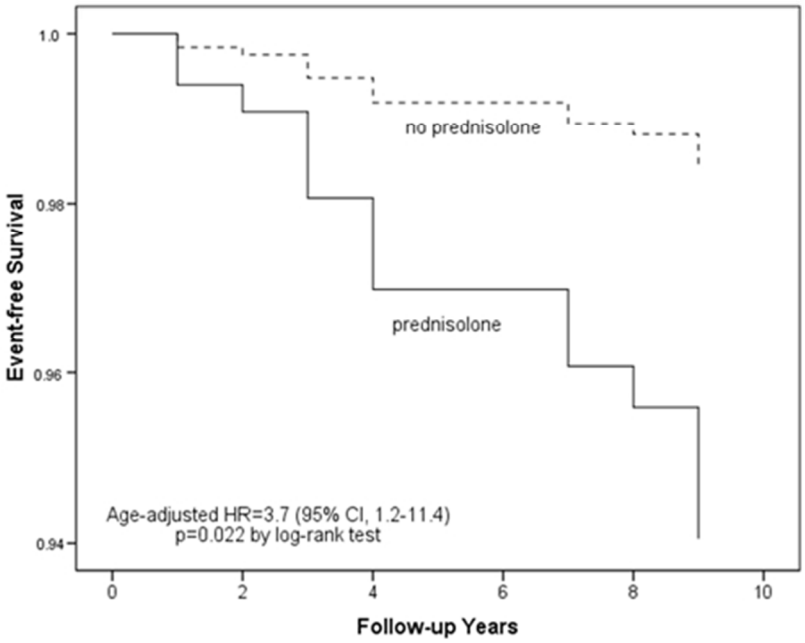
Incident Composite Cardiovascular Event End Point
46x44mm (300 x 300 DPI)



No. At Risk						
NoP-group	111 (0)	109 (3)	103 (1)	98 (2)	94 (3)	46 (1)
P-group	112 (1)	108 (2)	104 (2)	99 (0)	94 (2)	44 (0)

Incident Ischemic Coronary Artery Event End Point
50x44mm (300 x 300 DPI)

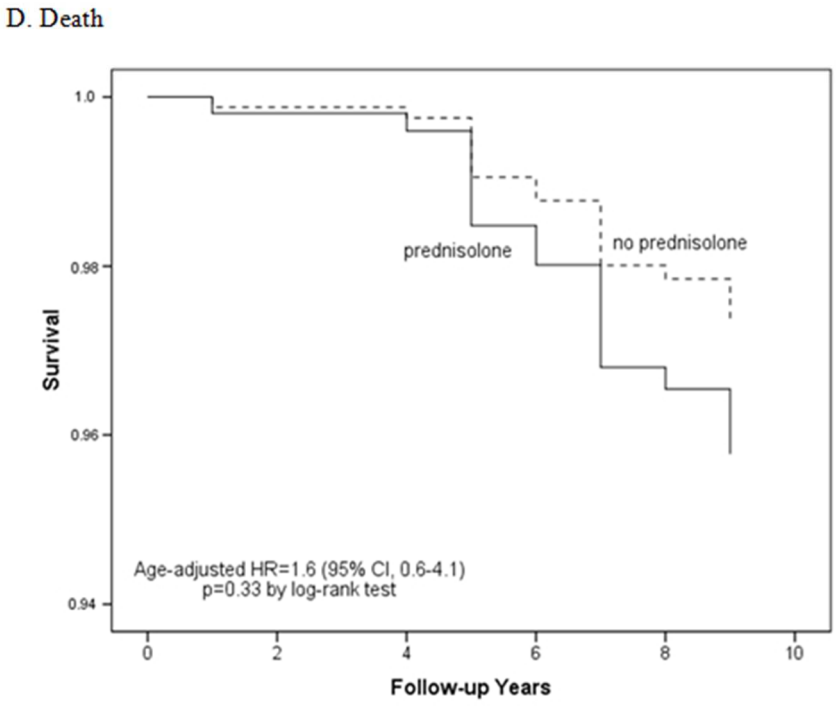
C. Incident Cerebrovascular Event End Point



No. At Risk

NoP-group	111 (1)	109 (2)	103 (2)	97 (0)	93 (0)	46 (0)
P-group	112 (1)	108 (2)	103 (1)	100 (2)	95 (4)	44 (0)

Incident Cerebrovascular Event End Point
52x49mm (300 x 300 DPI)



No. At Risk						
NoP-group	111 (0)	111 (0)	111 (4)	107 (5)	102 (0)	51 (0)
P-group	112 (1)	111 (0)	111 (2)	109 (2)	107 (4)	52 (0)

Death
51x48mm (300 x 300 DPI)