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The comparative efficacy and safety of alternative glucocorticoids regimens in patients with ANCA-associated vasculitis: A systematic review

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3 **The comparative efficacy and safety of alternative glucocorticoids regimens in**
4 **patients with ANCA-associated vasculitis: A systematic review**
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Abstract

Objective

To compare the efficacy and safety of alternative glucocorticoids (GC) regimens as induction therapy for patients with ANCA-associated vasculitis.

Design

Systematic review of RCTs.

Data sources

Medline, Embase, Clinicaltrials.gov and Cochrane Central Register of Controlled Trials up to 10 April 2020.

Study selection and Review methods

RCTs comparing two (or more) different dose regimens of GC in ANCA-associated vasculitis during induction of remission, regardless of other therapies. Pairs of reviewers independently screened records, extracted data and assessed risk of bias.

Two reviewers rated certainty of evidence using the GRADE approach.

Results

Of 3912 records identified, the full texts of only two records met the eligibility criteria, only one of which was completed and provided evidence. The trial compared reduced-dose and standard-dose regimen of GC, which the reduced-dose regimen was as 40% of the cumulative dose in the standard-dose regimen during the first 6 months. Compared with the standard-dose regimen, the reduced-dose regimen of GC may reduce death at the follow-up of longer than 1 year (relative risk: 0.86, 95% CI, 0.6 to 1.24, 21 fewer per 1000, low certainty), while not increase end-stage kidney disease (ESKD) longer than 1 year (relative risk: 1.02, 95% CI, 0.76 to 1.38, 4 more per 1000, moderate certainty). The reduced-dose regimen probably has an important reduction in serious infections at 1 year (relative risk: 0.82, 95% CI, 0.66 to 1.03, 59 fewer per 1000, moderate certainty). And the standard-dose regimen probably result in little or no increase on serious adverse events at follow-up of longer than 1 year (relative risk: 1.05, 95% CI, 0.94 to 1.18, 31 more per 1000, moderate certainty).

Conclusions

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3 The reduced-dose regimen of GC may reduce death at the follow-up of longer than 1
4 year and serious infections at 1 year while not increase ESKD longer than 1 year.
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7 **Systematic review registration**
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9 PROSPERO CRD42020179087.
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12 **Keywords:** glucocorticoids, Anti-Neutrophil Cytoplasmic Antibody-Associated
13 Vasculitis, systematic review
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For peer review only

Strengths and limitations of this study

This systematic review used the GRADE approach to assess the quality of evidence.

The included study is the largest global trial on the subject so far which has improved the generalizability of the results through the efforts of national and international vasculitis networks and extensive selection criteria.

Although the included study contained more events than any other trial in this disease, the total statistical information remains low which is particularly obvious for serious adverse events other than serious infection.

Despite the large scale of this study for a rare disease, the degree to which the results can be generalized to patients with non-severe AAV is uncertain, although it is likely safer to extrapolate the safety of the regimen from more severe illness to less severe illness rather than less severe to more severe.

Introduction

ANCA-associated vasculitis (AAV) comprises a subgroup of systemic vasculitis affecting small- to medium-sized vessels, a chronic inflammatory disease of the blood vessel wall¹, and includes granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis.² Patients with AAV usually test positive for antineutrophil cytoplasmic antibodies (ANCA). The cause of the disease remains unclear, and genetic and environmental factors play an important role in the onset of the disease.^{3,4} The annual incidence of AAV is about 20 per million inhabitants, and the prevalence is about 100 per million inhabitants.⁵ AAV has multiple clinical manifestations, characterized by leukocytes infiltrating the vessel walls, fibrinoid necrosis, and vascular damage with occlusion or aneurysm formation.⁶ The severity of AAV varies greatly, but after months to years of non-severe manifestations, patients with non-severe diseases often progress to severe diseases.⁷ The most common severe AAV manifestation is glomerulonephritis, which leads to renal failure and alveolar capillaritis causing pulmonary hemorrhage.⁸ Previous studies have showed that untreated AAV is typically fatal⁹, with 6-month and 1-year mortality rates of 60% and 80%, respectively.¹⁰

Since the 1950s, glucocorticoids (GCs), as immunosuppressants and anti-inflammatory drugs with a fast-acting and powerful anti-inflammatory effect, became the basis of therapy for AAV.^{11,12} The main mechanism of action is genomic and non-genomic effects mediated by cytosolic GC receptors or specific and non-specific interactions with membrane-bound GC receptors resulting in reduced production of pro-inflammatory proteins (transrepression).¹³ However, monotherapy has incomplete efficacy.¹⁴ Subsequently, standard therapy emerged using the combination of high-dose GC and cyclophosphamide to achieve remission in AAV^{15,16,17} This combination therapy proved to reduce mortality to 25% at 5 years and has high remission rates of 80% – 90%.¹⁸ In addition to cyclophosphamide, clinical remission can also be achieved with rituximab-based or methotrexate-based therapies.¹⁹ Although the combination of high-dose GC and cytotoxic drugs greatly enhances the therapeutic efficacy, high-dose GC may increase the toxicity associated with treatment. Infections and cardiovascular diseases due to the treatment are main causes of fatal side effects

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3 and also reduced patients' quality of life (QOL).^{20,21} Although these side effects may
4 be confused by disease activity and co-treatment with cytotoxic drugs, the
5 immunosuppressive effect will continue to be constant over time, the infection rate
6 will decrease at the same time as the reduced dose GC.⁸ Previous studies have shown
7 that lower GC doses during the induction period are associated with higher relapse
8 rates and long-term use of low-dose GC exposes patients to the potential toxicity of
9 high-cumulative GC.^{22,23} Thus, to achieve successful outcomes, a careful balance must
10 be achieved between the efficacy and safety of treatment with GC.
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20 The purpose of this systematic review is to evaluate the comparative efficacy and
21 safety of alternative glucocorticoid regimens (two (or more) different doses of GC) in
22 patients with ANCA-associated vasculitis. Our systematic review is a part of the BMJ
23 Rapid Recommendations project, which is based on the shared vision of the MAGIC
24 Evidence Ecosystem Foundation (www.magicproject.org) and The BMJ. When there
25 is evidence that may change the clinical practice, the cooperative organizations will
26 act quickly to provide a timely, trustworthy practice guideline. Under such
27 circumstance, the exciting evidence was the PEXIVAS trial²⁴. The systematic review
28 informed an associated BMJ Rapid Recommendations.
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39 **Methods**

40 **Registration and report**

41 A priori protocol of this systematic review is presented at PROSPERO
42 (CRD42020179087). We reported this systematic review and meta-analysis based on
43 the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)
44 statement (see Appendix 1).²⁵
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53 **Guideline panel and patient and public involvement**

54 According to the process of the BMJ Rapid Recommendations, the guideline panel on
55 this target provides critical process oversight and content guidance for the systematic
56 review. The guideline panel consisted of clinicians, methodologists, pharmacists,
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3 patient partners with AAV and caregiver partner. The selection of patients and
4 caregiver is mainly based on the judgment of clinicians and the opinions of the
5 guideline panel. Patients and caregiver received relevant training and support to meet
6 patient involvement content throughout the guideline development process. After the
7 guideline is formed, it will be distributed to all members of the guideline panel for
8 calibration. In this systematic review, patients and caregiver mainly participated in the
9 selection of outcome indicators and the selection of treatment preferences.
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18 **Study selection**

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20 We included studies of patients with a diagnosis of active AAV. AAV is defined as
21 the following categories according to the Chapel Hill Consensus Conference 2012
22 classification method: microscopic polyangiitis (MPA), granulomatosis with
23 polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA, Churg-
24 Strauss syndrome).²⁶ In addition, single organ damage AAV (eg, renal limited
25 vasculitis (RLV) or idiopathic rapidly progressive glomerulonephritis (RPGN)) can be
26 considered the fourth entity, although in practice it eventually corresponds to the
27 kidney-limited form of MPA or GPA.²⁷
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38 Eligible studies are defined as comparing two (or more) doses of GC in patients with
39 AAV during induction of remission, regardless of the use of other therapies. Other
40 therapies include, but are not limited to cyclophosphamide, azathioprine, rituximab,
41 methotrexate, mycophenolate mofetil and plasma exchange. We included only
42 randomized controlled trials (RCTs). Outcomes of interest included death, end-stage
43 kidney disease, serious infections, serious adverse events other than serious infection,
44 sustained remission and any other patient-important outcomes that are important to
45 the patient. The timepoint for the outcome assessment depends on what was specified
46 in individual studies.
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56 **Data sources and searches**

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3 We developed our literature search in collaboration with a medical librarian. We
4 searched Medline, Embase, Clinicaltrials.gov and Cochrane Central Register of
5 Controlled Trials (CENTRAL) for relevant studies from the inception to 10 April
6 2020. There were no restrictions on language. Appendix 2 presents the search
7 strategies and results. We would also review the reference lists of included studies for
8 additional references. Pairs of reviewers (YX, JD, TB, MA) independently screened
9 titles and abstracts, and reviewed the full texts of potentially eligible studies to
10 determine the final eligible studies. Disagreements were resolved by discussion. To
11 ensure the validity and consistency of the process, we provided reviewers with review
12 instruction and conducted calibration exercises before the formal start of each process.
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23 **Data extraction and risk of bias assessment**

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25 We collected data through a predesigned excel extraction form. Pairs of reviewers
26 (YX, JD, TB, MA) extracted data independently. We resolved disagreements by
27 discussion. For each eligible study, we collected the following: country/region, design
28 of the study, patient characteristics (mean age, sex and disease diagnosis), treatment
29 strategy, outcomes and measures, and follow-up duration. In addition, we emailed the
30 author of an unpublished registered trial for obtaining relevant data. Pair of reviewers
31 (YX, JD, TB, MA) independently assessed the risk of bias of each RCT using a
32 revised Cochrane risk of bias tool that includes sequence generation, concealment of
33 allocation, blinding (participants, personnel, and outcome assessors), loss to follow-
34 up, selective outcome reporting and other potential sources of bias.²⁸ The reviewers
35 judged each criterion as definitely or probably low risk of bias, or probably or
36 definitely high risk of bias.
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50 **Data synthesis or analysis, and grading of evidence**

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52 If evidence of studies permitted, we planned to conduct meta-analysis for each of the
53 outcomes. For continuous outcomes, we planned to use inverse variance statistical
54 method to calculate mean difference (MD) and 95% confidence interval (CI). For
55 binary outcomes, we would use the Mantel–Haenszel statistical method to calculate
56 risk ratio (RR) and 95% CI. We planned to conservatively use a priori random effects
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3 model assuming a great variability in treatment effects across the study. We planned
4 to use the I^2 statistic to assess statistical heterogeneity. And when the effect-estimated
5 I^2 value is >30%, we would attempt to determine the reason for the heterogeneity.
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7 Subgroups would depend on the outcomes of the included studies report. We planned
8 to check the funnel plot for potential publication bias if the number of eligible studies
9 in the analysis exceeded ten. We set significance at $P=0.05$ and would use RevMan
10 version 5.3 for all statistical analyses.
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18 We used the Grading of Recommendations Assessment, Development, and Evaluation
19 (GRADE) approach²⁹ to assess the quality of evidence at outcome level by two
20 reviewers (LZ and YX). We focused on the grading of the following outcomes after
21 our team discussion: death, end-stage kidney disease, serious infections at one year,
22 serious adverse events, and health-related quality of life. Disagreements were resolved
23 by discussion or through a third reviewer (GHG) adjudication. Randomized controlled
24 trials started as high quality. We summarized the quality of evidence in GRADE
25 summary of findings using the MAGICapp platform.^{30,31}
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35 **Results**

36 **Literature search**

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38 The search yielded, after removal of duplicates, 3912 records, 38 of which were
39 considered for full-text review. The PRISMA flow chart (Figure 1), presents the
40 reasons for excluding studies at the stage of full text screening. Ultimately, two RCTs
41 met the inclusion criteria.^{18,24}
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50 **Included studies**

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52 The study by Walsh et al (2020)²⁴ was a multicenter study (median duration of
53 follow-up 2.9 years) including 704 patients at 95 centers in 16 countries. This study
54 was a 2-by-2 factorial design and compared the efficacy of plasma exchange with or
55 without plasma exchange for AAV, as well as the efficacy of a reduced-dose regimen
56 and a standard-dose regimen of GC over the first 6 months of the treatment period.
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The two regimens of oral GC, specifically, patients in the reduced-dose regimen and standard-dose regimen received the same treatment in the first week (the dose was determined according to the patient's weight (50.0 mg/<50 kg, 60.0 mg/50 to 75 kg, 75.0 mg/> 75 kg). The reduced-dose regimen and the standard-dose regimen began to decrease gradually in the second and third weeks, respectively. Finally, at 6th months, the cumulative dose of oral GC in the reduced-dose regimen was less than 60% of the standard-dose regimen.

Furuta 2017¹⁸ was a research protocol describing an RCT enrolling 140 patients at 34 centers in Japan, evaluating whether a low-dose GC regimen (0.5 mg/kg/day) is non-inferior to a high-dose regimen (1.0 mg/kg/day) in efficacy when combined with rituximab for the treatment of AAV. In the protocol, the two treatment groups would use the same rituximab dosing regimen. In the low-dose group, prednisolone will be discontinued at 5 months, while in the high-dose group, prednisolone will be reduced to 10.0 mg/person/day until 6 months. For details see Table 1 "Characteristics of studies originally planned to be included". Because the results of Furuta et al were not publicly available, this review contained only one complete study, so no meta-analysis was conducted.

Table 1: Characteristics of studies originally planned to be included

Author, Year	Name of the study	Country	Study design	Disease	Intervention or contrast*	Outcome	Completed	Data availability	ClinicalTrials.gov number
Walsh et al. (2020)	PEXIV AS	Multiple countries	Phase III, randomized, open label, 704 patients	≥15 years severe AAV	reduced-dose GC therapy, standard-dose GC therapy	Primary outcome: a composite of death from any cause or ESKD. Secondary outcomes: death from any cause, ESKD, sustained remission, serious adverse events, serious infections within 1 year, and health-related quality of life.	Yes	Yes	NCT00987389

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Furuta et al. (2017) ⁶¹⁸	LoVAS	Japan, multicentric	Phase IV, randomized, open label, 140 patients	> 20 years new diagnosis of AAV	low-dose treatment, high-dose treatment	GC high-GC	Primary outcome: remission rate at 6 months. Secondary outcomes: time to remission, death, relapse, ESKD and the first serious adverse event, proportion of death, relapse and ESKD for efficacy at 6 months.	Unclear	No	NCT02198248
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11 * : Although these two trials are comparisons of different doses of glucocorticoids, the regimens are different, and
 12 the details are in the text. AAV: antineutrophil cytoplasmic antibodies associated vasculitis; Gcs: glucocorticoids;
 13 ESKD: end-stage kidney disease.
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17 In Walsh's study²⁴, 353 patients (female: 44.2%) were assigned reduced-dose GC
 18 regimen and 351 patients (female: 43.0%) were assigned standard-dose GC regimen.
 19 The mean age of reduced-dose group was 63.3 years, and the standard-dose group was
 20 63.1 years. In the reduced-dose group, there were 67 patients undergoing dialysis,
 21 compared with 73 in the standard-dose group. Pulmonary hemorrhage between the
 22 reduced-dose group and the standard-dose group was as follows: no hemorrhage
 23 (257/256), not severe (65/65), severe (31/30).
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32 **Risk of bias**

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 34 PEXIVAS trial was an open-label trial and patients and investigators were aware of
 35 the group assignments due to the complexity of the GC regimen. However, the
 36 recorded treatment adherence, lack of available co-interventions, and objective, easily
 37 ascertained nature of the outcomes, the lack of blinding may have introduced minimal
 38 bias. Considering the low risk of bias in the other domains this trial, the study is at
 39 low overall risk of bias.
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48 **Table 2: Risk of Bias assessment for outcomes using modified risk of bias criteria**
 49 **of RCT study.**
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Outcomes of Trials:	Sequence generation	Allocation concealment	Blinding (patients)	Blinding (health care providers)	Blinding (outcome assessors)	Blinding (data collectors)	Blinding (data analyst)	Loss to follow-up
Michael et al. (2013) Death	Definitely Low	Definitely Low	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Definitely Low

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3	ESKD	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
4		Low	Low	Low	Low	Low	Low	Low	Low
5									
6	Sustained remission	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
7		Low	Low	Low	Low	Low	Low	Low	Low
8									
9	Serious adverse events	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
10		Low	Low	Low	Low	Low	Low	Low	Low
11									
12	Serious infections at 1 year	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
13		Low	Low	Low	Low	Low	Low	Low	Low
14									
15	Health-related quality of life	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
16		Low	Low	Low	Low	Low	Low	Low	Low

ESKD: end-stage kidney disease; RCT: randomized controlled trial.

Effect of Interventions

Since the results of the Walsh's study²⁴ showed no interaction between the GC regimen and the plasma exchange, we only focus on the use of GC in conjunction with the purpose of this review. In this study, 330 patients (93.5%) in the reduced-dose regimen of GC and 325 (92.6%) in the standard-dose regimen of GC were included in the per-protocol population. Table 3 shows the statistical results of outcomes of this study. Table 4 summarizes the GRADE summary of findings for this study. We conducted absolute risk estimation and certainty of the evidence assessment for death or ESKD. Compared with standard-dose regimen, reduced-dose regimen of GC may reduce death (relative risk (RR): 0.86, 95% CI, 0.6 to 1.24, 21 fewer per 1000, low certainty), while not increasing ESKD (RR: 1.02, 95% CI, 0.76 to 1.38, 4 more per 1000, moderate certainty). Results showed that the rate of serious infection at 1 year in the reduced-dose regimen tended to be lower than in the standard-dose regimen (relative risk: 0.82, 95% CI, 0.66 to 1.03, 59 fewer per 1000, moderate certainty). And the standard-dose regimen probably result in little or no increase on serious adverse events at follow-up of longer than 1 year (relative risk: 1.05, 95% CI, 0.94 to 1.18, 31 more per 1000, moderate certainty). Although in further analysis, there were more serious kidney/urinary adverse events in the reduced-dose regimen than in the standard-dose regimen (RR: 1.84, 95% CI, 1.18 to 2.87), there was no significant difference in the incidence of ESKD between the two regimens (RR: 1.02, 95% CI, 0.76 to 1.38). There were no statistical differences in other outcomes between the two regimens, such as health related quality of life.

Table 3 The statistical results of outcomes

Outcomes	RR/MD (95% CI)
Death	RR: 0.86 (0.6, 1.24)
ESKD	RR: 1.02 (0.76, 1.38)
Sustained remission	RR: 1.04(0.92, 1.19)
Serious infections at 1 year	RR: 0.82 (0.66, 1.03)
Serious adverse events	RR: 1.05 (0.94, 1.18)
Health related quality of life following up at 1 year	
SF-36 PCS	MD: 1.29 (-0.26, 2.84)
SF-36 MCS	MD: 0.97 (-0.24, 2.18)
EQ-5D Index	MD: 0.02 (-0.01, 0.05)
EQ-5D Thermometer	MD: 1.04 (-1.09, 3.17)
Serious Adverse Event Type	
Cardiovascular	RR: 1.21 (0.88, 1.66)
Endocrine	RR: 0.50 (0.15, 1.64)
Gastrointestinal	RR: 1.43 (0.92, 2.22)
Hematologic	RR: 1.15 (0.63, 2.09)
Infection	RR: 0.90 (0.74, 1.10)
Kidney/Urinary	RR: 1.84 (1.18, 2.87)
Surgery	RR: 0.93 (0.45, 1.89)
Vasculitis relapse	RR: 1.38 (0.83, 2.32)
Other	RR: 1.18 (0.90, 1.53)

ESKD: end-stage kidney disease; SF-36 = short form 36; PCS = physical component score; MCS = mental component score; EQ = EuroQol; RR: relative risk; MD: mean difference; CI: confidence interval.

Table 4 GRADE summary of findings on the use of reduced-dose regimen versus standard-dose regimen of glucocorticoids in patients with ANCA-associated vasculitis

PICO

Population: Patients with ANCA-associated vasculitis

Intervention: Reduced-dose regimen of glucocorticoids

Comparator: Standard-dose regimen of glucocorticoids

Outcome	Study results and	Absolute effect estimates	Certainty of the Evidence	Plain text summary
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Timeframe	measurements	Standard-dose regimen of glucocorticoids	Reduced-dose regimen of glucocorticoids	(Quality of evidence)	
Death from any cause longer than 1 year	Relative risk: 0.86 (CI 95% 0.6 - 1.24) Based on data from 704 patients in 1 study Follow up median 2.9 years	151 per 1000 Difference: 21 fewer per 1000 (CI 95% 60 fewer - 36 more)	130 per 1000	Low Due to very serious imprecision ¹	Reduced dose of glucocorticoids may reduce death at follow-up of longer than 1 year
End-stage kidney disease longer than 1 year	Relative risk: 1.02 (CI 95% 0.76 - 1.38) Based on data from 704 patients in 1 study Follow up median 2.9 years	194 per 1000 Difference: 4 more per 1000 (CI 95% 47 fewer - 74 more)	198 per 1000	Moderate Due to serious imprecision ²	Reduced dose of glucocorticoids probably has little or no effect on end-stage kidney disease at follow-up of longer than 1 year
Serious infections at 1 year	Relative risk: 0.82 (CI 95% 0.66 - 1.03) Based on data from 704 patients in 1 study Follow up at 1 year	330 per 1000 Difference: 59 fewer per 1000 (CI 95% 112 fewer - 10 more)	271 per 1000	Moderate Due to serious imprecision ³	Reduced dose of glucocorticoids probably has an important reduction in serious infections at 1 year
Serious adverse events longer than 1 year	Relative risk: 1.05 (CI 95% 0.94 - 1.18) Based on data from 704 patients in 1 study Follow up median 2.9 years	621 per 1000 Difference: 31 more per 1000 (CI 95% 37 fewer - 112 more)	652 per 1000	Moderate Due to serious imprecision ⁴	Reduced dose of glucocorticoids may increase the risk of serious adverse events at follow-up of longer than 1 year.
Health related quality of life (SF-36 PCS) at 1 year ⁶	Measured by: SF-36 PCS Scale: - High better Based on data from 704 patients in 1 study Follow up at 1 year	37.84 Mean Difference: MD 1.29 higher (CI 95% 0.26 lower - 2.84 higher)	39.13 Mean	High	Reduced dose of glucocorticoids has little or no effect on health related quality of life (SF-36PCS) at 1 year
Health related quality of life (SF-36 MCS) at 1 year ⁷	Measured by: SF-36 MCS Scale: - High better Based on data from 704 patients in 1 study Follow up at 1 year	51.19 Mean Difference: MD 0.97 higher (CI 95% 0.24 lower - 2.18 higher)	52.16 Mean	High	Reduced dose of glucocorticoids has little or no effect on health related quality of life (SF-36MCS) at 1 year
Health related quality of life (EQ-5D Index) at 1 year ⁸	Measured by: EQ-5D Index Scale: - High better Based on data from 704 patients in 1 study	0.77 Mean Difference: MD 0.02 higher (CI 95% 0.01 lower - 0.05 higher)	0.79 Mean	Moderate Due to serious imprecision ⁵	Reduced dose of glucocorticoids probably has little or no effect on health related quality of life (EQ-5D) at 1 year

	Follow up at 1 year				
Health related quality of life (EQ-5D Thermometer) at 1 year ⁸	Measured by: EQ-5D Thermometer Scale: - High better Based on data from 704 patients in 1 study Follow up at 1 year	71.07 Mean Difference: MD 1.04 higher (CI 95% 1.09 lower - 3.17 higher)	72.11 Mean	High	Reduced dose of glucocorticoids has little or no effect on health related quality of life (EQ-5D Thermometer) at 1 year

1. **Imprecision: Very serious.** Because the 95% CI includes both the minimally important difference for benefit (20 fewer death in 1000 patients) and minimally important difference for harm (20 more death in 1000 patients), we rated down two levels for imprecision;

2. **Imprecision: Serious.** The 95% CI crosses the minimally important difference for benefit (30 fewer ESKD in 1000 patients) and minimally important difference for harm (30 more ESKD in 1000 patients) ;

3. **Imprecision: Serious.** The 95% CI crosses the minimally important difference (50 fewer serious infections in 1000 patients);

4. **Imprecision: Serious.** The 95% CI includes an increase in serious adverse event over 10%;

5. **Imprecision: Serious.** The 95% CI crosses the minimally important difference for benefit and the minimally important difference for harm (0.03 reduction or increase in EQ-5D Index) ;

6. SF-36 = short form 36; PCS = physical component score

7. SF-36 = short form 36; MCS =mental component score

8. EQ = EuroQol

Discussion

After full text screening, we identified 2 studies^{18,24} involving 844 patients that met our selection criteria for studies comparing different doses regimens of GC for the treatment of AAV. Because Furuta's article¹⁸ is a protocol and there are currently no study results available, this review ultimately analyzed the results of PEXIVAS. This study is by far the largest trial conducted in AAV or any form of vasculitis.

According to the results of this finally included trial, the results of the absolute effects of low certainty of evidence showed that reduced-dose regimen of GC may reduce death at the follow-up of longer than 1 year, while not increasing the rate of ESKD (moderate certainty) among patients with AAV when compared with standard-dose regimen. However, due to the wide CIs, the absolute effects of any intervention on these two outcomes were minimal, and the results were not significantly different. This may be due to the fact that patients included in the trial had severe AAV (kidney involvement or diffuse alveolar hemorrhage), were seriously ill and likely had a poor

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3 prognosis. Additionally, in this trial, the improvement of the disease by other
4 treatments may mask the benefits of reduced-doses regimen.
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10 In addition, relative to the standard-dose regimen, moderate certainty of evidence
11 indicated that the reduced-dose regimen probably has an important reduction in
12 serious infections at 1 year but may have little or no effect on the overall risk of
13 serious adverse events. This study showed that reduced-dose regimen does have an
14 obvious advantage in reducing infections, which echoes previous studies.^{17,32} For
15 example, Jayne et al. reported that when high-dose GC was used, infection was most
16 common in the first 6 months of treating severe renal vasculitis.¹⁷ Therefore,
17 considering that the most common cause of death more than one year after diagnosis
18 of AAV is infection or uncontrolled vasculitis,^{16,33,34,35} this is particularly important to
19 support the practice of the conclusion of this study.
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30 Although in the analysis of serious adverse event type, the reduced-dose regimen had
31 more renal/urinary adverse events than the standard-dose regimen, there was no
32 significant difference in the incidence of ESKD between the two regimens as
33 described above. This may be related to the treatment status of the included patients.
34 Among the patients included in the study, the number of patients in the standard-dose
35 regimen who had undergone dialysis before the start of the trial was more than that in
36 the reduced-dose regimen. It is well known that dialysis reduces the occurrence of
37 serious adverse events in the urinary system.
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47 The use of GC transformed AAV from an almost uniformly fatal condition to one
48 characterized by remissions and relapses complicated by drug-induced adverse events.
49 Despite the ubiquitous use of GC for AAV, there was no standardization of dose
50 regimens, guidelines were ambiguous and practice patterns varied substantially. The
51 PEXIVAS trial²⁴ supports the important role GC plays in causing adverse events and
52 highlights the need to optimize their use. Although PEXIVAS found evidence to
53 support one regimen of GC over another, further research is needed to determine
54 whether the GC regimen can be further improved for the treatment of AAV.
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6 The advantages of this systematic review include a comprehensive search of emerging
7 and past evidence across databases without being restricted by study design or
8 publication language, and the use of GRADE approach to assess the quality of
9 evidence. Decisions regarding eligible studies, data extraction, and risk of bias
10 assessments were all performed in duplicate, and calibration exercises were conducted
11 before the formal start of the project. By excluding non-RCT studies, we limited the
12 risk of bias. The RCT we included is of sound methodological quality. AAV is a rare
13 disease, and the study is the largest global trial on the subject so far which has
14 improved the generalizability of the results through the efforts of national and
15 international vasculitis networks and extensive selection criteria.
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26 The results of our systematic review also have some limitations. First, only one trial
27 was included and although it was broadly inclusive and contained more events than
28 any other trial in this disease, the total statistical information remains low. This is
29 particularly obvious for serious adverse events other than serious infection. However,
30 the reduced-dose GC regimen should not result in more treatment related adverse
31 events (i.e. it is illogical that a lower exposure to GC would have anything but the
32 same or lower rate of GC caused side effects) and there is reasonable precision around
33 the efficacy outcomes. This limitation is expected to result in an underappreciation of
34 the benefits of reducing the GC dose, a limitation that is supported by observational
35 studies of GC which suggest reducing GC exposure may also reduce fractures, peptic
36 ulcer disease, psychiatric disease, weight gain and dysglycemia. In addition, despite
37 the excellent methodological quality of the included trial, this is an open label and is
38 subject to biases despite our relative confidence that differential treatment or outcome
39 ascertainment was at low risk. Despite the large scale of this study for a rare disease,
40 the degree to which the results can be generalized to patients with non-severe AAV is
41 uncertain, although it is likely safer to extrapolate the safety of the regimen from more
42 severe illness to less severe illness rather than less severe to more severe.
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58 **Conclusion**

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3 An important general rule is that in routine clinical practice, the use of conventional
4 GC should be “as much as necessary, but as little as possible.”³⁶ Therefore, compared
5 with the standard-dose regimen, the reduced-dose regimen of GC may reduce death,
6 probably has little or no effect on ESKD among patients with AAV, and resulted in a
7 lower risk of serious infections at 1 year. Future clinical trials should evaluate whether
8 GC dosing can be further safely reduced.
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18 critical feedback on outcome and subgroup selection, GRADE judgments, and
19 manuscript feedback.
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23 performed the literature search. YX, JD, TB and MA performed the screening, data
24 abstraction, and risk of bias assessments. YX, LZ and MW performed the data
25 analysis. YX, GHG, LZ, RS, DJ, PM and MW interpreted the data. YX, GHG and LZ
26 performed the certainty assessment. YX, GHG, LZ and MW drafted the manuscript.
27 All authors critically revised the manuscript. All authors approved the final version of
28 the manuscript. YX and MW had full access to the data in the study and takes
29 responsibility for the integrity of the data and the accuracy of the data analysis. YX
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43

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45

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47

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49

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51

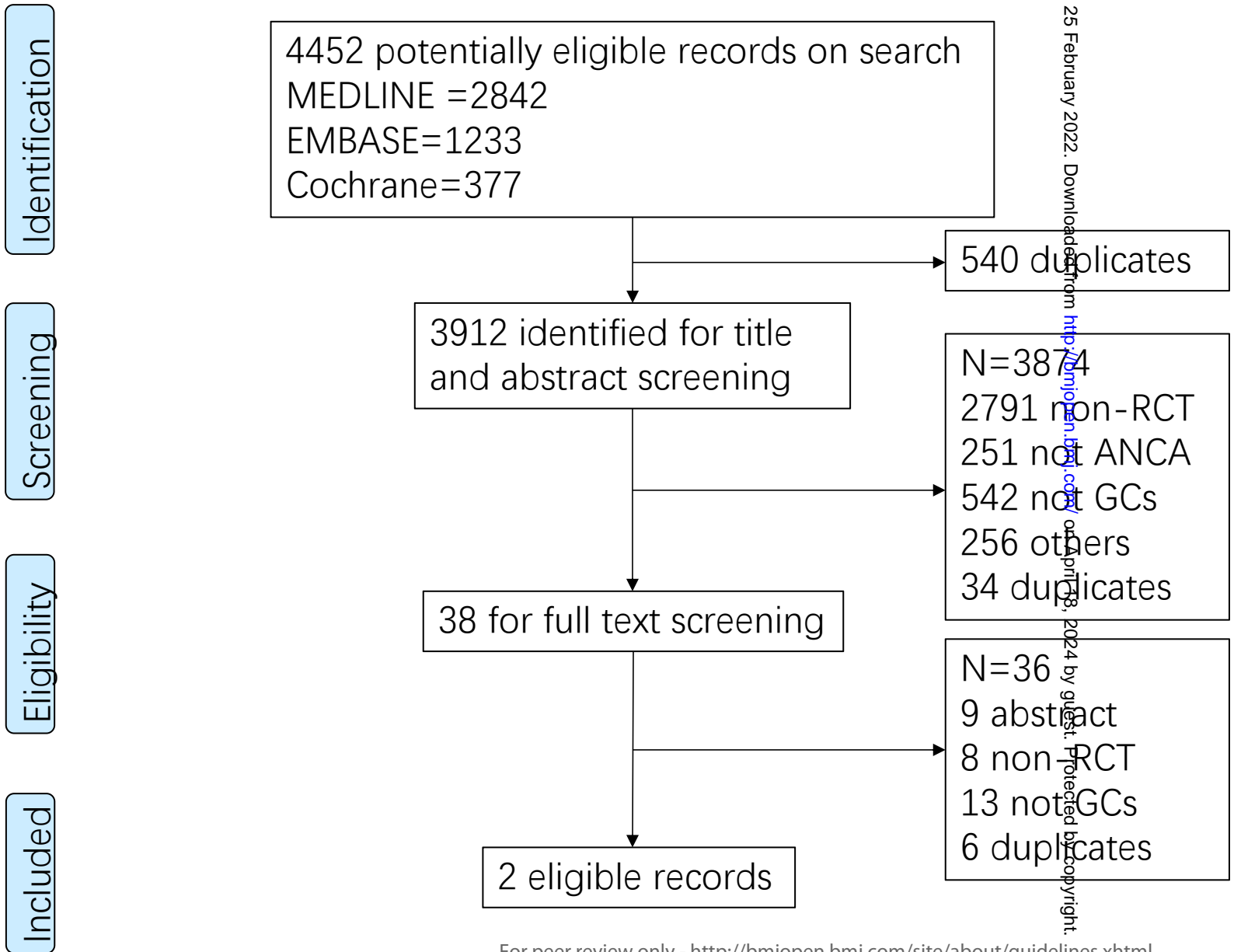
52 Transparency statement: YX and MW affirm that the manuscript is an honest,
53 accurate, and transparent account of the recommendation being reported; that no
54 important aspects of the recommendation have been omitted; and that any
55 discrepancies from the recommendation as planned (and, if relevant, registered) have
56 been explained.
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References

1. Houben E, Penne EL, Voskuyl AE, et al. Cardiovascular events in anti-neutrophil cytoplasmic antibody-associated vasculitis: a meta-analysis of observational studies. *Rheumatology (Oxford)* 2018;57(3):555-562.
2. Bosch X, Guilabert A, Font J. Antineutrophil cytoplasmic antibodies. *Lancet* 2006;368(9533):404-41816876669.
3. Wallace ZS, Miloslavsky EM. Management of ANCA associated vasculitis. *BMJ* 2020;368:m421.
4. Jennette JC, Falk RJ. Pathogenesis of antineutrophil cytoplasmic autoantibody-mediated disease. *Nat Rev Rheumatol* 2014;10:463-73.
5. Salvador F. ANCA Associated Vasculitis. *Eur J Intern Med* 2020;74:18-28.
6. Smith RM. Update on the treatment of ANCA associated vasculitis. *Presse Med* 2015;44(6 Pt 2):e241-9.
7. Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992;116:488-98.
8. Walsh M, Merkel PA, Peh CA, et al.; PEXIVAS Investigators. Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis (PEXIVAS): protocol for a randomized controlled trial. *Trials* 2013;14:73.
9. Keller SF, Miloslavsky EM. Corticosteroids in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. *Rheum Dis Clin North Am* 2016;42(1):91-101.
10. Booth AD, Almond MK, Burns A, et al., Pan-Thames Renal Research Group. Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. *Am J Kidney Dis* 2003; 41(4):776-84.
11. Jennette JC, Falk RJ. Small-vessel vasculitis. *N Engl J Med* 1997;337(21):1512–23.
12. Lally L, Spiera R. Current landscape of antineutrophil cytoplasmic antibody-associated vasculitis: classification, diagnosis, and treatment. *Rheum Dis Clin North Am* 2015;41(1):1–19, vii.
13. Stahn C, Buttgerit F. Genomic and nongenomic effects of glucocorticoids. *Nat Clin Pract Rheumatol* 2008;4:525-33.
14. Walton EW. Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). *Br Med J* 1958;2:265-70.
15. de Groot K, Harper L, Jayne DR, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med* 2009;150:670–80.
16. De Groot K, Rasmussen N, Bacon PA, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2005;52:2461–9.
17. Jayne DR, Gaskin G, Rasmussen N, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol* 2007;18:2180–8.

- 1
2
3 18. Furuta S, Sugiyama T, Umibe T, et al.. Low-dose glucocorticoids plus rituximab versus high-dose
4 glucocorticoids plus rituximab for remission induction in ANCA-associated vasculitis (LoVAS):
5 protocol for a multicentre, open-label, randomised controlled trial. *BMJ Open* 2017 Dec
6 14;7(12):e018748.
7
- 8 19. Keller SF, Miloslavsky EM. Corticosteroids in Antineutrophil Cytoplasmic Antibody-Associated
9 Vasculitis. *Rheum Dis Clin North Am* 2016;42(1):91-101.
10
- 11 20. Flossmann O , Berden A , de Groot K , et al . Long-term patient survival in ANCA-associated
12 vasculitis. *Ann Rheum Dis* 2011;70:488–94.
13
- 14 21. Furuta S , Chaudhry AN , Hamano Y , et al . Comparison of phenotype and outcome in microscopic
15 polyangiitis between Europe and Japan. *J Rheumatol* 2014;41:325–33.
16
- 17 22. Walsh M , Merkel PA , Mahr A , et al . Effects of duration of glucocorticoid therapy on relapse rate
18 in antineutrophil cytoplasmic antibody-associated vasculitis: a meta-analysis. *Arthritis Care Res*
19 2010;62:1166–73.
20
- 21 23. Wada T , Hara A , Arimura Y , et al . Risk factors associated with relapse in Japanese patients with
22 microscopic polyangiitis. *J Rheumatol* 2012;39:545–51.
23
- 24 24. Walsh M, Merkel PA, Peh CA, et al. Plasma Exchange and Glucocorticoids in Severe ANCA-
25 Associated Vasculitis. *N Engl J Med* 2020;382(7):622-631.
26
- 27 25. Moher D, Liberati A, Tetzlaff J, et al.; PRISMA Group. Preferred reporting items for systematic
28 reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006-12.
29
- 30 26. Salvador F. ANCA associated vasculitis. *Eur J Intern Med* 2020;74:18-28.
31
- 32 27. Pagnoux C. Updates in ANCA-associated vasculitis. *Eur J Rheumatol* 2016;3(3):122-133.
33
- 34 28. Guyatt G, Busse JW. Risk of bias in randomized trials. *GROWTH Evidence*; 2016. Available:
35 <https://growthevidence.com/gordon-h-guyatt-md-msc-and-jason-w-busse-dc-phd> (accessed 2020 April.
36 6).
37
- 38 29. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence
39 profiles and summary of findings tables. *J Clin Epidemiol* 2011; 64: 383-94.
40
- 41 30. Guyatt GH, Oxman AD, Santesso N, et al. GRADE guidelines: 12. Preparing summary of findings
42 tables-binary outcomes. *J Clin Epidemiol* 2013;66:158-72.
43
- 44 31. Guyatt GH, Thorlund K, Oxman AD, et al. GRADE guidelines: 13. Preparing summary of findings
45 tables and evidence profiles-continuous outcomes. *J Clin Epidemiol* 2013;66:173-83.
46
- 47 32. Illei GG, Yarboro CH, Kuroiwa T, et al.. Long-term effects of combination treatment with
48 fludarabine and low-dose pulse cyclophosphamide in patients with lupus nephritis. *Rheumatology*
49 (Oxford) 2007;46:952–956.
50
- 51 33. Flossmann O, Berden A, de Groot K, et al., European Vasculitis Study Group. Long-term patient
52 survival in ANCA-associated vasculitis. *Ann Rheum Dis* 2011;70:488-94.
53
- 54 34. Jones RB, Tervaert JWC, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-
55 associated renal vasculitis. *N Engl J Med* 2010;363(3):211-20.
56
- 57 35. Jayne D, Rasmussen N, Andrassy K, et al.; European Vasculitis Study Group: A randomized trial
58 of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N*
59 *Engl J Med* 349 : 36 –44, 2003.
60
36. Buttgereit F, Burmester GR, Lipworth BJ. Optimised glucocorticoid therapy: the sharpening of an
old spear. *Lancet* 2005;365(9461):801-3.

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Figure 1 PRISMA flow chart of literature search and screening process

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PRISMA 2009 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.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6-7
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.	7
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.	8
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.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	8
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).	8
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.	9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9
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.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9-10
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.	9-10



PRISMA 2009 Checklist

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).	9-10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-10
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.	10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICCO, follow-up period) and provide the citations.	10-11
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).	12
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.	11-12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13-15
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13-15
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).	16-17
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).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
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).	19

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Appendix 2: Search strategies and results for The comparative efficacy and safety of alternative glucocorticoids regimens in patients with ANCA-associated vasculitis: A systematic review

Database	No of records
MEDLINE	2842
EMBASE	1233
Cochrane Library	377
Subtotal	4452
-dupes	-540
Total	3912

Database: OVID MEDLINE

-
- 1 Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis/ (1682)
 - 2 Churg-Strauss Syndrome/ (2090)
 - 3 Microscopic Polyangiitis/ (507)
 - 4 Granulomatosis with Polyangiitis/ (6902)
 - 5 (vasculit* adj3 (ANCA or AAV or antineutrophil or anti-neutrophil or cytoplasm* or RLV or renal or churg or strauss or pauci immune)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (4968)
 - 6 churg strauss.mp. (2876)
 - 7 ((angiit* or vasculit*) adj3 (granulom* or necrot* or allergic)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (4297)
 - 8 ((polyangiit* or polyarterit*) adj3 (microscop* or MPA or granulom*)).mp. (9268)
 - 9 wegener*.mp. (6572)
 - 10 (glomerulonephrit* adj3 necrot*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (797)
 - 11 or/1-10 (18126)
 - 12 exp Glucocorticoids/ (190619)
 - 13 prednisolone/ or methylprednisolone/ (49855)
 - 14 Prednisone/ (39084)
 - 15 Adrenal Cortex Hormones/ (63823)

- 16 (corticosteroid* or glucocorticoid* or methylprednisolon* or prednison* or prednisolon*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (283874)
- 17 Corticosterone/ or corticosteron*.mp. (34191)
- 18 Hydrocortisone/ or hydrocortison*.mp. (76765)
- 19 Cortisone/ or cortison*.mp. (23710)
- 20 steroids.mp. or Steroids/ (112972)
- 21 Cortodoxone/ or cortodoxon*.mp. (856)
- 22 Hydroxycorticosteroids/ or hydroxycorticosteroid*.mp. (6731)
- 23 Dexamethasone/ or dexamethason*.mp. (71052)
- 24 adrenocorticosteroid*.mp. (313)
- 25 adrenocorticoid*.mp. (177)
- 26 corticoid*.mp. (6458)
- 27 or/12-26 (547377)
- 28 11 and 27 (4782)
- 29 randomized controlled trial.pt. (503644)
- 30 controlled clinical trial.pt. (93611)
- 31 randomized.ab. (475606)
- 32 placebo.ab. (206694)
- 33 drug therapy.fs. (2193818)
- 34 randomly.ab. (330775)
- 35 trial.ab. (501000)
- 36 groups.ab. (2031658)
- 37 or/29-36 (4675601)
- 38 exp animals/ not humans.sh. (4689197)
- 39 37 not 38 (4053127)
- 40 28 and 39 (2842)

Database: EMBASE

- 1 ANCA associated vasculitis/ (5871)
- 2 Churg Strauss syndrome/ (4947)
- 3 microscopic polyangiitis/ (3039)
- 4 Wegener granulomatosis/ (12860)
- 5 (vasculit* adj3 (ANCA or AAV or antineutrophil or anti-neutrophil or cytoplasm* or RLV or renal or churg or strauss or pauci immune)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (9651)
- 6 churg strauss.mp. (5425)
- 7 ((angiit* or vasculit*) adj3 (granulom* or necrot* or allergic)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug

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 3 manufacturer, device trade name, keyword, floating subheading word, candidate
 4 term word] (7160)
 5 8 ((polyangiit* or polyarterit*) adj3 (microscop* or MPA or granulom*)).mp.
 6 [mp=title, abstract, heading word, drug trade name, original title, device
 7 manufacturer, drug manufacturer, device trade name, keyword, floating subheading
 8 word, candidate term word] (7171)
 9 9 wegener*.mp. (14257)
 10 10 (glomerulonephrit* adj3 necrot*).mp. [mp=title, abstract, heading word, drug
 11 trade name, original title, device manufacturer, drug manufacturer, device trade
 12 name, keyword, floating subheading word, candidate term word] (1243)
 13 11 or/1-10 (29983)
 14 12 exp glucocorticoid/ (700322)
 15 13 prednisolone/ (122582)
 16 14 methylprednisolone/ (93152)
 17 15 prednisone/ (167298)
 18 16 corticosteroid/ (229322)
 19 17 (corticosteroid* or glucocorticoid* or methylprednisolon* or prednison* or
 20 prednisolon*).mp. [mp=title, abstract, heading word, drug trade name, original title,
 21 device manufacturer, drug manufacturer, device trade name, keyword, floating
 22 subheading word, candidate term word] (688798)
 23 18 corticosterone/ or corticosteron*.mp. (38497)
 24 19 hydrocortisone/ or hydrocortison*.mp. (135041)
 25 20 cortisone/ or cortison*.mp. (17205)
 26 21 steroids.mp. or steroid/ (245681)
 27 22 cortodoxone/ or cortodoxon*.mp. (2044)
 28 23 hydroxycorticosteroid*.mp. or hydroxycorticosteroid/ (2310)
 29 24 dexamethasone/ or dexamethason*.mp. (161446)
 30 25 adrenocorticosteroid*.mp. (286)
 31 26 adrenocorticoid*.mp. (169)
 32 27 corticoid*.mp. (7745)
 33 28 or/12-27 (1111323)
 34 29 11 and 28 (13676)
 35 30 randomized controlled trial/ (598366)
 36 31 Controlled clinical study/ (463908)
 37 32 random\$.ti,ab. (1520687)
 38 33 randomization/ (86548)
 39 34 intermethod comparison/ (258594)
 40 35 placebo.ti,ab. (303776)
 41 36 (compare or compared or comparison).ti. (505122)
 42 37 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or
 43 compared or comparing or comparison)).ab. (2085158)
 44 38 (open adj label).ti,ab. (78322)
 45 39 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
 46 (230181)
 47 40 double blind procedure/ (171296)
 48 41 parallel group\$.ti,ab. (25234)

42 (crossover or cross over).ti,ab. (104111)
 43 ((assign\$ or match or matched or allocation) adj5 (alternate or group\$1 or
 44 intervention\$1 or patient\$1 or subject\$1 or participant\$1)).ti,ab. (326088)
 45 (assigned or allocated).ti,ab. (383843)
 46 (controlled adj7 (study or design or trial)).ti,ab. (343989)
 47 (volunteer or volunteers).ti,ab. (244774)
 48 human experiment/ (490852)
 49 trial.ti. (296188)
 50 or/30-48 (4957675)
 29 and 49 (1233)

Database: Cochrane Library

ID	Search Hits
#1	MeSH descriptor: [Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis] explode all trees 157
#2	MeSH descriptor: [Churg-Strauss Syndrome] explode all trees 27
#3	MeSH descriptor: [Microscopic Polyangiitis] explode all trees 40
#4	MeSH descriptor: [Granulomatosis with Polyangiitis] explode all trees 82
#5	vasculit* near/3 (ANCA or AAV or antineutrophil or anti-neutrophil or cytoplasm* or RLV or renal or churg or strauss or pauci immune) 470
#6	churg strauss 112
#7	((angiit* or vasculit*) near/3 (granulom* or necrot* or allergic)) 102
#8	((polyangiit* or polyarterit*) near/3 (microscop* or MPA or granulom*)) 277
#9	wegener* 394
#10	(glomerulonephrit* near/3 necrot*) 13
#11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 867
#12	MeSH descriptor: [Glucocorticoids] explode all trees 4445
#13	MeSH descriptor: [Prednisolone] explode all trees 4804
#14	MeSH descriptor: [Methylprednisolone] explode all trees 2679
#15	MeSH descriptor: [Prednisone] explode all trees 3909
#16	MeSH descriptor: [Adrenal Cortex Hormones] explode all trees 14135
#17	corticosteroid* or glucocorticoid* or methylprednisolon* or prednison* or prednisolon* 41757
#18	MeSH descriptor: [Corticosterone] explode all trees 38
#19	MeSH descriptor: [Hydrocortisone] explode all trees 5886
#20	MeSH descriptor: [Cortisone] explode all trees 143
#21	MeSH descriptor: [Steroids] explode all trees 57500
#22	MeSH descriptor: [Cortodoxone] explode all trees 30
#23	MeSH descriptor: [Cortodoxone] explode all trees 30
#24	MeSH descriptor: [Hydroxycorticosteroids] explode all trees 7002
#25	MeSH descriptor: [Dexamethasone] explode all trees 4409

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3 #26 corticosteron* or hydrocortison or cortison* or steroids or cortodoxon* or
4 hydroxycorticosteroid* or dexamethason* or adrenocorticosteroid* or
5 adrenocorticoid* or corticoid* 22688
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7 #27 #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22
8 or #23 or #24 or #25 or #26 95898
9 #28 #11 and #27 in Trials 377
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For peer review only



PRISMA 2009 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.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6-7
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.	7
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.	8
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.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	8
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).	8
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.	9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9
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.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9-10
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.	9-10



PRISMA 2009 Checklist

Page 1 of 2

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).	9-10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-10
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.	10
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.	10-11
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).	12
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.	11-12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13-15
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13-15
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).	16-17
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).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
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.	19

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Page 2 of 2

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BMJ Open

The comparative efficacy and safety of alternative glucocorticoids regimens in patients with ANCA-associated vasculitis: A systematic review

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Haematology (incl blood transfusion), Evidence based practice
Keywords:	HAEMATOLOGY, ORAL MEDICINE, Clinical trials < THERAPEUTICS

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3 **The comparative efficacy and safety of alternative glucocorticoids regimens in**
4 **patients with ANCA-associated vasculitis: A systematic review**
5

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Abstract

Objective

To compare the efficacy and safety of alternative glucocorticoids (GC) regimens as induction therapy for patients with antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis.

Design

Systematic review of Randomized controlled trial (RCTs).

Data sources

Medline, Embase, Clinicaltrials.gov and Cochrane Central Register of Controlled Trials up to 10 April 2020.

Study selection and Review methods

RCTs comparing two (or more) different dose regimens of GC in ANCA-associated vasculitis during induction of remission, regardless of other therapies. Pairs of reviewers independently screened records, extracted data and assessed risk of bias. Two reviewers rated certainty of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Results

Of 3912 records identified, the full texts of two records met the eligibility criteria. Due to the heterogeneity of population and dose regimen of glucocorticoids between the two trials, we descriptively presented the two trials and did not combine the results using meta-analysis. Compared with the standard-dose regimen, the reduced-dose regimen of GC may reduce death risk difference [RD]: from -1.7% to -2.1%, low certainty), while not increasing end-stage kidney disease (ESKD) (RD: from -1.5% to 0.4%, moderate certainty). The reduced-dose regimen probably has an important reduction in serious infections at 1 year (RD: from -12.8% to -5.9%, moderate certainty). Reduced-dose regimen of glucocorticoids probably has trivial or no effect in disease remission, relapse or health related quality of life (moderate to high certainty).

Conclusions

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3 The reduced-dose regimen of GC may reduce death at the follow-up of 6 months to
4 longer than 1 year and serious infections while not increase ESKD.
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7 **Systematic review registration**

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9 PROSPERO CRD42020179087.
10

11 **Keywords:** glucocorticoids, Anti-Neutrophil Cytoplasmic Antibody-Associated
12 Vasculitis, systematic review
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14

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16 Word count for the main text: 3079
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19 **Strengths and limitations of this study**

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23 - This systematic review included a comprehensive search of literatures without
24 limitation on language.
25
26 - This systematic review applied GRADE approach assessing the quality of
27 evidence.
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29 - This systematic review included the largest global trial and the latest trial on the
30 subject so far that have improved the generalizability of the results through the
31 efforts of national and international vasculitis networks and extensive selection
32 criteria.
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34 - Despite the excellent methodological quality, the two eligible trials were open
35 labeled and were subject to bias.
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37 - This systematic review is mainly based on evidence from patients with severe
38 ANCA-associated vasculitis is uncertain.
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Introduction

ANCA-associated vasculitis (AAV) comprises a subgroup of systemic vasculitis affecting small- to medium-sized vessels, a chronic inflammatory disease of the blood vessel wall¹, and includes granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis.² Patients with AAV usually test positive for ANCA. The cause of the disease remains unclear. Genetic and environmental factors play an important role in the onset of the disease.^{3,4} The annual incidence of AAV is about 20 per million inhabitants, and the prevalence is about 100 per million inhabitants.⁵ AAV has multiple clinical manifestations, characterized by leukocytes infiltrating the vessel walls, fibrinoid necrosis, and vascular damage with occlusion or aneurysm formation.⁶ The severity of AAV varies greatly, but after months to years of non-severe manifestations, patients with non-severe diseases often progress to severe diseases.⁷ The most common severe AAV manifestation is glomerulonephritis, which leads to renal failure and alveolar capillaritis causing pulmonary hemorrhage.⁸ Previous studies have showed that untreated AAV is typically fatal⁹, with 6-month and 1-year mortality rates of 60% and 80%, respectively.¹⁰

Since the 1950s, glucocorticoids (GCs), as immunosuppressants and anti-inflammatory drugs with a fast-acting and powerful anti-inflammatory effect, became the basis of therapy for AAV.^{11,12} The main mechanism of action is genomic and non-genomic effects mediated by cytosolic GC receptors or specific and non-specific interactions with membrane-bound GC receptors resulting in reduced production of pro-inflammatory proteins (transrepression).¹³ However, monotherapy has incomplete efficacy.¹⁴ Subsequently, standard therapy emerged using the combination of high-dose GC and cyclophosphamide to achieve remission in AAV.^{15,16,17} This combination therapy proved to reduce mortality to 25% at 5 years and has high remission rates of 80% – 90%.¹⁸ In addition to cyclophosphamide, clinical remission can also be achieved with rituximab-based or methotrexate-based therapies.¹⁹ Although the combination of high-dose GC and cytotoxic drugs greatly enhances the therapeutic efficacy, high-dose GC may increase the toxicity associated with treatment. Infections and cardiovascular diseases due to the treatment are main causes

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3 of fatal side effects that reduced quality of life (QOL) in patients.^{20,21} Previous studies
4 have shown that lower GC doses during the induction period were associated with
5 higher relapse rates and longer term of GC use that might expose patients to the
6 potential toxicity of high-cumulative GC.^{22,23}
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13 The purpose of this systematic review is to evaluate the comparative efficacy and
14 safety of alternative GC regimens (two or more different doses of GC) in patients with
15 ANCA-associated vasculitis. Our systematic review is part of a BMJ Rapid
16 Recommendations project, which is based on the shared vision of the MAGIC
17 Evidence Ecosystem Foundation (www.magicproject.org) and The BMJ. When there
18 is evidence that may change the clinical practice, the cooperative organizations will
19 act quickly to provide a timely, trustworthy practice guideline. Under such
20 circumstance, the exciting evidence was the PEXIVAS trial²⁴. The systematic review
21 informed an associated BMJ Rapid Recommendations.
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31 **Methods**

32 **Registration and report**

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34 A priori protocol of this systematic review is presented at PROSPERO
35 (CRD42020179087). We reported this systematic review and meta-analysis based on
36 the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)
37 statement (see Appendix 1).²⁵
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47 **Patient and public involvement**

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49 According to the process of the BMJ Rapid Recommendations, the guideline panel on
50 this target provides critical process oversight and content guidance for the systematic
51 review. The guideline panel consisted of clinicians, methodologists, pharmacists,
52 patient partners with AAV and caregiver partner. Patients received relevant training
53 and support to meet patient involvement content throughout the guideline
54 development process, , including critical feedback on outcome and subgroup
55 selection, GRADE judgments, and manuscript feedback.
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Study selection

We included studies of patients with a diagnosis of active AAV. AAV is defined as the following categories according to the Chapel Hill Consensus Conference 2012 classification method: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss syndrome).²⁶ In addition, single organ damage AAV (eg, renal limited vasculitis (RLV) or idiopathic rapidly progressive glomerulonephritis (RPGN)) can be considered the fourth entity, although in practice it eventually corresponds to the kidney-limited form of MPA or GPA.²⁷

Eligible studies are defined as comparing two or more doses of GC in patients with AAV during induction of remission, regardless of the use of other therapies. Other therapies include, but are not limited to cyclophosphamide, azathioprine, rituximab, methotrexate, mycophenolate mofetil and plasma exchange. We included only RCTs. Outcomes of interest included death, ESKD, serious infections, serious adverse events other than serious infection, sustained remission and any other patient-important outcomes. The time point for the outcome assessment depends on what was specified in individual studies.

Data sources and searches

A professional medical librarian developed a literature search strategy and searched Medline, Embase, Clinicaltrials.gov and Cochrane Central Register of Controlled Trials (CENTRAL) for relevant studies from the inception to 10 April 2020 with no restriction on language. Appendix 2 presents the literature search strategies and results. We also reviewed the reference lists of included studies for additional references. Pairs of reviewers (YX, JD, TB, MA) independently screened titles and abstracts, and reviewed the full texts of potentially eligible studies to determine the final eligible studies. Disagreements were resolved by discussion. To ensure the validity and consistency of the process, we provided reviewers with review instruction and conducted calibration exercises before the formal start of each process.

Data extraction and risk of bias assessment

We collected data through a predesigned excel extraction form. Pairs of reviewers (YX, JD, TB, MA) extracted data independently. We resolved disagreements by discussion. For each eligible study, we collected the following: country/region, design of the study, patient characteristics (mean age, sex and disease diagnosis), treatment strategy, outcomes and measures, and follow-up duration. Pair of reviewers (YX, JD, TB, MA) independently assessed the risk of bias of each RCT using a revised Cochrane risk of bias tool that includes sequence generation, concealment of allocation, blinding (participants, personnel, and outcome assessors), loss to follow-up, selective outcome reporting and other potential sources of bias.²⁸ The reviewers judged each criterion as definitely or probably low risk of bias, or probably or definitely high risk of bias.

Data synthesis or analysis, and grading of evidence

If data permitted, we planned to conduct meta-analysis for each of the outcomes. For continuous outcomes, we planned to use inverse variance statistical method to calculate mean difference (MD) and 95% confidence interval (CI). For binary outcomes, we would use the Mantel–Haenszel statistical method to calculate risk ratio (RR) and 95% CI. We planned to conservatively use a priori random effects model assuming a great variability in treatment effects across the study. We planned to use the I^2 statistic to assess statistical heterogeneity. And when the effect-estimated I^2 value is >30%, we would attempt to determine the reason for the heterogeneity. Subgroups would depend on the outcomes of the included studies report. We planned to check the funnel plot for potential publication bias if the number of eligible studies in the analysis exceeded ten. We set significance at $P=0.05$ and would use RevMan version 5.3 for all statistical analyses.

We used the GRADE approach²⁹ to assess the quality of evidence at outcome level by two reviewers (LZ and YX). We focused on the grading of the following outcomes after our team discussion: death, ESKD, serious infections at one year, serious adverse

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3 events, and health-related quality of life. Disagreements were resolved by discussion
4 or through a third reviewer (GHG) adjudication. Randomized controlled trials started
5 as high quality. We summarized the quality of evidence in GRADE summary of
6 findings using the MAGICapp platform.^{30,31}
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10 11 12 13 **Results**

14 15 **Literature search**

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17 The search yielded, after removal of duplicates, 3912 records, 38 of which were
18 considered for full-text review. The PRISMA flow chart (Figure 1), presents the
19 reasons for excluding studies at the stage of full text screening. Ultimately, two RCTs
20 met the inclusion criteria.^{18,24} The full text of one of the two RCTs¹⁸ was published
21 after our initial submission of this systematic review. We updated our results after the
22 full text was published.
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31 32 **Included studies**

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34 The RCT by Walsh et al²⁴ was a multicenter trial including 704 patients with severe
35 AAV at 95 centers in 16 countries (median duration of follow-up 2.9 years). This
36 study was a 2-by-2 factorial design and compared the efficacy of plasma exchange
37 with or without plasma exchange for AAV, as well as the efficacy of a reduced-dose
38 regimen and a standard-dose regimen of GC over the first 6 months of the treatment
39 period. The two regimens of oral GC, specifically, patients in the reduced-dose
40 regimen and standard-dose regimen received the same treatment in the first week —
41 the dose was determined according to the patients' weight (50.0 mg/<50 kg, 60.0
42 mg/50 to 75 kg, 75.0 mg/> 75 kg). The reduced-dose regimen and the standard-dose
43 regimen began to decrease gradually in the second and third weeks, respectively.
44 Finally, at 6th months, the cumulative dose of oral GC in the reduced-dose regimen
45 was less than 60% of the standard-dose regimen. (Table 1)
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58 The RCT by Furuta et al¹⁸ was a multicenter trial enrolling 140 patients with newly
59 diagnosed AAV at 34 centers in Japan (with a follow-up of 6 months). This trial
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3 evaluated whether a low-dose GC regimen (initial dose at 0.5 mg/kg/day) is non-
4 inferior to a high-dose regimen (initial dose at 1.0 mg/kg/day) in efficacy when
5 combined with rituximab for the treatment of AAV. In the low-dose group,
6 prednisolone was discontinued at 5 months, while in the high-dose group,
7 prednisolone was reduced to 10.0 mg/ day until 6 months. (Table 1)
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Table 1: Characteristics of studies originally planned to be included

Author, Year	Name of the study (ClinicalTrials.gov number)	Country	Study design	Intervention and comparison (No. of patients) *	Patients	Outcomes
Walsh et al. (2020) ²⁴	PEXIVAS (NCT00987389)	Multiple countries	Phase III, randomized, open label, 704 patients	Intervention: reduced-dose GC therapy (initial dose : 50-75mg; maintenance dose continues at 5mg/day from the end of week 23 until at least week 52; accumulative dose less than 60% of the standard)	353 patients with severe AAV (mean age 63 years, 44% female)	Primary outcome: a composite of death from any cause or ESKD. Secondary outcomes: death from any cause, ESKD, sustained remission, serious adverse events, serious infections within 1 year, and health-related quality of life.
				Comparison: standard-dose GC therapy (initial dose : 50-75mg; maintenance dose continues at 5mg/day from the end of week 23 until at least week 52)	351 patients with severe AAV (mean age 63 years, 43% female)	
Furuta et al. (2021) ¹⁸	LoVAS (NCT02198248)	Japan, multicentric	Phase IV, randomized, open label, 140 patients	Intervention : low-dose GC treatment (initial dose : 0.5mg/kg/day; discontinued at 5 months)	70 patients with new diagnosis of AAV (median age: 73; 43% female)	Primary outcome: remission rate at 6 months. Secondary outcomes: time to remission, death, relapse, ESKD and the first serious adverse event, proportion of death, relapse and ESKD

				Comparison : high-dose GC treatment (initial dose : 1mg/kg/day; reduced to 10mg/day by 5 months)	70 patients with new diagnosis of AAV (median age: 74; 37% female)	for efficacy at 6 months.
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* : Although these two trials are comparisons of different doses of glucocorticoids, the regimens are different, and the details are in the text.

AAV: antineutrophil cytoplasmic antibodies associated vasculitis; Gcs: glucocorticoids. ESKD: end-stage kidney disease.

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Risk of bias

Both trials were open-label trials and patients and investigators were aware of the group assignments due to the complexity of the GC regimen. However, the recorded treatment adherence, lack of available co-interventions, and objective, easily ascertained nature of the outcomes, the lack of blinding may have introduced minimal bias. Considering the low risk of bias in the other domains this trial, both trials were at low overall risk of bias (Appendix 3).

Effect of Interventions

Due to the heterogeneity in the population and in the regimens of glucocorticoids between the two trials, we descriptively presented the two trials and did not combine the results using meta-analysis. Since the results of the Walsh's study²⁴ showed no interaction between the GC regimen and the plasma exchange, we only focus on the use of GC in conjunction with the purpose of this review.

Appendix 4 summarizes the GRADE summary of findings for these two trials. Compared with standard-dose regimen, reduced-dose regimen of GC may reduce death (risk difference [RD]: from -1.7% to -2.1%, low certainty), while not increasing ESKD (RD: from -1.5% to 0.4%, moderate certainty). Results showed that the rate of serious infection at 6 months to 1 year in the reduced-dose regimen tended to be lower than in the standard-dose regimen (RD: from -12.8% to -5.9%, moderate certainty). As one trial showed reduced-dose regimen might increase the risk of serious adverse events (RD: 3.1%, 95% CI -3.7% to 11.2%) while another trial showed reduced-dose regimen might reduce the risk (RD: -18.1%, 95% CI -33% to 3.2%), we are uncertain about the effect of reduced-dose regimen on serious effect (Very low certainty). Reduced-dose regimen of glucocorticoids probably has trivial or no effect in disease remission, relapse or health related quality of life (Moderate to high certainty).

Discussion

After full text screening, we identified 2 studies^{18,24} involving 844 patients that met our selection criteria for studies comparing different doses regimens of GC for the treatment of AAV. According to this systematic review, the results of the absolute effects of low certainty of evidence showed that reduced-dose regimen of GC may reduce death at a follow-up from 6 months to longer than 1 year, while not increasing the rate of ESKD (moderate certainty) among patients with AAV when compared with standard-dose regimen. However, due to the wide CIs, the absolute effects of any intervention on these two outcomes were minimal, and the results were not significantly different. This may be due to the fact that the improvement of the disease by other treatments may mask the benefits of reduced-doses regimen.

In addition, relative to the standard-dose regimen, moderate certainty of evidence indicated that the reduced-dose regimen probably has an important reduction in serious infections at 6 months to 1 year (moderate certainty) This study showed that reduced-dose regimen does have an obvious advantage in reducing infections, which echoes previous studies.^{17,32} For example, Jayne et al. reported that when high-dose GC was used, infection was most common in the first 6 months of treating severe renal vasculitis.¹⁷ Therefore, considering that the most common cause of death more than one year after diagnosis of AAV is infection or uncontrolled vasculitis,^{16,33,34,35} this is particularly important to support the practice of the conclusion of this study.

We are, however, uncertainty about the effect of the reduced dose regimen on other serious adverse events. While Furuta et al's trial showed a significant reduction in serious adverse events by reduced-dose regimen,¹⁸ Walsh et al's trial showed the reduced-dose regimen might increase the risk with a wide CI.²⁴ In Walsh et al's trial, although the reduced-dose regimen group had more renal/urinary adverse events than the standard-dose regimen, there was no significant difference in the incidence of ESKD between the two regimen groups as described above. This may be related to the treatment status of the included patients. Among the patients included in the study, the number of patients in the standard-dose regimen who had undergone dialysis before the start of the trial was more than that in the reduced-dose regimen.

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6 The use of GC transformed AAV from an almost uniformly fatal condition to one
7 characterized by remissions and relapses complicated by drug-induced adverse events.
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9 Despite the ubiquitous use of GC for AAV, there was no standardization of dose
10 regimens, guidelines were ambiguous and practice patterns varied substantially. The
11 two trials ^{18,24} supported the important role GC plays in causing adverse events and
12 highlights the need to optimize their use. Although the two trials found evidence to
13 support one regimen of GC over another, further research is needed to determine
14 whether the GC regimen can be further improved for the treatment of AAV.
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22 The advantages of this systematic review include a comprehensive search of emerging
23 and past evidence across databases without being restricted by study design or
24 publication language, and the use of GRADE approach to assess the quality of
25 evidence. Decisions regarding eligible studies, data extraction, and risk of bias
26 assessments were all performed in duplicate, and calibration exercises were conducted
27 before the formal start of the project. By excluding non-RCT studies, we limited the
28 risk of bias. The RCTs we included are of sound methodological quality. AAV is a
29 rare disease, and the PEXIVAS trial is the largest global trial on the subject so far
30 which has improved the generalizability of the results through the efforts of national
31 and international vasculitis networks and extensive selection criteria.
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43 The results of our systematic review also have some limitations. First, only two trials
44 were included and although they were broadly inclusive and contained more events
45 than any other trial in this disease, the total statistical information remains low. This is
46 particularly obvious for serious adverse events other than serious infection. However,
47 the reduced-dose GC regimen should not result in more treatment related adverse
48 events (i.e. it is illogical that a lower exposure to GC would have anything but the
49 same or lower rate of GC caused side effects) and there is reasonable precision around
50 the efficacy outcomes. This limitation is expected to result in an underappreciation of
51 the benefits of reducing the GC dose, a limitation that is supported by observational
52 studies of GC which suggest reducing GC exposure may also reduce fractures, peptic
53 ulcer disease, psychiatric disease, weight gain and dysglycemia. In addition, despite
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3 the excellent methodological quality of the included trial, this is an open label and is
4 subject to biases despite our relative confidence that differential treatment or outcome
5 ascertainment was at low risk. Despite the large scale of this study for a rare disease,
6 the degree to which the results can be generalized to patients with non-severe AAV is
7 uncertain, although it is likely safer to extrapolate the safety of the regimen from more
8 severe illness to less severe illness rather than less severe to more severe.
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17 **Conclusion**

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19 An important general rule is that in routine clinical practice, the use of conventional
20 GC should be “as much as necessary, but as little as possible.”³⁶ Therefore, compared
21 with the standard-dose regimen, the reduced-dose regimen of GC may reduce death,
22 probably has little or no effect on ESKD among patients with AAV, and resulted in a
23 lower risk of serious infections at 6 months to 1 year. Future clinical trials should
24 evaluate whether GC dosing can be further safely reduced.
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33 critical feedback on outcome and subgroup selection, GRADE judgments, and
34 manuscript feedback.
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39 performed the literature search. YX, JD, TB and MA performed the screening, data
40 abstraction, and risk of bias assessments. YX, LZ and MW performed the data
41 analysis. YX, GHG, LZ, RS, DJ, PM and MW interpreted the data. YX, GHG and LZ
42 performed the certainty assessment. YX, GHG, LZ and MW drafted the manuscript.
43 All authors critically revised the manuscript. All authors approved the final version of
44 the manuscript. YX and MW had full access to the data in the study and takes
45 responsibility for the integrity of the data and the accuracy of the data analysis. YX
46 and MW are the guarantors.
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56

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58 Ethical approval statement: Not required.
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3 Patient consent statement: Not required.

4
5 Provenance and peer review statement: Not commissioned; externally peer reviewed.

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7 Data sharing statement: No data are available.

8
9 Transparency statement: YX and MW affirm that the manuscript is an honest,
10 accurate, and transparent account of the recommendation being reported; that no
11 important aspects of the recommendation have been omitted; and that any
12 discrepancies from the recommendation as planned (and, if relevant, registered) have
13 been explained.
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References

1. Houben E, Penne EL, Voskuyl AE, et al.. Cardiovascular events in anti-neutrophil cytoplasmic antibody-associated vasculitis: a meta-analysis of observational studies. *Rheumatology (Oxford)* 2018;57(3):555-562.
2. Bosch X, Guilabert A, Font J. Antineutrophil cytoplasmic antibodies. *Lancet* 2006;368(9533):404-41816876669.
3. Wallace ZS, Miloslavsky EM. Management of ANCA associated vasculitis. *BMJ* 2020;368:m421.
4. Jennette JC, Falk RJ. Pathogenesis of antineutrophil cytoplasmic autoantibody-mediated disease. *Nat Rev Rheumatol* 2014;10:463-73.
5. Salvador F. ANCA Associated Vasculitis. *Eur J Intern Med* 2020;74:18-28.
6. Smith RM. Update on the treatment of ANCA associated vasculitis. *Presse Med* 2015;44(6 Pt 2):e241-9.
7. Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992;116:488-98.
8. Walsh M, Merkel PA, Peh CA, et al.; PEXIVAS Investigators. Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis (PEXIVAS): protocol for a randomized controlled trial. *Trials* 2013;14:73.
9. Keller SF, Miloslavsky EM. Corticosteroids in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. *Rheum Dis Clin North Am* 2016;42(1):91-101.
10. Booth AD, Almond MK, Burns A, et al., Pan-Thames Renal Research Group. Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. *Am J Kidney Dis* 2003; 41(4):776-84.
11. Jennette JC, Falk RJ. Small-vessel vasculitis. *N Engl J Med* 1997;337(21):1512-23.
12. Lally L, Spiera R. Current landscape of antineutrophil cytoplasmic antibody-associated vasculitis: classification, diagnosis, and treatment. *Rheum Dis Clin North Am* 2015;41(1):1-19, vii.
13. Stahn C, Buttgerit F. Genomic and nongenomic effects of glucocorticoids. *Nat Clin Pract Rheumatol* 2008;4:525-33.
14. Walton EW. Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). *Br Med J* 1958;2:265-70.
15. de Groot K, Harper L, Jayne DR, et al. Pulse versus daily oral cyclophosphamide for induction of

1
2
3 remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern*
4 *Med* 2009;150:670–80.

5
6 16. De Groot K , Rasmussen N , Bacon PA , et al . Randomized trial of cyclophosphamide versus
7 methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-
8 associated vasculitis. *Arthritis Rheum* 2005;52:2461–9.

9
10 17. Jayne DR , Gaskin G , Rasmussen N , et al . Randomized trial of plasma exchange or high-dosage
11 methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol* 2007;18:2180–
12 8.

13
14 18. Furuta S, Nakagomi D, Kobayashi Y, et al. Effect of Reduced-Dose vs High-Dose
15 Glucocorticoids Added to Rituximab on Remission Induction in ANCA-Associated Vasculitis: A
16 Randomized Clinical Trial. *JAMA*. 2021;325(21):2178–2187.

17
18 19. Keller SF, Miloslavsky EM. Corticosteroids in Antineutrophil Cytoplasmic Antibody-Associated
19 Vasculitis. *Rheum Dis Clin North Am* 2016;42(1):91-101.

20
21 20. Flossmann O , Berden A , de Groot K , et al . Long-term patient survival in ANCA-associated
22 vasculitis. *Ann Rheum Dis* 2011;70:488–94.

23
24 21. Furuta S , Chaudhry AN , Hamano Y , et al . Comparison of phenotype and outcome in microscopic
25 polyangiitis between Europe and Japan. *J Rheumatol* 2014;41:325–33.

26
27 22. Walsh M , Merkel PA , Mahr A , et al . Effects of duration of glucocorticoid therapy on relapse rate
28 in antineutrophil cytoplasmic antibody-associated vasculitis: a meta-analysis. *Arthritis Care Res*
29 2010;62:1166–73.

30
31 23. Wada T , Hara A , Arimura Y , et al . Risk factors associated with relapse in Japanese patients with
32 microscopic polyangiitis. *J Rheumatol* 2012;39:545–51.

33
34 24. Walsh M, Merkel PA, Peh CA, et al. Plasma Exchange and Glucocorticoids in Severe ANCA-
35 Associated Vasculitis. *N Engl J Med* 2020;382(7):622-631.

36
37 25.

38
39 Moher D, Liberati A, Tetzlaff J, et al.; PRISMA Group. Preferred reporting items for systematic
40 reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006-12.

41
42 26. Salvador F. ANCA associated vasculitis. *Eur J Intern Med* 2020;74:18-28.

43
44 27. Pagnoux C. Updates in ANCA-associated vasculitis. *Eur J Rheumatol* 2016;3(3):122-133.

45
46 28. Guyatt G, Busse JW. Risk of bias in randomized trials. *GROWTH Evidence*; 2016. Available:
47 <https://growthevidence.com/gordon-h-guyatt-md-msc-and-jason-w-busse-dc-phd> (accessed 2020 April.
48 6).

49
50 29. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence
51 profiles and summary of findings tables. *J Clin Epidemiol* 2011; 64: 383-94.

52
53 30. Guyatt GH, Oxman AD, Santesso N, et al. GRADE guidelines: 12. Preparing summary of findings
54 tables-binary outcomes. *J Clin Epidemiol* 2013;66:158-72.

55
56 31. Guyatt GH, Thorlund K, Oxman AD, et al. GRADE guidelines: 13. Preparing summary of findings
57 tables and evidence profiles-continuous outcomes. *J Clin Epidemiol* 2013;66:173-83.

58
59 32. Illei GG, Yarboro CH, Kuroiwa T, et al.. Long-term effects of combination treatment with
60 fludarabine and low-dose pulse cyclophosphamide in patients with lupus nephritis. *Rheumatology*
(Oxford) 2007;46:952–956.

33. Flossmann O, Berden A, de Groot K, et al., European Vasculitis Study Group. Long-term patient
survival in ANCA-associated vasculitis. *Ann Rheum Dis* 2011;70:488-94.

- 1
2
3 34. Jones RB, Tervaert JWC, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-
4 associated renal vasculitis. *N Engl J Med* 2010;363(3):211-20.
5
6 35. Jayne D, Rasmussen N, Andrassy K, et al.; European Vasculitis Study Group: A randomized trial
7 of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N*
8 *Engl J Med* 349 : 36 –44, 2003.
9
10 36. Buttgeit F, Burmester GR, Lipworth BJ. Optimised glucocorticoid therapy: the sharpening of an
11 old spear. *Lancet* 2005;365(9461):801-3.
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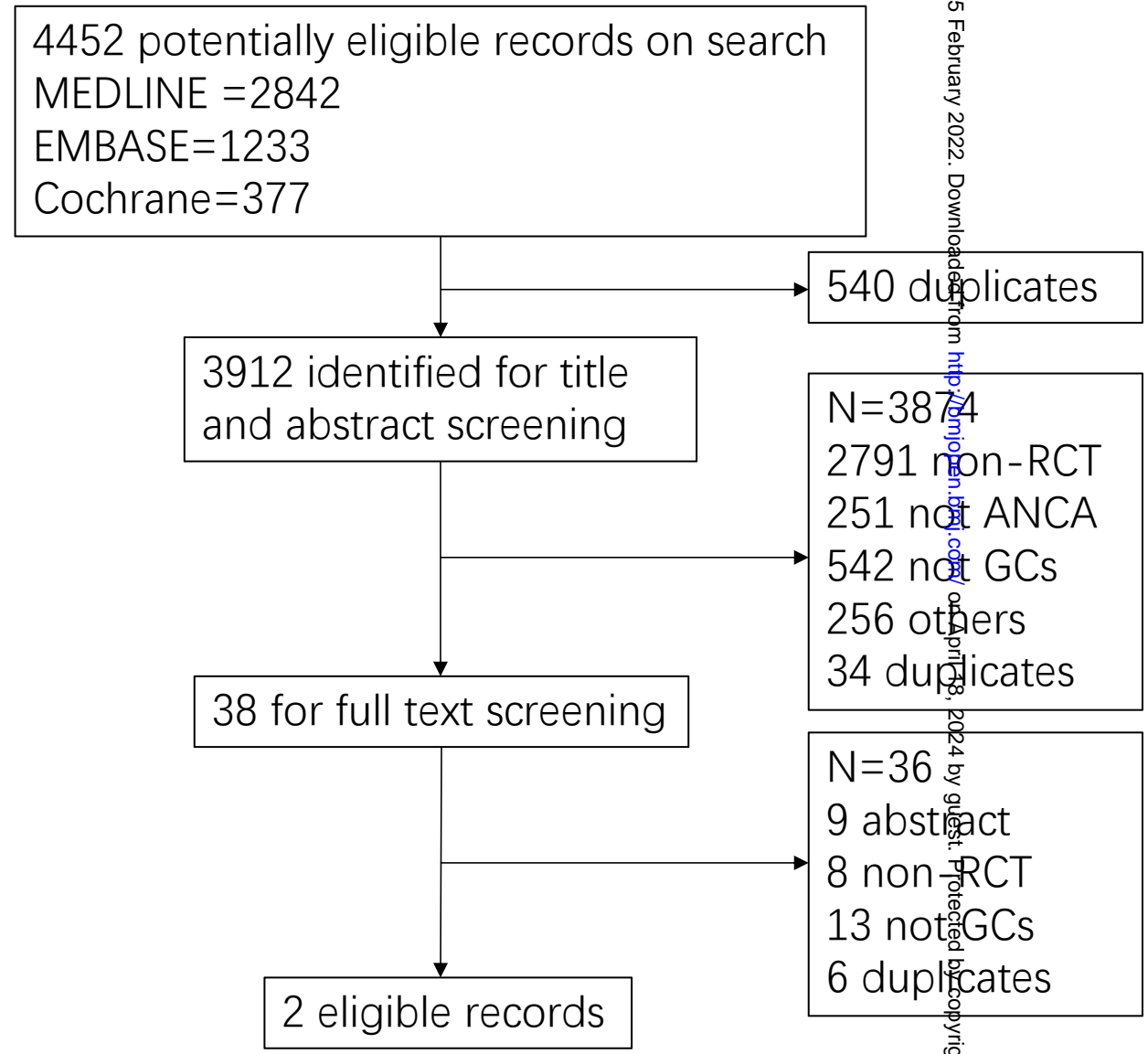
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Identification

Screening

Eligibility

Included





PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1-2
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.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
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.	6
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.	7
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.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
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).	8
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.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
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).	8
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.	8



PRISMA 2009 Checklist

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).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
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.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICCO, follow-up period) and provide the citations.	9-12
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).	13
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.	9-12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13-17
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13-17
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13-17
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).	18-19
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).	19-20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
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).	21

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Appendix 2: Search strategies and results for The comparative efficacy and safety of alternative glucocorticoids regimens in patients with ANCA-associated vasculitis: A systematic review

Database	No of records
MEDLINE	2842
EMBASE	1233
Cochrane Library	377
Subtotal	4452
-duplicates	-540
Total	3912

Database: OVID MEDLINE

-
- 1 Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis/ (1682)
 - 2 Churg-Strauss Syndrome/ (2090)
 - 3 Microscopic Polyangiitis/ (507)
 - 4 Granulomatosis with Polyangiitis/ (6902)
 - 5 (vasculit* adj3 (ANCA or AAV or antineutrophil or anti-neutrophil or cytoplasm* or RLV or renal or churg or strauss or pauci immune)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (4968)
 - 6 churg strauss.mp. (2876)
 - 7 ((angiit* or vasculit*) adj3 (granulom* or necrot* or allergic)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (4297)
 - 8 ((polyangiit* or polyarterit*) adj3 (microscop* or MPA or granulom*)).mp. (9268)
 - 9 wegener*.mp. (6572)
 - 10 (glomerulonephrit* adj3 necrot*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (797)
 - 11 or/1-10 (18126)
 - 12 exp Glucocorticoids/ (190619)
 - 13 prednisolone/ or methylprednisolone/ (49855)
 - 14 Prednisone/ (39084)
 - 15 Adrenal Cortex Hormones/ (63823)

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4 16 (corticosteroid* or glucocorticoid* or methylprednisolon* or prednison* or
5 prednisolon*).mp. [mp=title, abstract, original title, name of substance word, subject
6 heading word, floating sub-heading word, keyword heading word, organism
7 supplementary concept word, protocol supplementary concept word, rare disease
8 supplementary concept word, unique identifier, synonyms] (283874)
9 17 Corticosterone/ or corticosteron*.mp. (34191)
10 18 Hydrocortisone/ or hydrocortison*.mp. (76765)
11 19 Cortisone/ or cortison*.mp. (23710)
12 20 steroids.mp. or Steroids/ (112972)
13 21 Cortodoxone/ or cortodoxon*.mp. (856)
14 22 Hydroxycorticosteroids/ or hydroxycorticosteroid*.mp. (6731)
15 23 Dexamethasone/ or dexamethason*.mp. (71052)
16 24 adrenocorticosteroid*.mp. (313)
17 25 adrenocorticoid*.mp. (177)
18 26 corticoid*.mp. (6458)
19 27 or/12-26 (547377)
20 28 11 and 27 (4782)
21 29 randomized controlled trial.pt. (503644)
22 30 controlled clinical trial.pt. (93611)
23 31 randomized.ab. (475606)
24 32 placebo.ab. (206694)
25 33 drug therapy.fs. (2193818)
26 34 randomly.ab. (330775)
27 35 trial.ab. (501000)
28 36 groups.ab. (2031658)
29 37 or/29-36 (4675601)
30 38 exp animals/ not humans.sh. (4689197)
31 39 37 not 38 (4053127)
32 40 28 and 39 (2842)

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40 Database: EMBASE

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43 1 ANCA associated vasculitis/ (5871)
44 2 Churg Strauss syndrome/ (4947)
45 3 microscopic polyangiitis/ (3039)
46 4 Wegener granulomatosis/ (12860)
47 5 (vasculit* adj3 (ANCA or AAV or antineutrophil or anti-neutrophil or cytoplasm*
48 or RLV or renal or churg or strauss or pauci immune)).mp. [mp=title, abstract,
49 heading word, drug trade name, original title, device manufacturer, drug
50 manufacturer, device trade name, keyword, floating subheading word, candidate
51 term word] (9651)
52 6 churg strauss.mp. (5425)
53 7 ((angiit* or vasculit*) adj3 (granulom* or necrot* or allergic)).mp. [mp=title,
54 abstract, heading word, drug trade name, original title, device manufacturer, drug
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 3 manufacturer, device trade name, keyword, floating subheading word, candidate
 4 term word] (7160)
 5 8 ((polyangiit* or polyarterit*) adj3 (microscop* or MPA or granulom*)).mp.
 6 [mp=title, abstract, heading word, drug trade name, original title, device
 7 manufacturer, drug manufacturer, device trade name, keyword, floating subheading
 8 word, candidate term word] (7171)
 9 9 wegener*.mp. (14257)
 10 10 (glomerulonephrit* adj3 necrot*).mp. [mp=title, abstract, heading word, drug
 11 trade name, original title, device manufacturer, drug manufacturer, device trade
 12 name, keyword, floating subheading word, candidate term word] (1243)
 13 11 or/1-10 (29983)
 14 12 exp glucocorticoid/ (700322)
 15 13 prednisolone/ (122582)
 16 14 methylprednisolone/ (93152)
 17 15 prednisone/ (167298)
 18 16 corticosteroid/ (229322)
 19 17 (corticosteroid* or glucocorticoid* or methylprednisolon* or prednison* or
 20 prednisolon*).mp. [mp=title, abstract, heading word, drug trade name, original title,
 21 device manufacturer, drug manufacturer, device trade name, keyword, floating
 22 subheading word, candidate term word] (688798)
 23 18 corticosterone/ or corticosteron*.mp. (38497)
 24 19 hydrocortisone/ or hydrocortison*.mp. (135041)
 25 20 cortisone/ or cortison*.mp. (17205)
 26 21 steroids.mp. or steroid/ (245681)
 27 22 cortodoxone/ or cortodoxon*.mp. (2044)
 28 23 hydroxycorticosteroid*.mp. or hydroxycorticosteroid/ (2310)
 29 24 dexamethasone/ or dexamethason*.mp. (161446)
 30 25 adrenocorticosteroid*.mp. (286)
 31 26 adrenocorticoid*.mp. (169)
 32 27 corticoid*.mp. (7745)
 33 28 or/12-27 (1111323)
 34 29 11 and 28 (13676)
 35 30 randomized controlled trial/ (598366)
 36 31 Controlled clinical study/ (463908)
 37 32 random\$.ti,ab. (1520687)
 38 33 randomization/ (86548)
 39 34 intermethod comparison/ (258594)
 40 35 placebo.ti,ab. (303776)
 41 36 (compare or compared or comparison).ti. (505122)
 42 37 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or
 43 compared or comparing or comparison)).ab. (2085158)
 44 38 (open adj label).ti,ab. (78322)
 45 39 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
 46 (230181)
 47 40 double blind procedure/ (171296)
 48 41 parallel group\$.ti,ab. (25234)

42 (crossover or cross over).ti,ab. (104111)
 43 ((assign\$ or match or matched or allocation) adj5 (alternate or group\$1 or
 44 intervention\$1 or patient\$1 or subject\$1 or participant\$1)).ti,ab. (326088)
 45 (assigned or allocated).ti,ab. (383843)
 46 (controlled adj7 (study or design or trial)).ti,ab. (343989)
 47 (volunteer or volunteers).ti,ab. (244774)
 48 human experiment/ (490852)
 49 trial.ti. (296188)
 50 or/30-48 (4957675)
 29 and 49 (1233)

Database: Cochrane Library

ID	Search Hits
#1	MeSH descriptor: [Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis] explode all trees 157
#2	MeSH descriptor: [Churg-Strauss Syndrome] explode all trees 27
#3	MeSH descriptor: [Microscopic Polyangiitis] explode all trees 40
#4	MeSH descriptor: [Granulomatosis with Polyangiitis] explode all trees 82
#5	vasculit* near/3 (ANCA or AAV or antineutrophil or anti-neutrophil or cytoplasm* or RLV or renal or churg or strauss or pauci immune) 470
#6	churg strauss 112
#7	((angiit* or vasculit*) near/3 (granulom* or necrot* or allergic)) 102
#8	((polyangiit* or polyarterit*) near/3 (microscop* or MPA or granulom*)) 277
#9	wegener* 394
#10	(glomerulonephrit* near/3 necrot*) 13
#11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 867
#12	MeSH descriptor: [Glucocorticoids] explode all trees 4445
#13	MeSH descriptor: [Prednisolone] explode all trees 4804
#14	MeSH descriptor: [Methylprednisolone] explode all trees 2679
#15	MeSH descriptor: [Prednisone] explode all trees 3909
#16	MeSH descriptor: [Adrenal Cortex Hormones] explode all trees 14135
#17	corticosteroid* or glucocorticoid* or methylprednisolon* or prednison* or prednisolon* 41757
#18	MeSH descriptor: [Corticosterone] explode all trees 38
#19	MeSH descriptor: [Hydrocortisone] explode all trees 5886
#20	MeSH descriptor: [Cortisone] explode all trees 143
#21	MeSH descriptor: [Steroids] explode all trees 57500
#22	MeSH descriptor: [Cortodoxone] explode all trees 30
#23	MeSH descriptor: [Cortodoxone] explode all trees 30
#24	MeSH descriptor: [Hydroxycorticosteroids] explode all trees 7002
#25	MeSH descriptor: [Dexamethasone] explode all trees 4409

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3 #26 corticosteron* or hydrocortison or cortison* or steroids or cortodoxon* or
4 hydroxycorticosteroid* or dexamethason* or adrenocorticosteroid* or
5 adrenocorticoid* or corticoid* 22688
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Appendix 3 Risk of Bias assessment for outcomes of included RCTs

Outcomes of Trials	Sequence generation	Allocation concealment	Blinding (patients)	Blinding (health care providers)	Blinding (outcome assessors)	Blinding (data collectors)	Blinding (data analyst)	Loss to follow-up
Walsh et al. 2020								
Death	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
	Low	Low	Low	Low	Low	Low	Low	Low
ESKD	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
	Low	Low	Low	Low	Low	Low	Low	Low
Remission	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
	Low	Low	Low	Low	Low	Low	Low	Low
Serious adverse events	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
	Low	Low	Low	Low	Low	Low	Low	Low
Serious infections	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
	Low	Low	Low	Low	Low	Low	Low	Low
Health-related quality of life	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
	Low	Low	Low	Low	Low	Low	Low	Low
Furuta et al. 2021								
Death	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
	Low	Low	Low	Low	Low	Low	Low	Low
ESKD	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
	Low	Low	Low	Low	Low	Low	Low	Low
Remission	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
	Low	Low	Low	Low	Low	Low	Low	Low
Relapse	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
	Low	Low	Low	Low	Low	Low	Low	Low
Serious adverse events	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
	Low	Low	Low	Low	Low	Low	Low	Low
Serious infections	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
	Low	Low	Low	Low	Low	Low	Low	Low
Health-related quality of life	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
	Low	Low	Low	Low	Low	Low	Low	Low

ESKD: end-stage kidney disease; RCT: randomized controlled trial.

Appendix 4 GRADE summary of findings on the use of reduced-dose regimen versus standard-dose regimen of glucocorticoids in patients with ANCA-associated vasculitis

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard-dose regimen of glucocorticoids Reduced-dose regimen of glucocorticoids	Certainty of the Evidence (Quality of evidence)	Plain text summary
Death	Based on data from 838 patients in 2 study Follow up: 6 months to 2.9 years	Two RCTs reported death from any cause. In Walsh et al's trial, death occurred in 46 of 353 patients (13.0%) in the reduced-dose GC therapy group and in 53 of 351 patients (15.1%) in the standard-dose GC therapy group (Risk difference, -2.1%; 95% confidence interval, -6% to 3.6%). In Furuta et al's trial, death occurred in 2 of 69 patients (2.9%) in the reduced-dose GC treatment group and in 3 of 65 patients (4.6%) in the high-dose GC treatment group (Risk difference, -1.7%; 95% confidence interval, -4.7% to 8.2%).	Low Due to very serious imprecision ¹	Reduced dose of glucocorticoids may reduce death at follow-up of 6 months to 2.9 years
End-stage kidney disease	Based on data from 838 patients in 2 study Follow up: 6 months to 2.9 years	Two RCTs reported end-stage kidney disease. In Walsh et al's trial, end-stage kidney disease occurred in 70 of 353 patients (19.8%) in the reduced-dose GC therapy group and in 68 of 351 patients (19.4%) in the standard-dose GC therapy group (Risk difference, 0.4%; 95% confidence interval, -4.7%	Moderate Due to serious imprecision ²	Reduced dose of glucocorticoids probably has little or no effect on end-stage kidney disease at follow-up of 6 months to 2.9 years

		<p>to 7.4%). In Furuta et al's trial, end-stage kidney disease occurred in none of 69 patients (0%) in the reduced-dose GC treatment group and in 1 of 65 patients (1.5%) in the high-dose GC treatment group (Risk difference, -1.5; 95% confidence interval, -4.5 to 1.5).</p>		
<p>Remission</p>	<p>Based on data from 838 patients in 2 study Follow up: 6 months to 2.9 years</p>	<p>Two RCTs reported remission rate. In Walsh et al's trial, remission was analyzed in the two GC groups with the use of Cox proportional-hazards models resulting a hazard ratio of 1.04 (95% confidence interval, 0.81 to 1.33). In Furuta et al's trial, remission occurred in 49 of 69 patients (71.0%) in the reduced-dose GC treatment group and in 45 of 65 patients (69.2%) in the high-dose GC treatment group (Risk difference, 1.8%; 97.5% confidence interval, -13% to ∞).</p>	<p>Moderate Due to serious imprecision¹</p>	<p>Reduced dose of glucocorticoids probably has little or no effect on disease remission at follow-up of 6 months to 2.9 years</p>
<p>Relapse</p>	<p>Based on data from 838 patients in 2 study Follow up: 6 months to 2.9 years</p>	<p>Two RCTs reported remission rate. In Walsh et al's trial, relapse occurred in 32 of 353 patients (9.1%) in the reduced-dose GC therapy group and in 23 of 351 patients (6.6%) in the standard-dose GC therapy group (Risk difference, 2.5%; 95% confidence interval, -1.45% to 6.47%). In Furuta et al's trial, relapse occurred in 3</p>	<p>Moderate Due to serious imprecision³</p>	<p>Reduced dose of glucocorticoids probably has little or no effect on relapse in patients at follow-up of 6 months to 2.9 years</p>

		of 69 patients (4.3%) in the reduced-dose GC treatment group and in none of 65 patients (0%) in the high-dose GC treatment group (Risk difference, 4.4%; 95% confidence interval, -0.5% to 9.2%).		
19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47	Serious adverse events Based on data from 838 patients in 2 study Follow up: 6 months to 1 year	Two RCTs reported serious adverse events. In Walsh et al's trial, serious adverse events occurred in 230 of 353 patients (65.2%) in the reduced-dose GC therapy group and in 218 of 351 patients (62.1%) in the standard-dose GC therapy group (Risk difference, 3.1%; 95% confidence interval, -3.7% to 11.2%). In Furuta et al's trial, serious adverse events occurred in 13 of 69 patients (18.8%) in the reduced-dose GC treatment group and in 24 of 65 patients (36.9%) in the high-dose GC treatment group (Risk difference, -18.1%; 95% confidence interval, -33.0% to -3.2%).	Very Low Due to serious imprecision ⁴ Due to very serious inconsistency	We are uncertain whether reduced dose of glucocorticoids increases or reduce the risk of serious adverse events at 6 months to 1 year
48 49 50 51 52 53 54 55 56 57 58 59 60	Serious infections Based on data from 838 patients in 2 study Follow up: 6 months to 1 year	Two RCTs reported serious infections. In Walsh et al's trial, serious infections occurred in 230 of 353 patients (27.1%) in the reduced-dose GC therapy group and in 218 of 351 patients (33.0%) in the standard-dose GC therapy group (Risk difference, -5.9%;	Moderate Due to serious imprecision ³	Reduced dose of glucocorticoids probably reduces the risk of serious infections at 6 months to 1 year

		<p>95% confidence interval, -11.2% to 1.0%). In Furuta et al's trial, serious infections occurred in 5 of 69 patients (7.2%) in the reduced-dose GC treatment group and in 13 of 65 patients (20.0%) in the high-dose GC treatment group (Risk difference, -12.8%; 95% confidence interval, -24.2% to -1.3%).</p>		
<p>Health related quality of life (SF-36 PCS)</p>	<p>Measured by: SF-36 PCS Scale: - High better Based on data from 838 patients in 2 study Follow up: 6 months to 1 years</p>	<p>Two RCTs reported health related quality of life assessed by SF-36 PCS. Walsh et al's trial reported that the mean score of health related quality of life measured by SF-36PCS was 39.13 in the reduced-dose GC therapy group and 37.84 in the standard-dose GC therapy group (Mean difference, 1.29 higher; 95% confidence interval, 0.26 lower to 2.84 higher). Furuta et al's trial reported that the median score of health related quality of life measured by SF-36PCS was 38.3 (IQR : 21.1 to 47.4) in the reduced-dose GC treatment group and 31.7 (IQR : 22.0 to 49.4) in the high-dose GC treatment group (Mean difference, 6.3 higher; 95% confidence interval, 2.6 lower to 15.2 higher).</p>	<p>Moderate Due to serious imprecision</p>	<p>Reduced dose of glucocorticoids probably has little or no effect on health related quality of life (SF-36PCS) at 6 months to 1 years</p>

<p>Health related quality of life (SF-36 MCS)</p>	<p>Measured by: SF-36 MCS</p> <p>Scale: - High better</p> <p>Based on data from 838 patients in 2 study</p> <p>Follow up: 6 months to 1 years</p>	<p>Two RCTs reported health related quality of life assessed by SF-36 MCS. Walsh et al's trial reported that the mean score of health related quality of life measured by SF-36MCS was 52.16 in the reduced-dose GC therapy group and 51.19 in the standard-dose GC therapy group (Mean difference, 0.97 higher; 95% confidence interval, 0.24 lower to 2.18 higher).</p> <p>Furuta et al's trial reported that the median score of health related quality of life measured by SF-36MCS was 49.8 (IQR : 45.1 to 56.6) in the reduced-dose GC treatment group and 50.4 (IQR : 46.3 to 57.2) in the high-dose GC treatment group (Mean difference, 0.4 lower; 95% confidence interval, 4.7 lower to 4.0 higher).</p>	<p>High</p>	<p>Reduced dose of glucocorticoids has little or no effect on health related quality of life (SF-36MCS) at 6 months to 1 years</p>
<p>Health related quality of life (EQ-5D Index) at 1 year</p>	<p>Measured by: EQ-5D Index</p> <p>Scale: - High better</p> <p>Based on data from 704 patients in 1 study</p> <p>Follow up at 1 year</p>	<p>0.77 0.79</p> <p>Mean Mean</p> <p>Difference: MD 0.02 higher (CI 95% 0.01 lower - 0.05 higher)</p>	<p>Moderate</p> <p>Due to serious imprecision⁵</p>	<p>Reduced dose of glucocorticoids probably has little or no effect on health related quality of life (EQ-5D) at 1 year</p>
<p>Health related quality of life (EQ-5D Thermometer) at 1 year</p>	<p>Measured by: EQ-5D Thermometer</p> <p>Scale: - High better</p> <p>Based on data from 704 patients in 1 study</p> <p>Follow up at 1 year</p>	<p>71.07 72.11</p> <p>Mean Mean</p> <p>Difference: MD 1.04 higher (CI 95% 1.09 lower - 3.17 higher)</p>	<p>High</p>	<p>Reduced dose of glucocorticoids has little or no effect on health related quality of life (EQ-5D Thermometer) at 1 year</p>

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1. **Imprecision: Very serious.** Because the 95% CI includes both the minimally important difference for benefit (20 fewer death in 1000 patients) and minimally important difference for harm (20 more death in 1000 patients), we rated down two levels for imprecision;

2. **Imprecision: Serious.** The 95% CI crosses the minimally important difference for benefit (30 fewer ESKD in 1000 patients) and minimally important difference for harm (30 more ESKD in 1000 patients) ;

3. **Imprecision: Serious.** The 95% CI crosses the minimally important difference (50 fewer serious infections in 1000 patients);

4. **Imprecision: Serious.** The 95% CI includes an increase in serious adverse event over 10%;

5. **Imprecision: Serious.** The 95% CI crosses the minimally important difference for benefit and the minimally important difference for harm (0.03 reduction or increase in EQ-5D Index) ;

ESKD: end-stage kidney disease; SF-36 = short form 36; PCS = physical component score; MCS = mental component score; EQ = EuroQol; RR: relative risk; MD: mean difference; CI: confidence interval. IQR = interquartile range



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1-2
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.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
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.	6
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.	7
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.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
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).	8
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.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
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).	8
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.	8



PRISMA 2009 Checklist

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).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
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.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICCO, follow-up period) and provide the citations.	9-12
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).	13
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.	9-12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13-17
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13-17
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13-17
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).	18-19
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).	19-20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
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).	21

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

The comparative efficacy and safety of alternative glucocorticoids regimens in patients with ANCA-associated vasculitis: A systematic review

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Haematology (incl blood transfusion), Evidence based practice
Keywords:	HAEMATOLOGY, ORAL MEDICINE, Clinical trials < THERAPEUTICS

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3 **The comparative efficacy and safety of alternative glucocorticoids regimens in**
4 **patients with ANCA-associated vasculitis: A systematic review**
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Abstract

Objective

To compare the efficacy and safety of alternative glucocorticoids (GC) regimens as induction therapy for patients with antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis.

Design

Systematic review of randomized controlled trial (RCTs).

Data sources

Medline, Embase, Clinicaltrials.gov and Cochrane Central Register of Controlled Trials up to 10 April 2020.

Study selection and Review methods

RCTs comparing two (or more) different dose regimens of GC in ANCA-associated vasculitis during induction of remission, regardless of other therapies. Pairs of reviewers independently screened records, extracted data and assessed risk of bias. Two reviewers rated certainty of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Results

Of 3912 records identified, the full texts of two records met the eligibility criteria. Due to the heterogeneity of population and dose regimen of glucocorticoids between the two trials, we descriptively presented the two trials and did not combine the results using meta-analysis. Compared with the standard-dose regimen, the reduced-dose regimen of GC may reduce death, risk difference [RD] from -1.7% to -2.1%, low certainty), while not increasing end-stage kidney disease (ESKD) (RD: from -1.5% to 0.4%, moderate certainty). The reduced-dose regimen probably has an important reduction in serious infections at 1 year (RD: from -12.8% to -5.9%, moderate certainty). The reduced-dose regimen of glucocorticoids probably has trivial or no effect in disease remission, relapse or health related quality of life (moderate to high certainty).

Conclusions

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3 The reduced-dose regimen of GC may reduce death at the follow-up of 6 months to
4 longer than 1 year and serious infections while not increasing ESKD.
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7 **Systematic review registration**

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9 PROSPERO CRD42020179087.
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12 **Keywords:** Glucocorticoids, Anti-Neutrophil Cytoplasmic Antibody-Associated
13 Vasculitis, Systematic review
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16 Word count for the main text: 3079
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19 **Strengths and limitations of this study**

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23 - This systematic review included a comprehensive search of literatures without
24 limitation on language.
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26 - This systematic review applied GRADE approach assessing the quality of
27 evidence.
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29 - This systematic review included the largest global trial and the latest trial on the
30 subject so far that have improved the generalizability of the results through the
31 efforts of national and international vasculitis networks and extensive selection
32 criteria.
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34 - Despite the excellent methodological quality, the two eligible trials were open
35 labeled and were subject to bias.
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Introduction

Antineutrophil cytoplasmic antibodies (ANCA) -associated vasculitis (AAV) comprises a subgroup of systemic vasculitis affecting small- to medium-sized vessels, a chronic inflammatory disease of the blood vessel wall¹, and includes granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis.² Patients with AAV usually test positive for ANCA. The cause of the disease remains unclear. Genetic and environmental factors play an important role in the onset of the disease.^{3,4} The annual incidence of AAV is about 20 per million inhabitants, and the prevalence is about 100 per million inhabitants.⁵ AAV has multiple clinical manifestations, characterized by leukocytes infiltrating the vessel walls, fibrinoid necrosis, and vascular damage with occlusion or aneurysm formation.⁶ The severity of AAV varies greatly.⁷ The most common manifestation is glomerulonephritis, which leads to renal failure and alveolar capillaritis causing pulmonary hemorrhage.⁸ Previous studies have showed that untreated AAV is typically fatal⁹, with 6-month and 1-year mortality rates of 60% and 80%, respectively.¹⁰

Since the 1950s, glucocorticoids (GCs), as immunosuppressants and anti-inflammatory drugs with a fast-acting and powerful anti-inflammatory effect, became the basis of therapy for AAV.^{11,12} The main mechanism of action is genomic and non-genomic effects mediated by cytosolic GC receptors or specific and non-specific interactions with membrane-bound GC receptors resulting in reduced production of pro-inflammatory proteins (transrepression).¹³ However, monotherapy has incomplete efficacy.¹⁴ Subsequently, standard therapy emerged using the combination of high-dose GC and cyclophosphamide to achieve remission in AAV.^{15,16,17} This combination therapy proved to reduce mortality to 25% at 5 years and has high remission rates of 80% – 90%.¹⁸ In addition to cyclophosphamide, clinical remission can also be achieved with rituximab-based or methotrexate-based therapies.¹⁹ Although the combination of high-dose GC and cytotoxic drugs greatly enhances the therapeutic efficacy, high-dose GC may increase the toxicity associated with treatment. Infections and cardiovascular diseases due to the treatment are main causes of fatal side effects that reduced quality of life (QOL) in patients.^{20, 21} Previous studies

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3 have shown that lower GC doses during the induction period were associated with
4 higher relapse rates and longer term of GC use that might expose patients to the
5 potential toxicity of high-cumulative GC.^{22,23}
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11 The purpose of this systematic review is to evaluate the comparative efficacy and
12 safety of alternative GC regimens (two or more different doses of GC) in patients with
13 ANCA-associated vasculitis. Our systematic review is part of a BMJ Rapid
14 Recommendations project, which is based on the shared vision of the MAGIC
15 Evidence Ecosystem Foundation (www.magicproject.org) and The BMJ. The
16 systematic review informed an associated BMJ Rapid Recommendations. (to cite the
17 guideline paper).
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27 **Methods**

28 **Registration and report**

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30 A priori protocol of this systematic review is presented at PROSPERO
31 (CRD42020179087). We reported this systematic review and meta-analysis based on
32 the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)
33 statement (see Appendix 1).²⁴
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41 **Patient and public involvement**

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43 According to the process of the BMJ Rapid Recommendations, the guideline panel on
44 this target provides critical process oversight and content guidance for the systematic
45 review. The guideline panel consisted of clinicians, methodologists, pharmacists,
46 patient partners with AAV and caregiver partners. Patients received relevant training
47 and support to meet patient involvement content throughout the guideline
48 development process, including critical feedback on outcome and subgroup selection,
49 GRADE judgments, and manuscript feedback.
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59 **Study selection**

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3 We included studies of patients with a diagnosis of active AAV. AAV was defined as
4 the following categories according to the Chapel Hill Consensus Conference 2012
5 classification method: microscopic polyangiitis (MPA), granulomatosis with
6 polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA, Churg-
7 Strauss syndrome).²⁵ In addition, single organ damage AAV (eg, renal limited
8 vasculitis (RLV) or idiopathic rapidly progressive glomerulonephritis (RPGN)) could
9 be considered the fourth entity, although in practice it eventually corresponds to the
10 kidney-limited form of MPA or GPA.²⁶
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20 Eligible studies were defined as comparing two or more doses of GC in patients with
21 AAV during induction of remission, regardless of the use of other therapies. Other
22 therapies included, and not limited to cyclophosphamide, azathioprine, rituximab,
23 methotrexate, mycophenolate mofetil and plasma exchange. We included only RCTs.
24 Outcomes of interest included death, ESKD, serious infections, serious adverse events
25 other than serious infections, sustained remission and any other patient-important
26 outcomes. The time point for the outcome assessment depended on what was
27 specified in original trials.
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37 **Data sources and searches**

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39 A professional medical librarian developed a literature search strategy and searched
40 Medline, Embase, Clinicaltrials.gov and Cochrane Central Register of Controlled
41 Trials (CENTRAL) for relevant studies from the inception to 10 April 2020 with no
42 restriction on language. Appendix 2 presents the literature search strategies and
43 results. We also reviewed the reference lists of included studies for additional
44 references. Pairs of reviewers (YX, JD, TB, MA) independently screened titles and
45 abstracts, and reviewed the full texts of potentially eligible studies to determine the
46 final eligible studies. Disagreements were resolved by discussion. To ensure the
47 validity and consistency of the process, we provided reviewers with review instruction
48 and conducted calibration exercises before the formal start of each process.
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60 **Data extraction and risk of bias assessment**

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3 We collected data through a predesigned excel extraction form. Pairs of reviewers
4 (YX, JD, TB, MA) extracted data independently. We resolved disagreements by
5 discussion. For each eligible study, we collected the following: country/region, design
6 of the study, patient characteristics (mean age, sex and disease diagnosis), treatment
7 strategy, outcomes and measures, and follow-up duration. Pair of reviewers (YX, JD,
8 TB, MA) independently assessed the risk of bias of each RCT using a
9 revised Cochrane risk of bias tool that includes sequence generation, concealment of
10 allocation, blinding (participants, personnel, and outcome assessors), loss to follow-
11 up, selective outcome reporting and other potential sources of bias.²⁷ The reviewers
12 judged each criterion as definitely or probably low risk of bias, or probably or
13 definitely high risk of bias.
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25 **Data synthesis or analysis, and grading of evidence**

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27 For continuous outcomes, we used inverse variance statistical method to calculate
28 mean difference (MD) and 95% confidence interval (CI). For binary outcomes, we
29 used the Mantel–Haenszel statistical method to calculate risk ratio (RR) and 95% CI.
30 We conservatively used a priori random effects model assuming a great variability in
31 treatment effects across the study. We used the I^2 statistic to assess statistical
32 heterogeneity. When the effect-estimated I^2 value was >30%, we attempted to
33 determine the reason for the heterogeneity. We set significance at P=0.05 and used
34 RevMan version 5.3 for all statistical analyses.
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45 We used the GRADE approach²⁸ to assess the quality of evidence at outcome level by
46 two reviewers (LZ and YX). We focused on the grading of the following outcomes
47 after our team discussion: death, ESKD, serious infections, serious adverse events,
48 and health-related quality of life. Disagreements were resolved by discussion or
49 through a third reviewer (GHG) adjudication. We summarized the quality of evidence
50 in GRADE summary of findings using the MAGICapp platform.^{29,30}
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58 **Results**

Literature search

The search yielded, after removal of duplicates, 3912 records, 38 of which were considered for full-text review. The PRISMA flow chart (Figure 1), presents the reasons for excluding studies at the stage of full text screening. Ultimately, two RCTs met the inclusion criteria.^{18, 31} The full text of one of the two RCTs¹⁸ was published after our initial submission of this systematic review. We updated our results after the full text was published.

Included studies

The RCT by Walsh et al³¹ was a multicenter trial including 704 patients with severe AAV at 95 centers in 16 countries (median duration of follow-up 2.9 years). Eligible patients were 15 years of age or older, had new or relapsing granulomatosis with polyangiitis or microscopic polyangiitis, and kidney involvement or pulmonary involvement. This study was a 2-by-2 factorial design and compared the efficacy of plasma exchange with or without plasma exchange for AAV, as well as the efficacy of a reduced-dose regimen and a standard-dose regimen of GC over the first 6 months of the treatment period. The two regimens of oral GC, specifically, patients in the reduced-dose regimen and standard-dose regimen received the same treatment in the first week —the dose was determined according to the patients' weight (50.0 mg/<50 kg, 60.0 mg/50 to 75 kg, 75.0 mg/> 75 kg). The reduced-dose regimen and the standard-dose regimen began to decrease gradually in the second and third weeks, respectively. Finally, at the 6th month, the cumulative dose of oral GC in the reduced-dose regimen was less than 60% of the standard-dose regimen. (Table 1)

The RCT by Furuta et al¹⁸ was a multicenter trial enrolling 140 patients with newly diagnosed AAV at 34 centers in Japan (with a follow-up of 6 months). Patients with severe glomerulonephritis or pulmonary hemorrhage were excluded. This trial evaluated whether a low-dose GC regimen (initial dose at 0.5 mg/kg/day) was non-inferior to a high-dose regimen (initial dose at 1.0 mg/kg/day) in efficacy when combined with rituximab for the treatment of AAV. In the low-dose group, prednisolone was discontinued at 5 months, while in the high-dose group,

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3 prednisolone was reduced to 10.0 mg/ day until 6 months. (Table 1)
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For peer review only

Table 1: Characteristics of eligible randomized controlled trials

Author, Year	Name of the study (ClinicalTrials.gov number)	Country	Study design	Intervention and comparison (No. of patients)	Patients	Outcomes
Walsh et al. (2020) ³¹	PEXIVAS (NCT00987389)	Multiple countries	Phase III, randomized, open label, 704 patients	Intervention: reduced-dose GC therapy (initial dose : 50-75mg; maintenance dose continues at 5mg/day from the end of week 23 until at least week 52; accumulative dose less than 60% of the standard)	353 patients with severe AAV (mean age 63 years, 44% female)	Primary outcome: a composite of death from any cause or ESKD. Secondary outcomes: death from any cause, ESKD, sustained remission, serious adverse events, serious infections within 1 year, and health-related quality of life.
				Comparison: standard-dose GC therapy (initial dose : 50-75mg; maintenance dose continues at 5mg/day from the end of week 23 until at least week 52)	351 patients with severe AAV (mean age 63 years, 43% female)	
Furuta et al. (2021) ¹⁸	LoVAS (NCT02198248)	Japan, multicentric	Phase IV, randomized, open label, 140 patients	Intervention : low-dose GC treatment (initial dose : 0.5mg/kg/day; discontinued at 5 months)	70 patients with new diagnosis of AAV (median age: 73; 43% female)	Primary outcome: remission rate at 6 months. Secondary outcomes: time to remission, death, relapse, ESKD and the first serious adverse event, proportion of death, relapse and ESKD

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				Comparison : high-dose GC treatment (initial dose : 1mg/kg/day; reduced to 10mg/day by 5 months)	70 patients with new diagnosis of AAV (median age: 74; 37% female)	for efficacy at 6 months.
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AAV: antineutrophil cytoplasmic antibodies associated vasculitis; Ges: glucocorticoids. ESKD: end-stage kidney disease.

For peer review only

Risk of bias

Both trials were open-label trials and patients and investigators were aware of the group assignments due to the complexity of the GC regimen. However, due to the objective, easily ascertained nature of the outcomes, the lack of blinding may introduce minimal bias. Considering the low risk of bias in the other domains, overall risk of bias of both trials was low (Appendix 3).

Effect of interventions

Due to the heterogeneity in the population and in the regimens of glucocorticoids between the two trials, we descriptively presented the two trials and did not combine the results using meta-analysis. Since the results of Walsh's study³¹ showed no interaction between the GC regimen and the plasma exchange, we only focus on the use of GC in conjunction with the purpose of this review.

Appendix 4 summarizes the GRADE summary of findings for these two trials. Compared with standard-dose regimen, reduced-dose regimen of GC may reduce death in both newly diagnosed and severe ANCA-associated vasculitis (risk difference [RD]: from -1.7% to -2.1%, low certainty), while probably not increasing ESKD in either newly diagnosed or severe ANCA-associated vasculitis (RD: from -1.5% to 0.4%, moderate certainty). The rate of serious infections at six months to one year in the reduced-dose regimen tended to be lower than in the standard-dose regimen in both newly diagnosed and severe ANCA-associated vasculitis (RD: from -12.8% to -5.9%, moderate certainty). The PEXIVAS trial showed reduced-dose regimen might increase the risk of serious adverse events in a follow-up period of longer than one year (RD: 3.1%, 95% CI -3.7% to 11.2%) while the LoVAS trial showed reduced-dose regimen might reduce the risk at 6 month (RD: -18.1%, 95% CI -33% to 3.2%). We are uncertain about the effect of reduced-dose regimen on serious adverse events (Very low certainty). Reduced-dose regimen of glucocorticoids probably has trivial or no effect in disease remission, relapse or health related quality of life (Moderate to high certainty).

Discussion

After full text screening, we identified 2 RCTs^{18,31} involving 844 patients that met our selection criteria for studies comparing different dose regimens of GC for the treatment of AAV. According to this systematic review, the results of the absolute effects of low certainty of evidence showed that reduced-dose regimen of GC may reduce death at a follow-up from 6 months to longer than 1 year, while not increasing the risk of ESKD (moderate certainty) among patients with AAV when compared with standard-dose regimen.

In addition, relative to the standard-dose regimen, moderate certainty of evidence indicated that the reduced-dose regimen probably has an important reduction in serious infections in both newly diagnosed and severe AAV at 6 months to 1 year (moderate certainty). This study showed that reduced-dose regimen does have an obvious advantage in reducing infections, which echoes previous studies.^{17,32} Jayne et al. reported that when high-dose GC was used, infection was most common in the first 6 months of treating severe renal vasculitis.¹⁷ Considering that the most common cause of death more than one year after diagnosis of AAV was infection or uncontrolled vasculitis.^{16,33,34,35} the reduction in risk of serious infections explained the possible reduction of mortality by reduced dose-regimen of GC.

We are, however, uncertain about the effect of the reduced dose regimen of GC on other serious adverse events. While Furuta et al's trial showed a significant reduction in serious adverse events by reduced-dose regimen,¹⁸ Walsh et al's trial showed the reduced-dose regimen might increase the risk with a wide CI.³¹ In Walsh et al's trial, although the reduced-dose regimen of GC had more renal or urinary adverse events than the standard-dose regimen of GC, there was no significant difference in the incidence of ESKD between the two regimen groups. This may be related to the treatment status of the included patients. Among the patients included in Walsh et al's trial, the number of patients who had undergone dialysis before the beginning of the trial in the standard-dose regimen group was more than that in the reduced-dose regimen group.

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6 The use of GC transformed AAV from an almost uniformly fatal condition to one
7 characterized by remissions and relapses complicated by drug-induced adverse events.
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9 Despite the ubiquitous use of GC for AAV, there was no standardization of dose
10 regimens, guidelines were ambiguous and practice patterns varied substantially. The
11 two trials^{18,31} highlights the need to optimize the dose of GC. Although the two trials
12 found one regimen of GC might be superior over another, further research is needed
13 to determine whether the GC regimen can be further improved for the treatment of
14 AAV.
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22 The advantages of this systematic review include a comprehensive search of emerging
23 and past evidence across databases without being restricted by study design or
24 publication language, and the use of GRADE approach to assess the quality of
25 evidence. Decisions regarding eligible studies, data extraction, and risk of bias
26 assessments were all performed in duplicate, and calibration exercises were conducted
27 before the formal start of the project. By excluding non-RCT studies, we limited the
28 risk of bias. The RCTs we included are of sound methodological quality.
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38 Our systematic review also has some limitations. First, only two trials were included
39 and although they were broadly inclusive and contained more events than any other
40 trial in this disease, the total sample size was still not large. This is particularly
41 obvious for serious adverse events. However, the reduced-dose GC regimen should
42 not result in more treatment related adverse events (i.e. it is illogical that a lower
43 exposure to GC would have anything but the same or lower rate of GC caused side
44 effects) and there is reasonable precision around the efficacy outcomes. This
45 limitation is expected to result in an underappreciation of the benefits of reducing the
46 GC dose that is supported by observational studies of GC which suggested reducing
47 GC exposure may also reduce fractures, peptic ulcer disease, psychiatric disease,
48 weight gain and dysglycemia. In addition, despite the excellent methodological
49 quality of the included trials, they were open label trials and were subject to biases.
50 Despite the LoVAS trial enrolled patients with newly diagnosed AAV, due to the
51 limited sample size of this trial, the extent to which the results can be generalized to
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3 patients with non-severe AAV is uncertain. But at least, it is likely safer to extrapolate
4 the safety of the regimen from more severe to less severe patients rather than from
5 less severe to more severe patients.
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10 11 **Conclusion**

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13 An important general rule is that in routine clinical practice, the use of conventional
14 GC should be “as much as necessary, but as little as possible.”³⁶ Compared with the
15 standard-dose regimen, the reduced-dose regimen of GC may reduce death, probably
16 has little or no effect on ESKD among patients with AAV, and resulted in a lower risk
17 of serious infections at 6 months to 1 year. But the overall effect of reduce-dose
18 regimen of GC on serious adverse events is uncertain.
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26
27 Acknowledgements: We thank members of the Rapid Recommendations panel for
28 critical feedback on outcome and subgroup selection, GRADE judgments, and
29 manuscript feedback.
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33 Contributors: MW, AM, DJ, PM and GHG conceived of the study idea. RC
34 performed the literature search. YX, JD, TB and MA performed the screening, data
35 abstraction, and risk of bias assessments. YX, LZ and MW performed the data
36 analysis. YX, GHG, LZ, RS, DJ, PM and MW interpreted the data. YX, GHG and LZ
37 performed the certainty assessment. YX, GHG, LZ and MW drafted the manuscript.
38 All authors critically revised the manuscript. All authors approved the final version of
39 the manuscript. YX and MW had full access to the data in the study and takes
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56 Data sharing statement: No data are available.
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3 Transparency statement: YX and MW affirm that the manuscript is an honest,
4 accurate, and transparent account of the recommendation being reported; that no
5 important aspects of the recommendation have been omitted; and that any
6 discrepancies from the recommendation as planned (and, if relevant, registered) have
7 been explained.
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13 Figure legend PRISMA flow chart of literature search and screening process
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15 References

- 16 1. Houben E, Penne EL, Voskuyl AE, et al.. Cardiovascular events in anti-neutrophil cytoplasmic
17 antibody-associated vasculitis: a meta-analysis of observational studies. *Rheumatology (Oxford)*
18 2018;57(3):555-562.
- 19 2. Bosch X, Guilabert A, Font J. Antineutrophil cytoplasmic antibodies. *Lancet* 2006;368(9533):404-
20 41816876669.
- 21 3. Wallace ZS, Miloslavsky EM. Management of ANCA associated vasculitis. *BMJ* 2020;368:m421.
- 22 4. Jennette JC, Falk RJ. Pathogenesis of antineutrophil cytoplasmic autoantibody-mediated disease. *Nat*
23 *Rev Rheumatol* 2014;10:463-73.
- 24 5. Salvador F. ANCA Associated Vasculitis. *Eur J Intern Med* 2020;74:18-28.
- 25 6. Smith RM. Update on the treatment of ANCA associated vasculitis. *Presse Med* 2015;44(6 Pt
26 2):e241-9.
- 27 7. Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. *Ann*
28 *Intern Med* 1992;116:488-98.
- 29 8. Walsh M, Merkel PA, Peh CA, et al.; PEXIVAS Investigators. Plasma exchange and glucocorticoid
30 dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis (PEXIVAS):
31 protocol for a randomized controlled trial. *Trials* 2013;14:73.
- 32 9. Keller SF, Miloslavsky EM. Corticosteroids in Antineutrophil Cytoplasmic Antibody-Associated
33 Vasculitis. *Rheum Dis Clin North Am* 2016;42(1):91-101.
- 34 10. Booth AD, Almond MK, Burns A, et al., Pan-Thames Renal Research Group. Outcome of ANCA-
35 associated renal vasculitis: a 5-year retrospective study. *Am J Kidney Dis* 2003; 41(4):776-84.
- 36 11. Jennette JC, Falk RJ. Small-vessel vasculitis. *N Engl J Med* 1997;337(21):1512–23.
- 37 12. Lally L, Spiera R. Current landscape of antineutrophil cytoplasmic antibody-associated vasculitis:
38 classification, diagnosis, and treatment. *Rheum Dis Clin North Am* 2015;41(1):1–19, vii.
- 39 13. Stahn C, Buttgerit F. Genomic and nongenomic effects of glucocorticoids. *Nat Clin Pract*
40 *Rheumatol* 2008;4:525-33.
- 41 14. Walton EW. Giant-cell granuloma of the respiratory tract (Wegener' s granulomatosis). *Br Med J*
42 1958;2:265-70.
- 43 15. de Groot K , Harper L , Jayne DR , et al . Pulse versus daily oral cyclophosphamide for induction of
44 remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern*
45 *Med* 2009;150:670–80.
- 46 16. De Groot K , Rasmussen N , Bacon PA , et al . Randomized trial of cyclophosphamide versus
47 methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-
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3 associated vasculitis. *Arthritis Rheum* 2005;52:2461–9.
- 4
5 17. Jayne DR , Gaskin G , Rasmussen N , et al . Randomized trial of plasma exchange or high-dosage
6 methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol* 2007;18:2180–
7 8.
- 8
9 18. Furuta S, Nakagomi D, Kobayashi Y, et al. Effect of Reduced-Dose vs High-Dose
10 Glucocorticoids Added to Rituximab on Remission Induction in ANCA-Associated Vasculitis: A
11 Randomized Clinical Trial. *JAMA*. 2021;325(21):2178–2187.
- 12
13 19. Keller SF, Miloslavsky EM. Corticosteroids in Antineutrophil Cytoplasmic Antibody-Associated
14 Vasculitis. *Rheum Dis Clin North Am* 2016;42(1):91-101.
- 15
16 20. Flossmann O , Berden A , de Groot K , et al . Long-term patient survival in ANCA-associated
17 vasculitis. *Ann Rheum Dis* 2011;70:488–94.
- 18
19 21. Furuta S , Chaudhry AN , Hamano Y , et al . Comparison of phenotype and outcome in microscopic
20 polyangiitis between Europe and Japan. *J Rheumatol* 2014;41:325–33.
- 21
22 22. Walsh M , Merkel PA , Mahr A , et al . Effects of duration of glucocorticoid therapy on relapse rate
23 in antineutrophil cytoplasmic antibody-associated vasculitis: a meta-analysis. *Arthritis Care Res*
24 2010;62:1166–73.
- 25
26 23. Wada T , Hara A , Arimura Y , et al . Risk factors associated with relapse in Japanese patients with
27 microscopic polyangiitis. *J Rheumatol* 2012;39:545–51.
- 28
29 24. Moher D, Liberati A, Tetzlaff J, et al.; PRISMA Group. Preferred reporting items for systematic
30 reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006-12.
- 31
32 25. Salvador F. ANCA associated vasculitis. *Eur J Intern Med* 2020;74:18-28.
- 33
34 26. Pagnoux C. Updates in ANCA-associated vasculitis. *Eur J Rheumatol* 2016;3(3):122-133.
- 35
36 27. Guyatt G, Busse JW. Risk of bias in randomized trials. *GROWTH Evidence*; 2016. Available:
37 <https://growthevidence.com/gordon-h-guyatt-md-msc-and-jason-w-busse-dc-phd> (accessed 2020 April.
38 6).
- 39
40 28. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence
41 profiles and summary of findings tables. *J Clin Epidemiol* 2011; 64: 383-94.
- 42
43 29. Guyatt GH, Oxman AD, Santesso N, et al. GRADE guidelines: 12. Preparing summary of findings
44 tables-binary outcomes. *J Clin Epidemiol* 2013;66:158-72.
- 45
46 30. Guyatt GH, Thorlund K, Oxman AD, et al. GRADE guidelines: 13. Preparing summary of findings
47 tables and evidence profiles-continuous outcomes. *J Clin Epidemiol* 2013;66:173-83.
- 48
49 31. Walsh M, Merkel PA, Peh CA, et al. Plasma Exchange and Glucocorticoids in Severe ANCA-
50 Associated Vasculitis. *N Engl J Med* 2020;382(7):622-631.
- 51
52 32. Illei GG, Yarboro CH, Kuroiwa T, et al.. Long-term effects of combination treatment with
53 fludarabine and low-dose pulse cyclophosphamide in patients with lupus nephritis. *Rheumatology*
54 (Oxford) 2007;46:952–956.
- 55
56 33. Flossmann O, Berden A, de Groot K, et al., European Vasculitis Study Group. Long-term patient
57 survival in ANCA-associated vasculitis. *Ann Rheum Dis* 2011;70:488-94.
- 58
59 34. Jones RB, Tervaert JWC, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-
60 associated renal vasculitis. *N Engl J Med* 2010;363(3):211-20.
35. Jayne D, Rasmussen N, Andrassy K, et al.; European Vasculitis Study Group: A randomized trial
of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N
Engl J Med* 349 : 36 –44, 2003.

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36. Buttgereit F, Burmester GR, Lipworth BJ. Optimised glucocorticoid therapy: the sharpening of an old spear. *Lancet* 2005;365(9461):801-3.

For peer review only

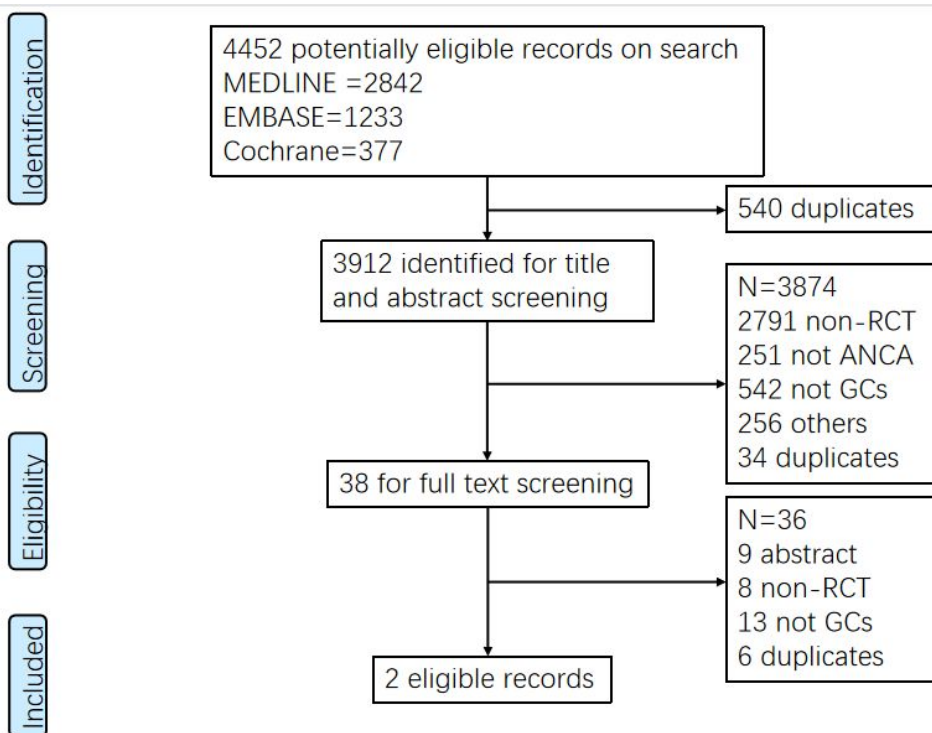


Figure 1 PRISMA flow chart of literature search and screening process
 RCT:randomized controlled trial; ANCA:Antineutrophil cytoplasmic antibodies; GCs:glucocorticoids

review only

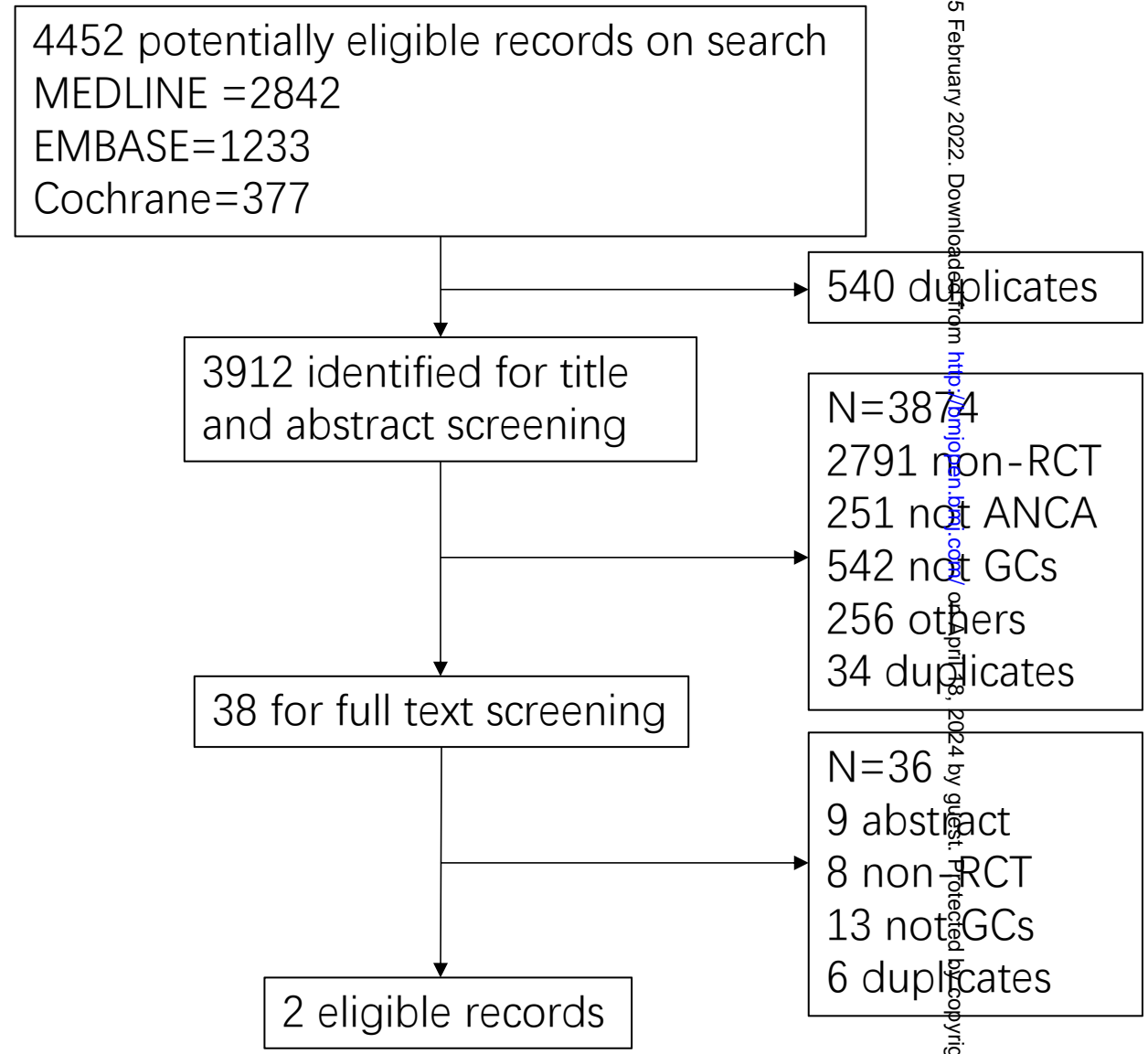
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Identification

Screening

Eligibility

Included



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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1-2
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.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
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.	6
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.	7
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.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
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).	8
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.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
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).	8
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.	8



PRISMA 2009 Checklist

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).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
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.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICCO, follow-up period) and provide the citations.	9-12
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).	13
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.	9-12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13-17
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13-17
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13-17
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).	18-19
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).	19-20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
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).	21

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Appendix 2: Search strategies and results for The comparative efficacy and safety of alternative glucocorticoids regimens in patients with ANCA-associated vasculitis: A systematic review

Database	No of records
MEDLINE	2842
EMBASE	1233
Cochrane Library	377
Subtotal	4452
-duplicates	-540
Total	3912

Database: OVID MEDLINE

-
- 1 Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis/ (1682)
 - 2 Churg-Strauss Syndrome/ (2090)
 - 3 Microscopic Polyangiitis/ (507)
 - 4 Granulomatosis with Polyangiitis/ (6902)
 - 5 (vasculit* adj3 (ANCA or AAV or antineutrophil or anti-neutrophil or cytoplasm* or RLV or renal or churg or strauss or pauci immune)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (4968)
 - 6 churg strauss.mp. (2876)
 - 7 ((angiit* or vasculit*) adj3 (granulom* or necrot* or allergic)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (4297)
 - 8 ((polyangiit* or polyarterit*) adj3 (microscop* or MPA or granulom*)).mp. (9268)
 - 9 wegener*.mp. (6572)
 - 10 (glomerulonephrit* adj3 necrot*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (797)
 - 11 or/1-10 (18126)
 - 12 exp Glucocorticoids/ (190619)
 - 13 prednisolone/ or methylprednisolone/ (49855)
 - 14 Prednisone/ (39084)
 - 15 Adrenal Cortex Hormones/ (63823)

16 (corticosteroid* or glucocorticoid* or methylprednisolon* or prednison* or prednisolon*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (283874)

17 Corticosterone/ or corticosteron*.mp. (34191)

18 Hydrocortisone/ or hydrocortison*.mp. (76765)

19 Cortisone/ or cortison*.mp. (23710)

20 steroids.mp. or Steroids/ (112972)

21 Cortodoxone/ or cortodoxon*.mp. (856)

22 Hydroxycorticosteroids/ or hydroxycorticosteroid*.mp. (6731)

23 Dexamethasone/ or dexamethason*.mp. (71052)

24 adrenocorticosteroid*.mp. (313)

25 adrenocorticoid*.mp. (177)

26 corticoid*.mp. (6458)

27 or/12-26 (547377)

28 11 and 27 (4782)

29 randomized controlled trial.pt. (503644)

30 controlled clinical trial.pt. (93611)

31 randomized.ab. (475606)

32 placebo.ab. (206694)

33 drug therapy.fs. (2193818)

34 randomly.ab. (330775)

35 trial.ab. (501000)

36 groups.ab. (2031658)

37 or/29-36 (4675601)

38 exp animals/ not humans.sh. (4689197)

39 37 not 38 (4053127)

40 28 and 39 (2842)

Database: EMBASE

1 ANCA associated vasculitis/ (5871)

2 Churg Strauss syndrome/ (4947)

3 microscopic polyangiitis/ (3039)

4 Wegener granulomatosis/ (12860)

5 (vasculit* adj3 (ANCA or AAV or antineutrophil or anti-neutrophil or cytoplasm* or RLV or renal or churg or strauss or pauci immune)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (9651)

6 churg strauss.mp. (5425)

7 ((angiit* or vasculit*) adj3 (granulom* or necrot* or allergic)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug

1 manufacturer, device trade name, keyword, floating subheading word, candidate
 2 term word] (7160)
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 4 8 ((polyangiit* or polyarterit*) adj3 (microscop* or MPA or granulom*)).mp.
 5 [mp=title, abstract, heading word, drug trade name, original title, device
 6 manufacturer, drug manufacturer, device trade name, keyword, floating subheading
 7 word, candidate term word] (7171)
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 9 9 wegener*.mp. (14257)
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 11 10 (glomerulonephrit* adj3 necrot*).mp. [mp=title, abstract, heading word, drug
 12 trade name, original title, device manufacturer, drug manufacturer, device trade
 13 name, keyword, floating subheading word, candidate term word] (1243)
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 15 11 or/1-10 (29983)
 16 12 exp glucocorticoid/ (700322)
 17 13 prednisolone/ (122582)
 18 14 methylprednisolone/ (93152)
 19 15 prednisone/ (167298)
 20 16 corticosteroid/ (229322)
 21 17 (corticosteroid* or glucocorticoid* or methylprednisolon* or prednison* or
 22 prednisolon*).mp. [mp=title, abstract, heading word, drug trade name, original title,
 23 device manufacturer, drug manufacturer, device trade name, keyword, floating
 24 subheading word, candidate term word] (688798)
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 26 18 corticosterone/ or corticosteron*.mp. (38497)
 27 19 hydrocortisone/ or hydrocortison*.mp. (135041)
 28 20 cortisone/ or cortison*.mp. (17205)
 29 21 steroids.mp. or steroid/ (245681)
 30 22 cortodoxone/ or cortodoxon*.mp. (2044)
 31 23 hydroxycorticosteroid*.mp. or hydroxycorticosteroid/ (2310)
 32 24 dexamethasone/ or dexamethason*.mp. (161446)
 33 25 adrenocorticosteroid*.mp. (286)
 34 26 adrenocorticoid*.mp. (169)
 35 27 corticoid*.mp. (7745)
 36 28 or/12-27 (1111323)
 37 29 11 and 28 (13676)
 38 30 randomized controlled trial/ (598366)
 39 31 Controlled clinical study/ (463908)
 40 32 random\$.ti,ab. (1520687)
 41 33 randomization/ (86548)
 42 34 intermethod comparison/ (258594)
 43 35 placebo.ti,ab. (303776)
 44 36 (compare or compared or comparison).ti. (505122)
 45 37 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or
 46 compared or comparing or comparison)).ab. (2085158)
 47 38 (open adj label).ti,ab. (78322)
 48 39 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
 49 (230181)
 50 40 double blind procedure/ (171296)
 51 41 parallel group\$.ti,ab. (25234)

42 (crossover or cross over).ti,ab. (104111)
 43 ((assign\$ or match or matched or allocation) adj5 (alternate or group\$1 or
 44 intervention\$1 or patient\$1 or subject\$1 or participant\$1)).ti,ab. (326088)
 45 (assigned or allocated).ti,ab. (383843)
 46 (controlled adj7 (study or design or trial)).ti,ab. (343989)
 47 (volunteer or volunteers).ti,ab. (244774)
 48 human experiment/ (490852)
 49 trial.ti. (296188)
 50 or/30-48 (4957675)
 29 and 49 (1233)

Database: Cochrane Library

ID	Search Hits	
#1	MeSH descriptor: [Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis] explode all trees	157
#2	MeSH descriptor: [Churg-Strauss Syndrome] explode all trees	27
#3	MeSH descriptor: [Microscopic Polyangiitis] explode all trees	40
#4	MeSH descriptor: [Granulomatosis with Polyangiitis] explode all trees	82
#5	vasculit* near/3 (ANCA or AAV or antineutrophil or anti-neutrophil or cytoplasm* or RLV or renal or churg or strauss or pauci immune)	470
#6	churg strauss	112
#7	((angiit* or vasculit*) near/3 (granulom* or necrot* or allergic))	102
#8	((polyangiit* or polyarterit*) near/3 (microscop* or MPA or granulom*))	277
#9	wegener*	394
#10	(glomerulonephrit* near/3 necrot*)	13
#11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10	867
#12	MeSH descriptor: [Glucocorticoids] explode all trees	4445
#13	MeSH descriptor: [Prednisolone] explode all trees	4804
#14	MeSH descriptor: [Methylprednisolone] explode all trees	2679
#15	MeSH descriptor: [Prednisone] explode all trees	3909
#16	MeSH descriptor: [Adrenal Cortex Hormones] explode all trees	14135
#17	corticosteroid* or glucocorticoid* or methylprednisolon* or prednison* or prednisolon*	41757
#18	MeSH descriptor: [Corticosterone] explode all trees	38
#19	MeSH descriptor: [Hydrocortisone] explode all trees	5886
#20	MeSH descriptor: [Cortisone] explode all trees	143
#21	MeSH descriptor: [Steroids] explode all trees	57500
#22	MeSH descriptor: [Cortodoxone] explode all trees	30
#23	MeSH descriptor: [Cortodoxone] explode all trees	30
#24	MeSH descriptor: [Hydroxycorticosteroids] explode all trees	7002
#25	MeSH descriptor: [Dexamethasone] explode all trees	4409

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3 #26 corticosteron* or hydrocortison or cortison* or steroids or cortodoxon* or
4 hydroxycorticosteroid* or dexamethason* or adrenocorticosteroid* or
5 adrenocorticoid* or corticoid* 22688
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7 #27 #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22
8 or #23 or #24 or #25 or #26 95898
9 #28 #11 and #27 in Trials 377
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4 **Appendix 3 Risk of Bias assessment for outcomes of included RCTs**

5 Outcomes of Trials	Sequence	Allocation	Blinding	Blinding	Blinding	Blinding	Blinding	Loss to
6	generation	concealment	(patients)	(health care	(outcome	(data	(data	follow-up
7				providers)	assessors)	collectors)	analyst)	
8								
9 Walsh et al. 2020								
10 Death	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
11	Low	Low	Low	Low	Low	Low	Low	Low
12								
13 ESKD	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
14	Low	Low	Low	Low	Low	Low	Low	Low
15								
16 Remission	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
17	Low	Low	Low	Low	Low	Low	Low	Low
18								
19 Serious adverse	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
20	Low	Low	Low	Low	Low	Low	Low	Low
21 events	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
22	Low	Low	Low	Low	Low	Low	Low	Low
23 Serious infections	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
24	Low	Low	Low	Low	Low	Low	Low	Low
25								
26 Health-related quality	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
27	Low	Low	Low	Low	Low	Low	Low	Low
28 of life								
29 Furuta et al. 2021								
30 Death	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
31	Low	Low	Low	Low	Low	Low	Low	Low
32								
33 ESKD	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
34	Low	Low	Low	Low	Low	Low	Low	Low
35								
36 Remission	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
37	Low	Low	Low	Low	Low	Low	Low	Low
38								
39 Relapse	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
40	Low	Low	Low	Low	Low	Low	Low	Low
41								
42 Serious adverse	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
43	Low	Low	Low	Low	Low	Low	Low	Low
44 events	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
45	Low	Low	Low	Low	Low	Low	Low	Low
46								
47 Health-related quality	Definitely	Definitely	Probably	Probably	Probably	Probably	Probably	Definitely
48	Low	Low	Low	Low	Low	Low	Low	Low
49 of life								

ESKD: end-stage kidney disease; RCT: randomized controlled trial.

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Appendix 4 GRADE summary of findings on the use of reduced-dose regimen versus standard-dose regimen of glucocorticoids in patients with ANCA-associated vasculitis

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard-dose regimen of glucocorticoids Reduced-dose regimen of glucocorticoids	Certainty of the Evidence (Quality of evidence)	Plain text summary
Death	Based on data from 838 patients in 2 study Follow up: 6 months to 2.9 years	Two RCTs reported death from any cause. In Walsh et al's trial, death occurred in 46 of 353 patients (13.0%) in the reduced-dose GC therapy group and in 53 of 351 patients (15.1%) in the standard-dose GC therapy group (Risk difference, -2.1%; 95% confidence interval, -6% to 3.6%). In Furuta et al's trial, death occurred in 2 of 69 patients (2.9%) in the reduced-dose GC treatment group and in 3 of 65 patients (4.6%) in the high-dose GC treatment group (Risk difference, -1.7%; 95% confidence interval, -4.7% to 8.2%).	Low Due to very serious imprecision ¹	Reduced dose of glucocorticoids may reduce death at follow-up of 6 months to 2.9 years
End-stage kidney disease	Based on data from 838 patients in 2 study Follow up: 6 months to 2.9 years	Two RCTs reported end-stage kidney disease. In Walsh et al's trial, end-stage kidney disease occurred in 70 of 353 patients (19.8%) in the reduced-dose GC therapy group and in 68 of 351 patients (19.4%) in the standard-dose GC therapy group (Risk difference, 0.4%; 95% confidence interval, -4.7%	Moderate Due to serious imprecision ²	Reduced dose of glucocorticoids probably has little or no effect on end-stage kidney disease at follow-up of 6 months to 2.9 years

		to 7.4%). In Furuta et al's trial, end-stage kidney disease occurred in none of 69 patients (0%) in the reduced-dose GC treatment group and in 1 of 65 patients (1.5%) in the high-dose GC treatment group (Risk difference, -1.5; 95% confidence interval, -4.5 to 1.5).		
Remission	Based on data from 838 patients in 2 study Follow up: 6 months to 2.9 years	Two RCTs reported remission rate. In Walsh et al's trial, remission was analyzed in the two GC groups with the use of Cox proportional-hazards models resulting a hazard ratio of 1.04 (95% confidence interval, 0.81 to 1.33). In Furuta et al's trial, remission occurred in 49 of 69 patients (71.0%) in the reduced-dose GC treatment group and in 45 of 65 patients (69.2%) in the high-dose GC treatment group (Risk difference, 1.8%; 97.5% confidence interval, -13% to ∞).	Moderate Due to serious imprecision ¹	Reduced dose of glucocorticoids probably has little or no effect on disease remission at follow-up of 6 months to 2.9 years
Relapse	Based on data from 838 patients in 2 study Follow up: 6 months to 2.9 years	Two RCTs reported remission rate. In Walsh et al's trial, relapse occurred in 32 of 353 patients (9.1%) in the reduced-dose GC therapy group and in 23 of 351 patients (6.6%) in the standard-dose GC therapy group (Risk difference, 2.5%; 95% confidence interval, -1.45% to 6.47%). In Furuta et al's trial, relapse occurred in 3	Moderate Due to serious imprecision ³	Reduced dose of glucocorticoids probably has little or no effect on relapse in patients at follow-up of 6 months to 2.9 years

		of 69 patients (4.3%) in the reduced-dose GC treatment group and in none of 65 patients (0%) in the high-dose GC treatment group (Risk difference, 4.4%; 95% confidence interval, -0.5% to 9.2%).		
19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47	<p>Serious adverse events</p> <p>Based on data from 838 patients in 2 study</p> <p>Follow up: 6 months to 1 year</p>	<p>Two RCTs reported serious adverse events. In Walsh et al's trial, serious adverse events occurred in 230 of 353 patients (65.2%) in the reduced-dose GC therapy group and in 218 of 351 patients (62.1%) in the standard-dose GC therapy group (Risk difference, 3.1%; 95% confidence interval, -3.7% to 11.2%). In Furuta et al's trial, serious adverse events occurred in 13 of 69 patients (18.8%) in the reduced-dose GC treatment group and in 24 of 65 patients (36.9%) in the high-dose GC treatment group (Risk difference, -18.1%; 95% confidence interval, -33.0% to -3.2%).</p>	<p>Very Low</p> <p>Due to serious imprecision⁴</p> <p>Due to very serious inconsistency</p>	<p>We are uncertain whether reduced dose of glucocorticoids increases or reduce the risk of serious adverse events at 6 months to 1 year</p>
48 49 50 51 52 53 54 55 56 57 58 59 60	<p>Serious infections</p> <p>Based on data from 838 patients in 2 study</p> <p>Follow up: 6 months to 1 year</p>	<p>Two RCTs reported serious infections. In Walsh et al's trial, serious infections occurred in 230 of 353 patients (27.1%) in the reduced-dose GC therapy group and in 218 of 351 patients (33.0%) in the standard-dose GC therapy group (Risk difference, -5.9%;</p>	<p>Moderate</p> <p>Due to serious imprecision³</p>	<p>Reduced dose of glucocorticoids probably reduces the risk of serious infections at 6 months to 1 year</p>

		<p>95% confidence interval, -11.2% to 1.0%). In Furuta et al's trial, serious infections occurred in 5 of 69 patients (7.2%) in the reduced-dose GC treatment group and in 13 of 65 patients (20.0%) in the high-dose GC treatment group (Risk difference, -12.8%; 95% confidence interval, -24.2% to -1.3%).</p>		
<p>Health related quality of life (SF-36 PCS)</p>	<p>Measured by: SF-36 PCS Scale: - High better Based on data from 838 patients in 2 study Follow up: 6 months to 1 years</p>	<p>Two RCTs reported health related quality of life assessed by SF-36 PCS. Walsh et al's trial reported that the mean score of health related quality of life measured by SF-36PCS was 39.13 in the reduced-dose GC therapy group and 37.84 in the standard-dose GC therapy group (Mean difference, 1.29 higher; 95% confidence interval, 0.26 lower to 2.84 higher). Furuta et al's trial reported that the median score of health related quality of life measured by SF-36PCS was 38.3 (IQR : 21.1 to 47.4) in the reduced-dose GC treatment group and 31.7 (IQR : 22.0 to 49.4) in the high-dose GC treatment group (Mean difference, 6.3 higher; 95% confidence interval, 2.6 lower to 15.2 higher).</p>	<p>Moderate Due to serious imprecision</p>	<p>Reduced dose of glucocorticoids probably has little or no effect on health related quality of life (SF-36PCS) at 6 months to 1 years</p>

<p>Health related quality of life (SF-36 MCS)</p>	<p>Measured by: SF-36 MCS Scale: - High better Based on data from 838 patients in 2 study Follow up: 6 months to 1 years</p>	<p>Two RCTs reported health related quality of life assessed by SF-36 MCS. Walsh et al's trial reported that the mean score of health related quality of life measured by SF-36MCS was 52.16 in the reduced-dose GC therapy group and 51.19 in the standard-dose GC therapy group (Mean difference, 0.97 higher; 95% confidence interval, 0.24 lower to 2.18 higher). Furuta et al's trial reported that the median score of health related quality of life measured by SF-36MCS was 49.8 (IQR : 45.1 to 56.6) in the reduced-dose GC treatment group and 50.4 (IQR : 46.3 to 57.2) in the high-dose GC treatment group (Mean difference, 0.4 lower; 95% confidence interval, 4.7 lower to 4.0 higher).</p>	<p>High</p>	<p>Reduced dose of glucocorticoids has little or no effect on health related quality of life (SF-36MCS) at 6 months to 1 years</p>
<p>Health related quality of life (EQ-5D Index) at 1 year</p>	<p>Measured by: EQ-5D Index Scale: - High better Based on data from 704 patients in 1 study Follow up at 1 year</p>	<p>0.77 0.79 Mean Mean Difference: MD 0.02 higher (CI 95% 0.01 lower - 0.05 higher)</p>	<p>Moderate Due to serious imprecision⁵</p>	<p>Reduced dose of glucocorticoids probably has little or no effect on health related quality of life (EQ-5D) at 1 year</p>
<p>Health related quality of life (EQ-5D Thermometer) at 1 year</p>	<p>Measured by: EQ-5D Thermometer Scale: - High better Based on data from 704 patients in 1 study Follow up at 1 year</p>	<p>71.07 72.11 Mean Mean Difference: MD 1.04 higher (CI 95% 1.09 lower - 3.17 higher)</p>	<p>High</p>	<p>Reduced dose of glucocorticoids has little or no effect on health related quality of life (EQ-5D Thermometer) at 1 year</p>

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6 **1. Imprecision: Very serious.** Because the 95% CI includes both the minimally important difference for
7 benefit (20 fewer death in 1000 patients) and minimally important difference for harm (20 more death in 1000
8 patients, we rated down two levels for imprecision;
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10 **2. Imprecision: Serious.** The 95% CI crosses the minimally important difference for benefit (30 fewer ESKD
11 in 1000 patients) and minimally important difference for harm (30 more ESKD in 1000 patients) ;
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14 **3. Imprecision: Serious.** The 95% CI crosses the minimally important difference (50 fewer serious
15 infections in 1000 patients);
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17 **4. Imprecision: Serious.** The 95% CI includes an increase in serious adverse event over 10%;
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20 **5. Imprecision: Serious.** The 95% CI crosses the minimally important difference for benefit and the
21 minimally important difference for harm (0.03 reduction or increase in EQ-5D Index) ;
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23 ESKD: end-stage kidney disease; SF-36 = short form 36; PCS = physical component score; MCS = mental
24 component score; EQ = EuroQol; RR: relative risk; MD: mean difference; CI: confidence interval. IQR = interquartile
25 range
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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1-2
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.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
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.	6
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.	7
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.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
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).	8
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.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
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).	8
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.	8



PRISMA 2009 Checklist

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).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
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.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICCO, follow-up period) and provide the citations.	9-12
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).	13
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.	9-12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13-17
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13-17
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13-17
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).	18-19
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).	19-20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
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).	21

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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