Running head: AAV remission induction therapy

Title: Efficacy and Safety of Low- vs High-Dose Glucocorticoid Regimens for Induction of Remission of ANCA-Associated Vasculitis: A Systematic Review and Meta-Analysis

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Abstract

Objective Glucocorticoids (GC) remain a cornerstone of the initial management of anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis but have several dose-dependent side effects, in particular infections. The optimal dosing and tapering of oral GC for remission induction are unknown. A systematic review and meta-analysis to determine the efficacy and safety of low versus high-dose GC regimens has been undertaken.

Methods A systematic search of Medline, Embase and PubMed databases was conducted. Clinical studies using a GC-based induction protocol were selected. A daily dose of 0.5mg/kg or less than 30mg/d oral prednisolone equivalent by the start of week four of the induction tapering schedule marked the threshold between high- and low-dose GC. The risk ratio (RR) was calculated by the random effects model for outcomes of remission and infection. Relapse events were summarised using risk differences (RD).

Results 1145 participants were included in 3 RCTs and 2 observational studies, of whom 543 were assigned to the low-dose GC group and 602 treated with high-dose GC. A low-dose GC regimen is non-inferior to high-dose with respect to outcomes of remission (RR 0.98 [95% CI, 0.95-1.02; p = 0.37], $I^2 = 0\%$) and relapse (RD 0.03 [95% CI, -0.01-0.06; p = 0.15], $I^2 = 12\%$], while significantly reducing the incidence of infection (RR 0.60 [95% CI, 0.39-0.91, p = 0.02], $I^2 = 65\%$).

Conclusion Studies with low-dose GC regimens in AAV are associated with fewer infections while obtaining equivalent efficacy.

Introduction

ANCA-associated vasculitis (AAV) is a group of autoimmune diseases characterised by inflammation of small-to-medium blood vessels resulting in multi-system organ involvement (1). Early diagnosis is imperative to prevent serious end-organ damage and death. The prognosis of untreated AAV is poor, with a 1-year mortality of 80%, usually due to respiratory or renal failure (2-5). The introduction of remission induction therapy with cyclophosphamide (CYC) and high-dose GC in the 1970s markedly reduced mortality and helped to control the disease in up to 90% of patients (6). Randomised clinical trials (RCTs) showed equal efficacy in disease control between CYC and rituximab (RTX) but did not confirm the hope that the substitution of CYC with RTX would reduce the rate of serious infections (7, 8).

In the setting of severe AAV, i.e., life or organ threatening disease, physicians frequently administer pulse intravenous methylprednisolone (MP) prior to starting oral steroids to prevent progression to end-stage renal disease and the requirement for dialysis. The rationale for methylprednisolone is related to its rapid and strong anti-inflammatory effect, with high-doses contributing to a reduction in ANCA-producing plasma cells. Treatment guidelines recommend an IV MP pulse of 0.25-1g per day for a maximum of three days (9, 10). High-dose GC remain a cornerstone of the initial management of AAV; however, this approach carries a significant risk of infection, which is the leading cause of death within 12 months of diagnosis (11). On the other hand, suboptimal initial steroid therapy may contribute to inadequate disease control, exposing patients to the toxicity of high cumulative steroid doses and morbidity associated with active vasculitis.

Studies comparing low- versus high-dose GC regimens for remission induction have been limited. There is significant variation of clinical practice in the dosing of initial intravenous MP and oral GC therapy. To date, no RCTs have examined the clinical benefits and risks of pulse MP against placebo.

The aim of the present meta-analysis was to assess the efficacy and safety of low- versus high-dose GC regimens on three outcomes: clinical remission, relapse and infections.

Methods

Database and search strategy

Literature searches for studies published from January 2000 to December 2021 were conducted using three electronic databases - Medline, Embase and PubMed. The search strategy was based on the following algorithm: "(anti-neutrophil cytoplasmic antibody OR granulomatosis with polyangiitis (GPA) OR Wegener's granulomatosis OR microscopic polyangiitis (MPA) OR ANCA-associated vasculitis) AND (glucocorticoid OR corticosteroid OR prednisone OR prednisolone OR methylprednisolone) AND (remission induction)." All search terms were used as keywords including subject headings. The initial search strategy generated 916 records, from which duplicates were removed. Limits were then applied to refine the search to human adult studies with AAV. Case series and reports were excluded due to the lack of sufficient data regarding efficacy outcomes and adverse events. Reviews were excluded but provided a source of additional articles. Reference lists from primary studies were screened to capture all potentially relevant studies.

Eligibility criteria

Studies including only patients with eosinophilic granulomatosis with polyangiitis (EGPA)/Churg-Strauss syndrome were excluded. Clinical trials and observational studies of only relapsing or refractory disease as well as maintenance therapies in GPA and/or MPA were excluded.

Selection was restricted to treatment-focused studies in which the terms glucocorticoid, corticosteroid, prednisone, prednisolone, methylprednisolone, rituximab, cyclophosphamide, avacopan, methotrexate, mycophenolate mofetil or plasma exchange (PLEX) appeared in the title. This search strategy identified articles reporting treatment-related outcomes pertaining to the use of glucocorticoids.

Thirty studies were chosen for full-text review. Studies were eligible for inclusion if they met the following criteria: [1] patients diagnosed with AAV (GPA, MPA, EGPA) and/or renal-limited vasculitis, [2] induction regimen that included GC with mention of initial doses [3] GC tapering protocol defined to at least four weeks or throughout the entirety of induction phase for RCTs [4] outcomes of remission, serious adverse events including relapses and infectious complications were reported.

A daily dose of 0.5mg/kg or less than 30mg/d oral prednisolone equivalent by the start of week four was defined as the threshold between high- and low-dose GC for the meta-analysis. This cut-off was chosen to accommodate most of the studies.

Data extraction and quality assessment

Data were exported from full texts into a structured Excel sheet and classified by study and patient characteristics. The following data were extracted: type of study, sample size, study design and aims, follow-up duration and eligibility criteria. Patients' age at enrolment, diagnosis, serological evidence of disease indicated by anti-PR3 or -MPO positivity and baseline disease activity scores were also recorded. Full details of remission induction treatment were obtained including use of intravenous MP. The methodological quality of each randomised controlled trial was assessed according to the 5-point Jadad scale (12). Quality and risk of bias of cohort studies were assessed using the Newcastle-Ottawa scale (NOS) (13).

Outcomes

The primary outcome of interest was the proportion of patients with clinical remission. The time frame selected for data collection on remission rates differed within the range of 3-12 months. Remission was defined as in the original articles as having a Birmingham Vasculitis Activity Score (BVAS) of zero, indicating the absence of symptoms and signs of disease activity (14). Secondary outcomes were proportion of patients with vasculitis relapse and infection. Relapse was defined as recurrent or new-onset clinical symptoms/signs after initial remission (15).

Statistical analysis

The meta-analysis was performed using Review Manager 5.4 software (The Nordic Cochrane Center, The Cochrane Collaboration, 2014, Copenhagen, Denmark). The Mantel-Haenszel random effects-model was used to estimate the pooled risk ratio with 95% confidence intervals (CIs) for dichotomous outcomes of remission and infection. Relapse events were summarised using risk differences. P values less than 0.05 were considered statistically significant. The presence of heterogeneity across all studies was evaluated using inconsistency index I^2. Subgroup and sensitivity analysis were performed for the secondary outcome of infection, the results of which are provided in the supplementary (Table S3, Fig. S1-2).

Results

Study selection

Of the thirty studies selected for full-text review, two observational studies (16, 17) and three RCTs (18-20) comparing oral GC regimens were included in the meta-analysis. Progress through stages of the systematic review is shown in figure 1.

Study characteristics

A total of 1145 patients were included in 3 RCTs and 2 observational studies, of whom 543 were assigned to the low-dose GC group and 602 treated with high-dose GC. Study characteristics are summarised in table 1.

In the PEXIVAS trial, the low-dose cohort followed a rapid tapering protocol with an approximate 60% decrease in daily dose from the start of induction treatment to the fourth week, as compared with a 20% decrease in the high-dose cohort. The LoVAS trial enrolled patients with mild-to-moderate AAV, using an initial dose of 0.5mg/kg/d prednisolone in the low-dose arm.

The observational study by Matsumoto et al compared two different tapering strategies for GC induction therapy, a monthly-reduction regimen and weekly-reduction regimen. The weekly-reduction regimen closely mirrored the lower dose PEXIVAS regimen. Similarly in the case of the CORTAGE trial, the experimental arm tested rapid GC dose tapering and limited CYC exposure (18). For a patient weighing 60kg, the cumulative dose difference of prednisone between the experimental and conventional arm (extended tapering) was 3152.5mg. This is comparable to high versus low dose steroids. The study by Sada et al is a safety outcome analysis of two prospective cohort studies of remission induction therapy in Japanese patients (21, 22). AAV patients with details of GC dosing in their medical records were included in the safety analysis. Out of 477 patients, 179 satisfied inclusion criteria. The patients were classified according to their initial prednisolone dosage: high-dose, 0.8 mg/kg/d; medium-dose, 0.6 and < 0.8 mg/kg/d; and low-dose, < 0.6 mg/kg/d.

The definition of disease remission varied between studies. In the LoVAS trial, remission was defined as a BVAS of 0 while taking 10mg/d of oral prednisolone. A score of 1 was allowed if there were no new/worse features. PEXIVAS used a modified version of BVAS called BVAS/WG (23) and used sustained remission defined as a BVAS/WG of 0 by week 26 without relapse by 12 months. Two other studies defined remission as the absence of new or worse signs of disease for > 1 month (17, 18). The study by Sada et al defined remission according to EULAR recommendations: BVAS of 0 on two consecutive occasions at least one month apart.

Patient characteristics

Patient characteristics are summarised in table 2. Two studies included patients with EGPA (17, 18) and one study included ten patients with polyarteritis nodosa (18). 17% (n=31) of patients in the cohort study by Sada et al had an unclassifiable diagnosis. Renal involvement was not reported in two studies (16, 17).

Study quality and publication bias

Details of individual study quality and risk of bias assessment can be found in supplementary table S1-2. All three RCTs scored the maximum number of points allocated for randomisation but received a score of 3 out of 5 due to inadequate description of blinding. A minimisation algorithm was commonly adopted to ensure balance of prognostic factors between treatment groups. These may include but are not limited to: age at entry, eGFR and ANCA-specificity (PR3 or MPO). The observational studies by Sada and Matsumoto et al received a score of 7. Visual inspection of the funnel plots showed symmetry with respect to the secondary outcomes of relapse (supplementary Fig. S4) but not for remission or infection (supplementary Fig. S3,5).

Meta-analysis

All five studies reported on clinical remission, relapse and infections. There was no statistically significant difference in the proportion of patients who achieved remission throughout the observation period: 474 (87%) and 530 (88%) in the low-dose GC group and high-dose GC group, respectively (RR 0.98 [95% CI, 0.95-1.02; p = 0.37], $I^2 = 0\%$) (Fig. 2). The overall pooled risk difference (0.03 [95% CI, -0.01-0.06] between low-dose GC and high-dose GC for relapse events showed no statistically significant difference (p = 0.15). Heterogeneity between trials was minimal (P = 0.34; $I^2 = 12\%$).

Infections of any severity occurred in 155 (28%) patients in the low-dose GC group and 226 (38%) patients in the high-dose GC group. The risk ratio of infection is 0.60 (95% CI, 0.39-0.91, p = 0.02). The variability between studies was moderate as shown by an I^2 value of 65%. The time frames evaluated for ascertainment of infection varied between 3, 6, 12 and 36 months. Sensitivity analysis was performed according to the duration of observation period by limiting the analysis to one year of follow-up (supplementary Fig. S1). The CORTAGE trial was omitted as the outcome measure of the study was the occurrence of infections during three years of follow-up. The results of the remaining studies combined remained consistent with the primary analysis, revealing a risk ratio of infection of 0.59 (0.36, 0.98), p = 0.04 (< 0.05). Serious infections are defined in figure 2. All patients enrolled in the LoVAS trial, CORTAGE trial and study by Matsumoto et al received prophylactic treatments against *Pneumocystis jirovecii* pneumonia (PJP). Prophylaxis was only offered to 153 of 178 patients in the study by Sada et al.

Discussion

The present meta-analysis provides evidence for non-inferiority of low-dose GC to high-dose regimens with respect to clinical outcomes of remission and relapse, with a lower incidence of infection in patients assigned to the low-dose regimens within the first year of treatment.

To our knowledge, this is the first review that has addressed the strategy of reduced GC dosing for remission induction therapy of AAV. A systematic review of maintenance immunosuppressant therapy by Walsh et al with a total of 983 patients detected a 3-fold higher rate of relapse in patients withdrawn from GC than studies in which patients continued GC during the observation periods (24). The ability to assess the incidence of adverse events from maintenance regimens of low-dose GC in their review was complicated by the presence of multiple confounding variables.

In the area of autoimmune and inflammatory diseases, there has been a drive to reduce GC exposure. Lower-dose GC regimens have been trialled in both AAV and lupus nephritis (25-27). Although there is no consensus on the speed of GC taper, guidelines recommend maintaining a high-dose GC for a maximum of four weeks before beginning a gradual taper (9). The landmark PEXIVAS study provided reassurance that GC can be rapidly and cumulatively (by approximately 60%) tapered in severe disease without compromising efficacy while reducing the risk of serious infections. However, physicians require additional evidence that reduced-dose regimens do not impact renal function. In PEXIVAS, renal outcomes other than end-stage kidney disease (ESKD) were not assessed (supplementary Fig. S6).

While our review included patients of all types of AAV, the population was dominated by MPO-positive patients, particularly in the studies by Sada and Furuta et al. This is because the regions in which the studies were conducted have a higher incidence of MPO-AAV. Epidemiological data show MPO-AAV is more common in Asian countries (28) while GPA (PR3-AAV) accounts for half the AAV cases in Caucasian populations (29). The heterogeneity of ANCA-positivity rates among these patients may limit the generalisability of the results. Although MPA and GPA share many features, clinical courses vary between the two. The risk of mortality is higher in MPO-AAV while relapses are more common in GPA/PR3-AAV (30). The higher mortality in MPA patients is in part due to the more frequent occurrence of advanced-kidney disease at presentation and reduced renal recovery after treatment (2). This clinical observation raises the question of whether patients with MPA require higher doses of GC at induction compared to GPA.

Other differences between the study populations included in this review should be highlighted and patient selection criteria for individual studies are summarised in supplementary table S4. The LoVAS trial included newly diagnosed patients exclusively while PEXIVAS included patients with relapsing disease. LoVAS also excluded patients with severe glomerulonephritis (eGFR <15mL/min/1.73m^2) or alveolar haemorrhage whereas PEXIVAS only enrolled patients with severe AAV. Given PEXIVAS accounted for a large proportion of the study population in this review, its exclusion from the analysis did not change the significance of the overall effect size (supplementary Fig. S2).

It should be noted that the use of RTX or CYC may affect the ability to rapidly taper GC. Compared with CYC, RTX has a narrower immunosuppressive action by targeting the surface antigen CD20 on B cells. Although trials have shown RTX to have equivalent efficacy to CYC for remission induction, it remains unclear whether RTX effectively and safely induces remission without organ damage in combination with low-dose GC in newly diagnosed AAV patients (7, 8). In a prespecified subgroup analysis of the PEXIVAS trial, there was a trend to a higher risk of primary outcome (ESKD or death) occurring with low dose GC in the RTX group compared to IV or oral CYC (HR 1.86 95% CI 0.83-4.14). This conflicts with the main finding of the LoVAS trial in which a low-dose GC regimen combined with RTX was non-inferior to a high-dose GC regimen with RTX, certainly in MPO-AAV patients. In the trials included, all patients received remission induction therapy with either RTX or CYC. The efficacy and safety of low-dose GC regimens in patients induced with other agents such as mycophenolate mofetil or methotrexate remains unclear. We note that for example the rate of relapse was high in anti-PR3 positive patients randomised to remission induction with mycophenolate mofetil on weaning prednisolone in the MYCYC trial (31).

The results of the clinical outcomes studied are in part due to the glucocorticoid-sparing effect of immunosuppressive therapies including rituximab. More recently, steroid sparing regimens including the novel complement C5a receptor antagonist avacopan have been studied. Following validation of the complement C5a receptor as a therapeutic target in AAV, results from the phase III ADVOCATE trial suggested C5a inhibition by avacopan is equally, if not more effective than glucocorticoids in inducing and sustaining remission of AAV (32). The phase II CLEAR trial demonstrated the steroid sparing effects of avacopan when given in combination with cyclophosphamide or rituximab, resulting in a reduction in glucocorticoid adverse effects (26).

Infections pose a significant risk factor for early mortality. Several reports have shown that infection accounts for more deaths than active disease, highlighting the importance of infection prevention (11, 33-35).

The occurrence of infection is approximately ten times greater during remission induction than maintenance therapy (33). Many previously published clinical investigations have documented a significant association between infections and high-doses or prolonged courses of GC (21, 36-39). An observational study found high-dose GC use (prednisolone > 0.8mg/kg/d) was a predictive risk factor for early severe infections among elderly AVV patients (40). Although the prevalence of CYC or RTX administration was significantly higher in patients with early severe infections (p = 0.036), the impact of high-dose GC on infection risk was greater (p = 0.003) (40). In a French cohort of AAV patients, 89% of severe infections occurred during GC treatment (41). Nonetheless, fatal and opportunistic infections have been observed under CYC therapy with the intensity of cytotoxic treatment correlating with leukopenia (41, 42). In this review, evidence was too scarce to stratify the risk of infections according to immunosuppressive treatment in combination with GC.

Intravenous MP is frequently initiated in patients with life- or organ-threatening disease with the hope of improving early mortality and renal recovery. There have been three observational studies on the use of pulse methylprednisolone in ANCA-vasculitis. Ma et al reported (43) that intravenous methylprednisolone improves renal recovery in those who present with advanced renal failure with a trend towards decreased mortality. In contrast, no difference in patient survival, kidney recovery and rates of adverse events was observed between MP- treated and untreated groups in another cohort of patients comparable for epidemiology and disease severity (44). Ma et al reported 22 cases of fatal infections, accounting for 70% of deaths in the study. Chanouzas et al found the greatest difference in the onset of infections between MP-treated patients and non-MP treated patients within the first three months following commencement of therapy (45). Whether intravenous MP improves renal recovery and patient survival remains uncertain. An RCT is warranted to examine the efficacy and safety of IV MP in AAV patients.

Prior to PEXIVAS, the largest RCT evaluating PLEX in AAV patients with rapidly progressive glomerulonephritis was MEPEX (46). Short-term results of MEPEX suggested that PLEX was associated with a higher rate of renal recovery compared with pulse MP. In comparison, PEXIVAS concluded that PLEX does not reduce the incidence of death or ESKD. A recent meta-analysis including nine trials with 1060 patients has concluded that PLEX has no important effect on mortality, reduces the 12-month risk of ESRD, but increases the risk of serious infections (47).

Strengths and Limitations

The review has several strengths. The comprehensive search strategy using electronic databases brought together relevant trials and observational studies of the most contemporary cohorts. The follow-up of the individual studies was adequate for ascertainment of outcomes. A sensitivity analysis for incidence of infection was performed yielding results consistent with the primary analysis, strengthening the validity of the results. Although the number of studies was limited, data were obtained from a sample size of well over 1000 patients. With the most up-to-date evidence, this novel study addresses a question of high clinical interest to physicians treating AAV.

The review has some limitations to consider. Firstly, GC tapering schedules of the studies varied. The defined threshold between high and low dose was not applicable to the CORTAGE trial. However, there was a large difference in the total cumulative dose between the reduced and standard-dose GC arm by the end of the tapering schedule. Secondly, the timing of outcome measurement was not consistent between studies, particularly with respect to infection. Thirdly, the true effect of reduced-dose glucocorticoids on outcomes of remission induction and relapse may differ between studies due to the variability in non-GC treatment interventions (table 1). Lastly, apart from infection, only GC-induced diabetes was reported across all included studies (supplementary Fig. S7). Other GC-related adverse effects were incompletely reported.

In conclusion, a low-dose GC regimen is non-inferior to high-dose GC for induction of remission in newly diagnosed AAV while reducing the risk of infections within the first 12 months of therapy. Recognition of the early and potentially fatal side effects of high-dose GC has spurred the development of clinical trials evaluating lower-dose regimens. Therapeutic strategies that reduce the reliance of GC, whether via rapid dose tapering, combination therapies or targeted drugs offer the long-awaited possibility of steroid-sparing disease remission.

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Figure legends

Flow diagram of systematic review inclusion and exclusion process

AAV = antineutrophil cytoplasmic antibody-associated vasculitis; GC = glucocorticoids

Forest plots of primary and secondary outcomes between low-dose and high-dose glucocorticoid groups

Clinical remission rates are reported within one year after allocation to treatment groups. Serious infections were defined as those requiring treatment with intravenous antibiotics in hospital and are related to mortality or disability.

Abbreviations: GC, glucocorticoid; RR, risk ratio or risk difference; CI, confidence interval

Clinical trial registration number

PEXIVAS - NCT00987389

CORTAGE - NCT00307671

LoVAS - NCT02198248

Funding

Table 1. Characteristics of studies included in the meta-analysis

Author, year [ref.]	Design	Follow up, months	Induction treatment	IV MP Yes or No	Plasma exchange Yes or No	Initial dose mg/kg	Daily dose at 4 weeks mg/kg	Theoretical cumulative GC dose/mg*
Matsumoto et al, 2011 (16)	cohort	12	CYC	15/24 patients	N	0.97 = LD 0.67 = HD	0.41 = LD (weekly-reduction) 0.57 = HD (monthly-reduction)	3220 = LD NR = HD
CORTAGE Pagnoux et al, 2015 (18)	open-label RCT	36	IV CYC low dose vs IV CYC high dose	77/104 patients	N	1.0 = LD 1.0 = HD	0.92 = LD 1.0 = HD	5152.5 =LD 8305 = HD
Sada et al, 2020 (17)	safety outcome analysis of 2 cohort studies	24	CYC in 54 patients	NR	NR	0.47 = LD 0.69 = MD 0.98 = HD	NR	NR

						(mean)		
PEXIVAS Walsh et al, 2020 [19]	open-label RCT	12	CYC or RTX PLEX	Y	Y PLEX 352/704 No PLEX 352/704	1.0 = LD 1.0 = HD	0.41 = LD 0.83 = HD	2172 = LD 3850 = HD
LoVAS Furuta et al, 2021 [20]	open-label RCT	6	RTX	N	N	0.5 = LD 1.0 = HD	0.25 = LD 0.8 = HD	966 = LD 3937.5 = HD

CYC = cyclophosphamide; RTX = rituximab; PLEX = plasma exchange; GC = glucocorticoid; RD = reduced dose; MD = medium dose;
SD = standard dose; NR = not reported *Theoretical cumulative dose of steroids for a patient weighing 60kg

Table 2. Characteristics of patients in studies included in the meta-analysis

Author, year	No. of patients included in analysis	Mean age (years)	Sex (M/F)	GPA	MPA	EGPA	Renal involvement (%)	Pulmonary involvement (%)	Patients in remission no. (%)	Patients with relapse no. (%)
Matsumoto et al, 2011	24	71	5:19	NR	NR	0	NR	NR	24 (100)	2 (8)
Pagnoux et al, 2015	104/108	75	59:45	44	36	14	68	64	86 (83)	32 (37)
Sada et al, 2020	179/477	79	68:111	28	113	7	NR	46	151 (84)	17 (11)
Walsh et al, 2020	704	63	307:397	286	418	0	98	42	649 (92)	55 (8)
Furuta et al, 2021	134/140	73, 74 /median	54:80	29	104	0	60	58	94 (70)	3 (2)

GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; EGPA = eosinophilic granulomatosis with polyangiitis

FIGURE. 1

Electronic database searches: Medline (n=118), Embase (n=339), PubMed (n=459)
Potentially relevant citations retrieved for screening (n=916 records)

→ Records after duplicates removed (n=739)

Titles/abstracts screened (n=739)

→ Excluded (n=323)
age <18 years, animal studies, review articles, case series, case reports

Titles screened (n=416)

→ Excluded (n=89)
not related to GPA, MPA or EGPA/Churg-Strauss syndrome, maintenance of remission studies, refractory disease or relapsing presentation

Titles/abstracts screened (n=327)

→ Exclude publications not treatment-focused (n=198)

Titles/abstracts screened (n=129)

→ Studies reporting outcomes based on glucocorticoid exposure

Full-text articles assessed for eligibility (n=30)

→ Publications excluded (n=25)
    GC doses not defined/protocol driven (n=5)
    No control and experimental arm/single GC regimen used (n=12)
    Lack of suitable comparator group (n=2)
    Lack of reduced dose group (n=3)
    Unrelated outcome (n=2)
    Duration of GC investigated as independent variable, not dose (n=1)

Publications included in meta-analysis (n=5)

FIGURE. 2

Outcome 1. Clinical remission

Study or Subgroup	Reduced-dose GC Events	Total	Standard-dose GC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Matsumoto 2011	9	9	15	15	5.2%	1.00 [0.85, 1.18]	2011
Pagnoux 2015	45	53	41	51	4.7%	1.06 [0.88, 1.26]	2015
Walsh 2020	321	353	328	351	78.9%	0.97 [0.93, 1.02]	2020
Sada 2020	50	59	101	120	8.2%	1.01 [0.88, 1.15]	2020
Furuta 2021	49	69	45	65	3.0%	1.03 [0.82, 1.28]	2021
Total (95% CI)		543		602	100.0%	0.98 [0.95, 1.02]	
Total events	474		530				

Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.31, df = 4 (P = 0.86); I^2 = 0%
Test for overall effect: Z = 0.90 (P = 0.37)

Risk Ratio M-H, Random, 95% CI — 0.5 0.7 1 1.5 2 — favours standard GC favours reduced GC

Outcome 2. Vasculitis relapse

Study or Subgroup	Reduced-dose GC Events	Total	Standard-dose GC Events	Total	Weight	Risk Difference M-H, Random, 95% CI	Year
Matsumoto 2011	0	9	2	15	2.5%	-0.13 [-0.36, 0.09]	2011
Pagnoux 2015	20	45	12	41	3.1%	0.15 [-0.05, 0.35]	2015
Sada 2020	5	50	12	101	10.8%	-0.02 [-0.12, 0.09]	2020
Walsh 2020	32	353	23	351	51.5%	0.03 [-0.01, 0.06]	2020
Furuta 2021	3	69	0	65	32.2%	0.04 [-0.01, 0.10]	2021
Total (95% CI)		526		573	100.0%	0.03 [-0.01, 0.06]	
Total events	60		49				

Heterogeneity: Tau^2 = 0.00; Chi^2 = 4.56, df = 4 (P = 0.34); I^2 = 12%
Test for overall effect: Z = 1.44 (P = 0.15)

Risk Difference M-H, Random, 95% CI — -1 -0.5 0 0.5 1 — favours reduced dose GC favours standard dose GC

Outcome 3. Severe or mild infection

Study or Subgroup	Reduced-dose GC Events	Total	Standard-dose GC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Matsumoto 2011	2	9	10	15	8.2%	0.33 [0.09, 1.19]	2011
Pagnoux 2015	10	53	17	51	18.0%	0.57 [0.29, 1.12]	2015
Walsh 2020	119	353	131	351	32.0%	0.90 [0.74, 1.10]	2020
Sada 2020	13	59	39	120	21.7%	0.68 [0.39, 1.17]	2020
Furuta 2021	11	69	29	65	20.0%	0.36 [0.19, 0.65]	2021
Total (95% CI)		543		602	100.0%	0.60 [0.39, 0.91]	
Total events	155		226				

Heterogeneity: Tau^2 = 0.13; Chi^2 = 11.43, df = 4 (P = 0.02); I^2 = 65%
Test for overall effect: Z = 2.42 (P = 0.02)

Risk Ratio M-H, Random, 95% CI — 0.05 0.2 1 5 20 — favours reduced dose GC favours standard dose GC

Supplementary File

Supplement to: **Efficacy and Safety of Low- vs High-dose Glucocorticoid Regimens for Induction of Remission of ANCA-associated Vasculitis: A Systematic Review and Meta-Analysis**

Table of Contents

Supplementary Table S1-2. Risk of bias assessment

Table1. *Quality assessment of RCTs using the Jadad scale*

Study reference NCT number	Randomisation is mentioned	Appropriateness of randomisation	Blinding is mentioned	Appropriateness of blinding	An account of all patients of description of withdrawal or drop out	Total /5
LoVAS Furuta 2021 NCT02198248	1	1	0	0	1	3
PEXIVAS Walsh 2020 NCT00987389	1	1	0	0	1	3
CORTAGE Pagnoux 2015 NCT00307671	1	1	0	0	1	3

Table 2. *Detailed Newcastle-Ottawa quality assessment scale of each observational study*

	Selection				Comparability		Outcome			
Study	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Adjusts for confounders	Adjusts for other risk factors	Assessment of outcome	Follow-up length	Loss to follow-up rate	Total quality score
Sada 2020	0	0	1	1	1	1	1	1	1	7
Matsumoto 2011	0	1	1	1	1	0	1	1	1	7

Supplementary Table S3. Results of subgroup analysis of the effect of low-dose oral glucocorticoid regimens on the secondary outcome of infection

A subgroup analysis stratified by inclusion of IV methylprednisolone in remission induction therapy is presented in table 3. This was undertaken to examine the differences in infection risk between patients who received IV methylprednisolone pulses and those who did not. Two RCTs were combined in the analysis: PEXIVAS and LoVAS. The other four studies were excluded as only a proportion of patients received methylprednisolone in each cohort (see table 1). All patients in the PEXIVAS trial were treated with a daily IV MP for 1-3 days for a cumulative dose of 1-3g.

Table 3. Subgroup analysis of two trials involving 704 MP treated participants and 134 non-MP treated participants
GC = glucocorticoid, MP = methylprednisolone

Study	Low-dose GC		High-dose GC		Risk ratio M-H, Random 95% CI
	Events	Total	Events	Total	
IV methylprednisolone given Walsh 2020	119	353	131	351	0.90 [0.74,1.10]
IV methylprednisolone not given Furuta 2021	11	69	29	65	0.36 [0.19,0.65]
Total	130	422	160	416	0.59 [0.24,1.48] favours low-dose GC

The point estimate for the LoVAS study's effect size lies at 0.36 [95% CI 0.19, 0.65], indicating a decreased risk of infection in patients not treated with high-dose IV methylprednisolone. As for PEXIVAS, the RR is 0.90 [95% CI 0.74-1.10], demonstrating a higher risk of infection in patients who received IV MP treatment. The LoVAS trial included patients treated with RTX while three studies used CYC alone. Of these studies, the CORTAGE trial tested two levels of CYC exposure in separate arms which would have confounded the results. In addition, two studies used a combination of immunosuppressive treatment including one testing RTX or CYC with avacopan - a steroid-sparing targeted drug.
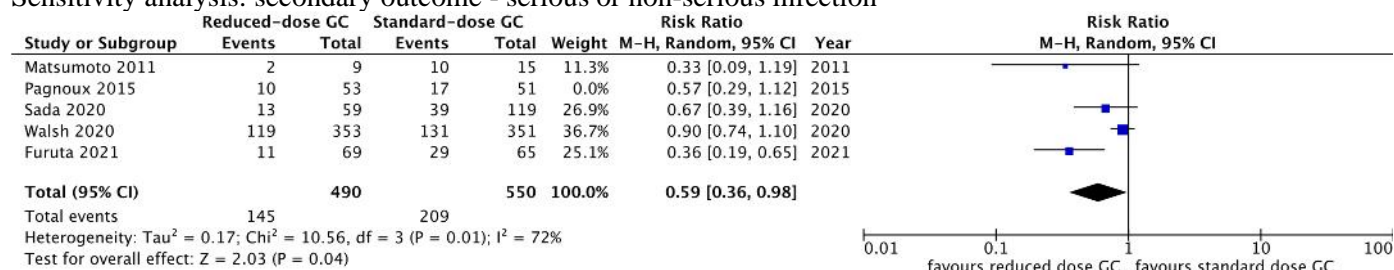
Supplementary Table S4. Patient eligibility criteria of studies

Please refer to individual studies for full list of eligibility criteria

Study	Inclusion criteria	Exclusion criteria
LoVAS Furuta 2021	1. New diagnosis of AAV (MPA, GPA or renal-limited vasculitis) 2. Positive test for either MPO-ANCA or PR3-ANCA	1. Previous treatment for AAV 2. Glomerulonephritis with eGFR <15mL/min or pulmonary alveolar haemorrhage

PEXIVAS Walsh 2020	1. New or previous relapsing clinical diagnosis of GPA or MPA
	2. Severe vasculitis defined by at least one of the following:
	  a. Renal involvement – evidence of glomerulonephritis and eGFR < 50mL/min/1.73m^2
	  b. Pulmonary haemorrhage due to active vasculitis
		1. Diagnosis of vasculitis other than GPA or MPA
		2. Receipt of dialysis for greater than 21 days prior to randomisation or previous renal transplant
		3. Plasma exchange in 3 months prior to randomisation
		4. Treatment with > 1 IV CYC and/or > 14 days oral CYC and/or > 14 days of prednisone/prednisolone (>30mg/d) and/or treatment with > 1 dose of RTX within the last 28 days

CORTAGE Pagnoux 2015	1. Newly diagnosed PAN, EGPA, GPA or MPA 2. In or after the year of their 65th birthday	1. No more than 1 month corticosteroid treatment prior to enrolment 2. Not started CYC and/or received any other immunosuppressant before inclusion
Sada 2020	1. Patients with elderly-onset > 75 years AAV were enrolled	1. Patients for whom data about the GC dose were lacking were excluded
Matsumoto 2011	1. Newly diagnosed with MPA or GPA 2. Treated with GCs in combination with intravenous CYC	Not specified

Supplementary Figure S1. Results of sensitivity analysis of the secondary outcome of serious or non-serious infection
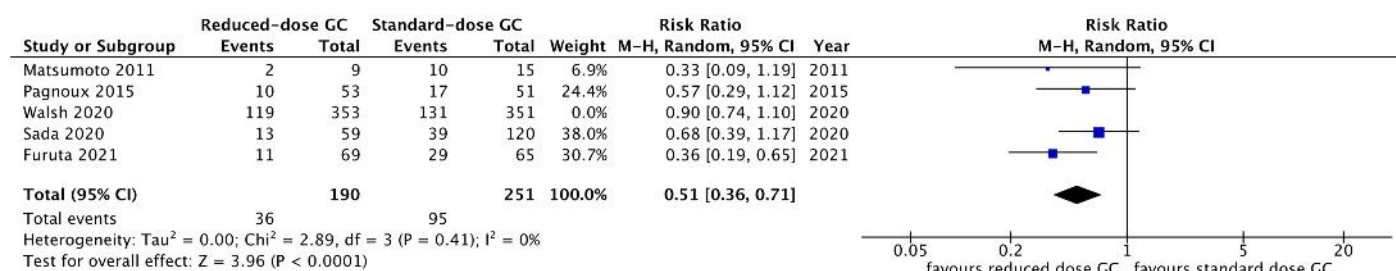
Sensitivity analysis: secondary outcome - serious or non-serious infection

	Reduced-dose GC		Standard-dose GC			Risk Ratio			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year		M-H, Random, 95% CI
Matsumoto 2011	2	9	10	15	11.3%	0.33 [0.09, 1.19]	2011		
Pagnoux 2015	10	53	17	51	0.0%	0.57 [0.29, 1.12]	2015		
Sada 2020	13	59	39	119	26.9%	0.67 [0.39, 1.16]	2020		
Walsh 2020	119	353	131	351	36.7%	0.90 [0.74, 1.10]	2020		
Furuta 2021	11	69	29	65	25.1%	0.36 [0.19, 0.65]	2021		
Total (95% CI)		490		550	100.0%	0.59 [0.36, 0.98]			
Total events	145		209						

Heterogeneity: Tau² = 0.17; Chi² = 10.56, df = 3 (P = 0.01); I² = 72%
Test for overall effect: Z = 2.03 (P = 0.04)

favours reduced dose GC   favours standard dose GC

CORTAGE trial - Pagnoux 2015 excluded as follow-up period surpassed one year window

Supplementary Figure S2. Results of sensitivity analysis of the secondary outcome of serious or non-serious infection

Sensitivity analysis: secondary outcome - serious or non-serious infection

	Reduced-dose GC		Standard-dose GC			Risk Ratio			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year		M-H, Random, 95% CI
Matsumoto 2011	2	9	10	15	6.9%	0.33 [0.09, 1.19]	2011		
Pagnoux 2015	10	53	17	51	24.4%	0.57 [0.29, 1.12]	2015		
Walsh 2020	119	353	131	351	0.0%	0.90 [0.74, 1.10]	2020		
Sada 2020	13	59	39	120	38.0%	0.68 [0.39, 1.17]	2020		
Furuta 2021	11	69	29	65	30.7%	0.36 [0.19, 0.65]	2021		
Total (95% CI)		190		251	100.0%	0.51 [0.36, 0.71]			
Total events	36		95						

Heterogeneity: Tau² = 0.00; Chi² = 2.89, df = 3 (P = 0.41); I² = 0%
Test for overall effect: Z = 3.96 (P < 0.0001)

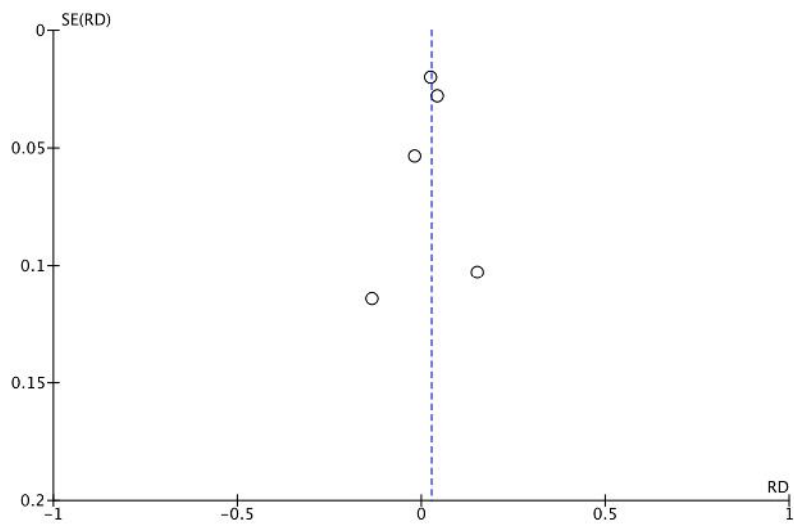favours reduced dose GC   favours standard dose GC
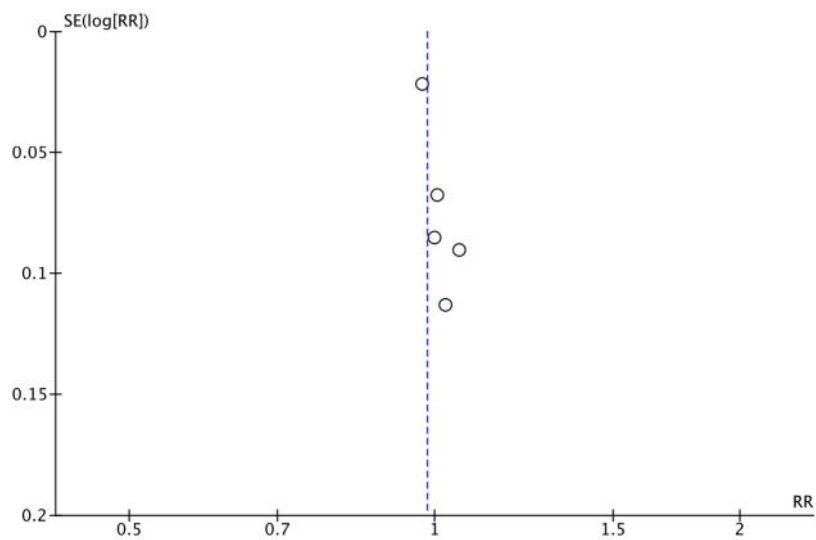
PEXIVAS trial excluded

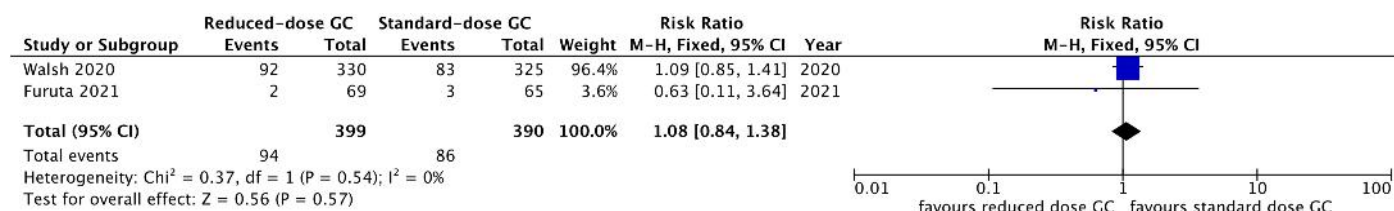**Supplementary Figure S3. Funnel plot of the meta-analysis for infection**
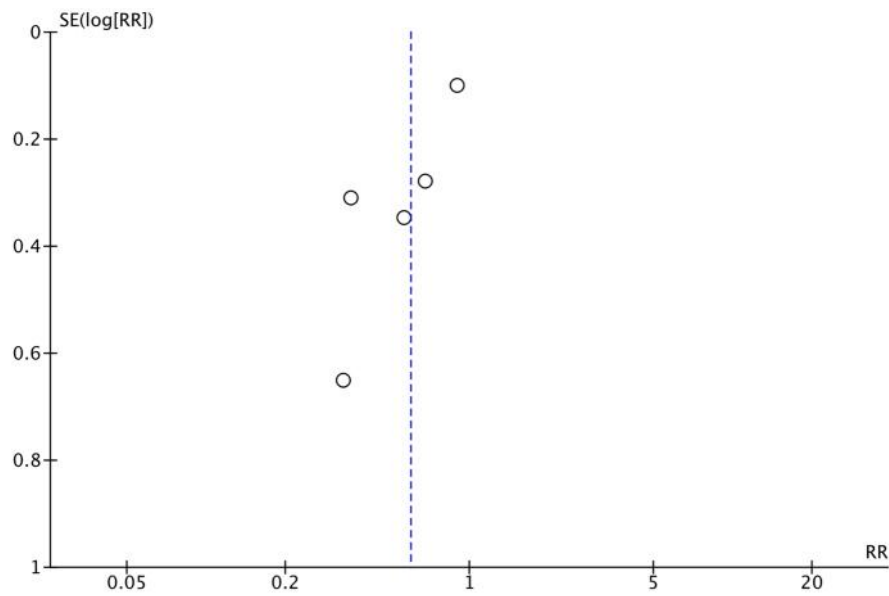
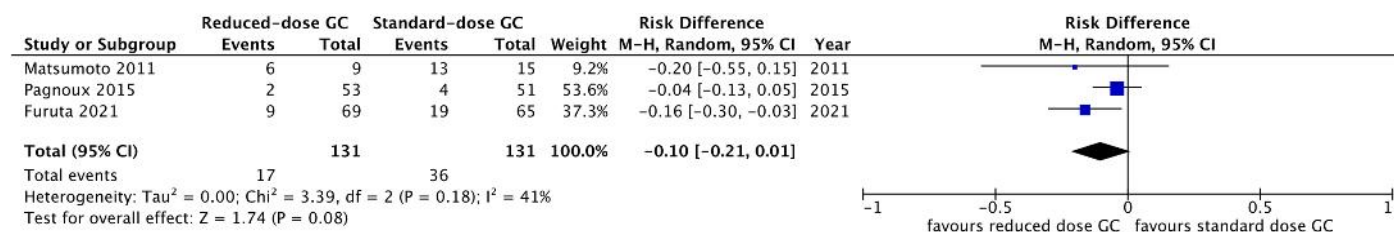**Supplementary Figure S4. Funnel plot of the meta-analysis for vasculitis relapse**

Supplementary Figure S5. Funnel plot of the meta-analysis for remission

Supplementary Figure S6. Forest plot for the composite outcome of death or ESKD in patients with low-dose glucocorticoids vs high-dose glucocorticoids

Study or Subgroup	Reduced-dose GC Events	Total	Standard-dose GC Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Walsh 2020	92	330	83	325	96.4%	1.09 [0.85, 1.41]	2020
Furuta 2021	2	69	3	65	3.6%	0.63 [0.11, 3.64]	2021
Total (95% CI)		399		390	100.0%	1.08 [0.84, 1.38]	
Total events	94		86				

Heterogeneity: Chi² = 0.37, df = 1 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.56 (P = 0.57)

Risk Ratio M-H, Fixed, 95% CI

favours reduced dose GC favours standard dose GC

Supplementary Figure S7. Forest plot for new-onset/worsening diabetes mellitus

Study or Subgroup	Reduced-dose GC Events	Total	Standard-dose GC Events	Total	Weight	Risk Difference M-H, Random, 95% CI	Year
Matsumoto 2011	6	9	13	15	9.2%	-0.20 [-0.55, 0.15]	2011
Pagnoux 2015	2	53	4	51	53.6%	-0.04 [-0.13, 0.05]	2015
Furuta 2021	9	69	19	65	37.3%	-0.16 [-0.30, -0.03]	2021
Total (95% CI)		131		131	100.0%	-0.10 [-0.21, 0.01]	
Total events	17		36				

Heterogeneity: Tau² = 0.00; Chi² = 3.39, df = 2 (P = 0.18); I² = 41%
Test for overall effect: Z = 1.74 (P = 0.08)

Risk Difference M-H, Random, 95% CI

favours reduced dose GC favours standard dose GC

PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Fig. 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4, Fig. 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6, Fig. 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6, table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8, supplementary table S1-2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8, Fig. 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8 Fig. 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplementary table S1-2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8, Supplementary Fig. 1-2, table S3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9-12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A