Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Walsh M, Merkel PA, Peh C-A, et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. N Engl J Med 2020;382:622-31. DOI: 10.1056/NEJMoa1803537

Supplementary Appendix

Contents

Section S1. PEXIVAS Collaborators by Country

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Section S2. Eligibility Criteria

Inclusion Criteria

Participants must meet all of the following criteria:

1. New or previous relapsing clinical diagnosis of granulomatosis with polyangiitis (Wegener's), or microscopic polyangiitis consistent with the Chapel-Hill consensus definitions AND
2. Positive test, at any point in the subjects' disease course, by ELISA, for proteinase 3-ANCA or myeloperoxidase-ANCA AND
3. Severe vasculitis defined by at least one of the following manifestations:
    a. Renal involvement characterized by <u>both</u> of the following:
        i. Evidence of glomerulonephritis by either of the following:
            1. Renal biopsy demonstrating focal necrotizing glomerulonephritis or
            2. Active urine sediment characterized by glomerular haematuria/cellular casts and proteinuria

        AND

        ii. An estimated glomerular filtration (eGFR) rate of <50 ml/min/1.73 m^2. Patients known to have a stable eGFR <50 ml/min/1.73 m^2 for greater than three months prior to enrollment are NOT eligible.
    b. Pulmonary hemorrhage due to active vasculitis defined by the following:
        i. A compatible chest x-ray or CT scan (diffuse pulmonary infiltrates)
        AND

        ii. The absence of an alternative explanation for all pulmonary infiltrates (i.e. volume overload or pulmonary infection)
        AND

        iii. At least one of the following:
            1. Evidence of alveolar hemorrhage on bronchoscopic examination or increasingly bloody returns with bronchoalveolar lavage
            2. Observed hemoptysis
            3. Unexplained anemia (<10 g/dL) or documented drop in hemoglobin (>1 g/dL) from less than 10g/dl
            4. An increased diffusing capacity of carbon dioxide
4. Provision of informed consent by patient or a surrogate decision maker. In some participating countries permission has also been granted to use deferred consent for enrolling a patient until a legal representative becomes available to consent on their behalf.

Exclusion Criteria

Participants must have none of the following:

1. A diagnosis of vasculitis other than granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis
2. A positive serum test for anti-glomerular basement membrane or a renal biopsy demonstrating linear glomerular immunoglobulin deposition
3. Receipt of dialysis for greater than 21 days immediately prior to randomization or prior renal transplant
4. Age <15 years. In centres that do not routinely treat patients <18 years or if no local investigator routinely treats patients <18 years, enrollment may be restricted to patients 18 years or older
5. Pregnant at time of study entry

6. Treatment with >1 IV dose of cyclophosphamide and/or >14 days of oral cyclophosphamide and/or >14 days of prednisone/prednisolone (>30 mg/day) and/or treatment with >1 dose of rituximab within the last 28 days
7. A comorbidity or condition that, in the opinion of the investigator, precludes the use of cyclophosphamide/rituximab, glucocorticoids, or plasma exchange or absolutely mandates the use of plasma exchange
8. Plasma exchange in 3 months prior to randomization

Section S3. Cyclophosphamide Induction Regimen

Standard induction therapy with cyclophosphamide (CYC) will be prescribed for at least 13 weeks and no more than 26 weeks. As the experience of using either oral or intra-venous (IV) routes of administration varies between centres and there is no apparent difference in efficacy or safety, the study protocol will allow the use of either oral or IV CYC. The CYC regimens will be identical for all treatment groups.

A starting dose of 15 mg/kg/pulse will be used for pulse CYC (maximum 1.2 g/dose) or 2 mg/kg/day for oral CYC (maximum 200 mg/day) with reductions made for age and renal function in each group according to previous trials conducted in Europe. Oral CYC will be administered daily with the recommendation for morning administration of full dose, if tolerated. Pulse CYC will be administered IV at a frequency of every two weeks for the first 3 doses then every three weeks thereafter. Modifications to dose and frequency will be made in the case of leucopenia.

For patients undergoing PLEX, PLEX will not occur for at least 24 hours following an IV dose of CYC.

For patients receiving PLEX and daily CYC (oral or IV), on days when PLEX is performed, CYC will be given following PLEX. PLEX will not be performed for at least 12 hours following a dose of oral CYC.

Full (complete) blood counts will be performed according to local protocol but the following minimum is recommended: patients receiving oral CYC should have their blood count monitored weekly for the first four weeks and weekly for four weeks after any dose adjustment and every other week thereafter. Patients receiving pulse CYC should have their blood count monitored 10 to 14 days after each dose and within 1 day prior to each dose.

Concomitant use of mesna is optional and left to the discretion of the investigator and local practice.

Dosage Modifications for Renal Function and Age

Starting doses of CYC should be adjusted for advanced age or reduced renal function. Renal function may change over the course of the trial and medication dosages may be adjusted to reflect these changes.

Dosage Modification for Leucopenia

Oral CYC should be held if the total WBC count is $<4x10^9$/L. Oral CYC may be restarted at a dose at 25 mg/day less than previous once the WBC count is $>4x10^9$ on two consecutive tests or $>5x10^9$ on at least 1 test. After an episode of leucopenia, WBC counts should be monitored at least weekly for at least four weeks.

In the case of severe (WBC < $1x10^9$/L) or prolonged (< $4x10^9$/L for >2 weeks) leucopenia, oral CYC should be restarted at a dose at least 50 mg/day lower than the previous dose once the weekly WBC count permits. In cases of severe leucopenia, consideration should also be given to granulocyte-colony stimulating factor (G-CSF), fungal prophylaxis, and other precautions for patients with severe leucopenia.

Patients with a declining WBC count but no overt leucopenia (i.e. WBC count $<6x10^9$ and at least $2x10^9$/L lower than previous) should have their WBC count rechecked within 1 week and have their oral CYC reduced by at least 25 mg/day if the WBC count continues to fall.

For pulse CYC the WBC count should be determined within 1 day prior to an IV pulse CYC. If the WBC count is $<4x10^9$/L, the CYC dose should be postponed until the WBC count is $>4x10^9$/L and the dose should be reduced to 75% of the planned dose (planned dose x 0.75).

The WBC count nadir should also be determined 10 to 14 days after the pulse dose is given. If the nadir is $<3x10^9$/L, the next pulse should be reduced even if the next pre-dose WBC count is $>4x10^9$/L. For a nadir

$<2x10^9$/L, the next dose should be 60% of the previous dose (previous dose x 0.6). For a nadir of 2-$3x10^9$/L, the next dose should be 80% of the previous dose (previous dose x 0.8).

Similar dose reductions to those made for leucopenia may be made for thrombocytopenia and anemia at the investigator's discretion. Dose alterations should also be made in the event of infectious complications.

Section S4. Rituximab Induction Regimen

Rituximab may be prescribed to patients as induction remission therapy. Rituximab will be prescribed as 4 intravenous doses of 375 mg/m² according to the following schedule:

1. Dose 1 within first 14 days of participation
2. Subsequent doses should occur 7 days after the previous dose. Doses may, however, occur 5 to 14 days to accommodate practical considerations of administering rituximab and to accommodate plasma exchange. All doses must be given within 42 days of the first dose. PLEX should not be given within the first 48 hours after administering rituximab.

Prophylaxis against infusion reactions must be given as 100 mg of intravenous hydrocortisone or equivalent with or without an anti-histamine agent immediately preceding the first rituximab infusion, and local guidelines should be followed before subsequent infusions of rituximab.

Section S5. Glucocorticoid Dosing Regimen

1. Intravenous Glucocorticoids

a. For Patients Who Have Not Received Any Glucocorticoid Therapy Prior To Randomization

Glucocorticoid therapy commenced with intravenous (IV) methylprednisolone irrespective of the glucocorticoid group the patient was allocated to. IV methylprednisolone was given as three daily pulse doses (minimum 1g maximum 3g, total dose). Each pulse dose could be between 0.5 g and 1 g at the local investigators discretion. The day following the last IV methylprednisolone dose, patients commenced the randomized oral glucocorticoid regimen.

b. For Patients Who Have Received <3 g IV Methylprednisolone Within 14 days Prior To Randomization

IV methylprednisolone that was administered within 14 days prior to randomization contributed to the maximum allowable dose of 3g. If <3 g of IV methylprednisolone were given within 14 days prior to randomization, participants could receive additional IV methylprednisolone over 3 days after randomization to reach a minimum of 1 g and a maximum of 3 g (including all IV methylprednisolone given within 14 days prior to randomization). The day following the last IV methylprednisolone dose, patients commenced the randomized oral glucocorticoid regimen.

c. For Participants Who Have Received Oral GC But No IV Methylprednisolone Within 14 Days Prior to Randomization

Oral glucocorticoid given prior to randomization did not impact on the protocol glucocorticoid regimen in terms of either IV methylprednisolone or oral GC. These patients were treated as if they had not received any glucocorticoid prior to randomization.

d. Patients Who Have Received ≥3 g Of IV Methylprednisolone Within 14 Days Prior to Randomization

Patients that received ≥3 g IV methylprednisolone within 14 days prior to randomization began the oral glucocorticoid regimen according to their randomized group within 24 hours of randomization.

2. Randomized Oral Glucocorticoid Therapy

Oral glucocorticoid therapy consisted of non-enteric coated prednisone or prednisolone at equivalent mg to mg doses. Dosing was weight based with three possible weight categories. All oral glucocorticoids were given as a single daily dose. Patients intolerant of oral medications or for whom oral medications were contraindicated could be given an equivalent daily IV dose. Pre-printed prescriptions or pre-packaged medication were provided for each patient in the trial after randomization to enhance adherence to the allocated glucocorticoid regimen. The standard-dose regimen and reduced-dose regimen are summarized below in Table S3.

Oral glucocorticoid therapy continued from the end of week 23 at a dose of 5 mg/day until at least week 52 of the study after which glucocorticoid therapy reverted to the local investigator's choice of dosing. Alternate day dosing regimens (i.e. those that use two different doses on alternate days) could be used to achieve the appropriate average daily dose required by the protocol but differences in alternative day doses could not be >5 mg. For example, a dose of 12.5 mg/day may be achieved by alternating daily doses of 15 mg/day and 10 mg/day.

Section S6. Plasma Exchange Regimen

Plasma exchange therapy was only prescribed in addition to standard induction therapy. Plasma exchange consisted of 7 exchanges within 14 days of randomization, at a dose of at least 60 ml/kg (based on actual body weight) per session using albumin (3% to 5% depending on local availability, with or without crystalloid) as a replacement solution. Intravenous immunoglobulin was not used after plasma exchange.

The following parameters were determined according to local practice: 1) plasma exchange was allowed to be performed by centrifugation or filter separation technique but double filtration apheresis was not permitted 2) Anticoagulation could be provided by citrate or by heparin but it was suggested that in patients with active bleeding, regional citrate anticoagulation be utilized, 3) plasma exchange could be performed via a central venous catheter if the participant was deemed unsuitable for peripheral venous access but the latter was strongly recommended, and 4) monitoring of coagulation parameters or immunoglobulin levels, and 5) plasma exchange dose could be reduced for plasma exchange related complications according to local best medical practice and indications.

Patients with Bleeding Risks

Renal biopsy the day of PLEX was to be avoided, to minimize the risk of bleeding from dilutional coagulopathy.

Local practice was to be followed for patients with active bleeding including patients with known pulmonary hemorrhage or a bleeding episode from any source within the 24 hours prior to plasma exchange treatment. This could have included fresh frozen plasma at the end of the exchange.

Additional Plasma Exchange Treatments

Patients were not permitted additional plasma exchange treatments for ongoing signs or symptoms of AAV, serological markers of disease (e.g. elevated ANCA titres), elevated markers of inflammation, or histologic evidence of disease activity. Any plasma exchange treatments considered outside of the treatment protocol were to be discussed with the trial medical monitor.

Section S7. Outcome Definitions

End-stage kidney disease: the requirement of a renal replacement therapy (hemodialysis or peritoneal dialysis) for at least 12 consecutive weeks or the receipt of a renal transplantation.

Major relapse: new or worsened disease activity that occurs after remission has been initially induced and affects a major item of the BVAS/WG.

Minor relapse: new or worsening disease activity that occurs after remission has been initially induced that does NOT affect a major item of the BVAS/WG.

Serious adverse event: any medical occurrence that results in permanent disability, hospitalization or the prolongation of a hospitalization, is life threatening or results in death.

Serious Infection: an infectious syndrome that requires intravenous antibiotics or hospitalization for treatment or caused death.

Sustained remission: remission that occurs within 6 months of randomization and lasts until at least 12 months after randomization without a relapse of disease.

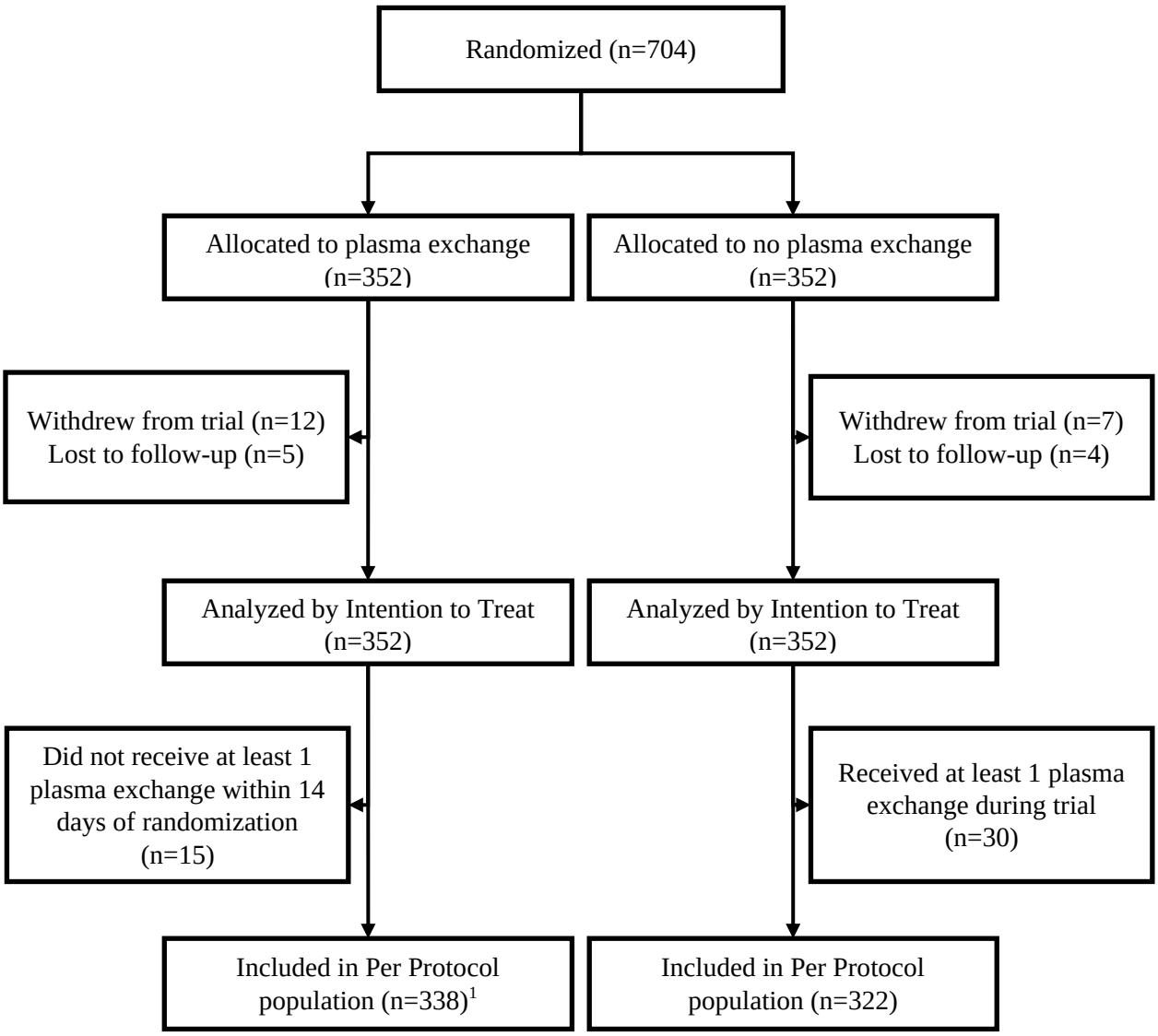

Figure S1. Plasma exchange participants

[1]The per-protocol population included 336 participants known to have received at least one plasma exchange within 14 days of randomization and two participants who died before they could receive plasma exchange.

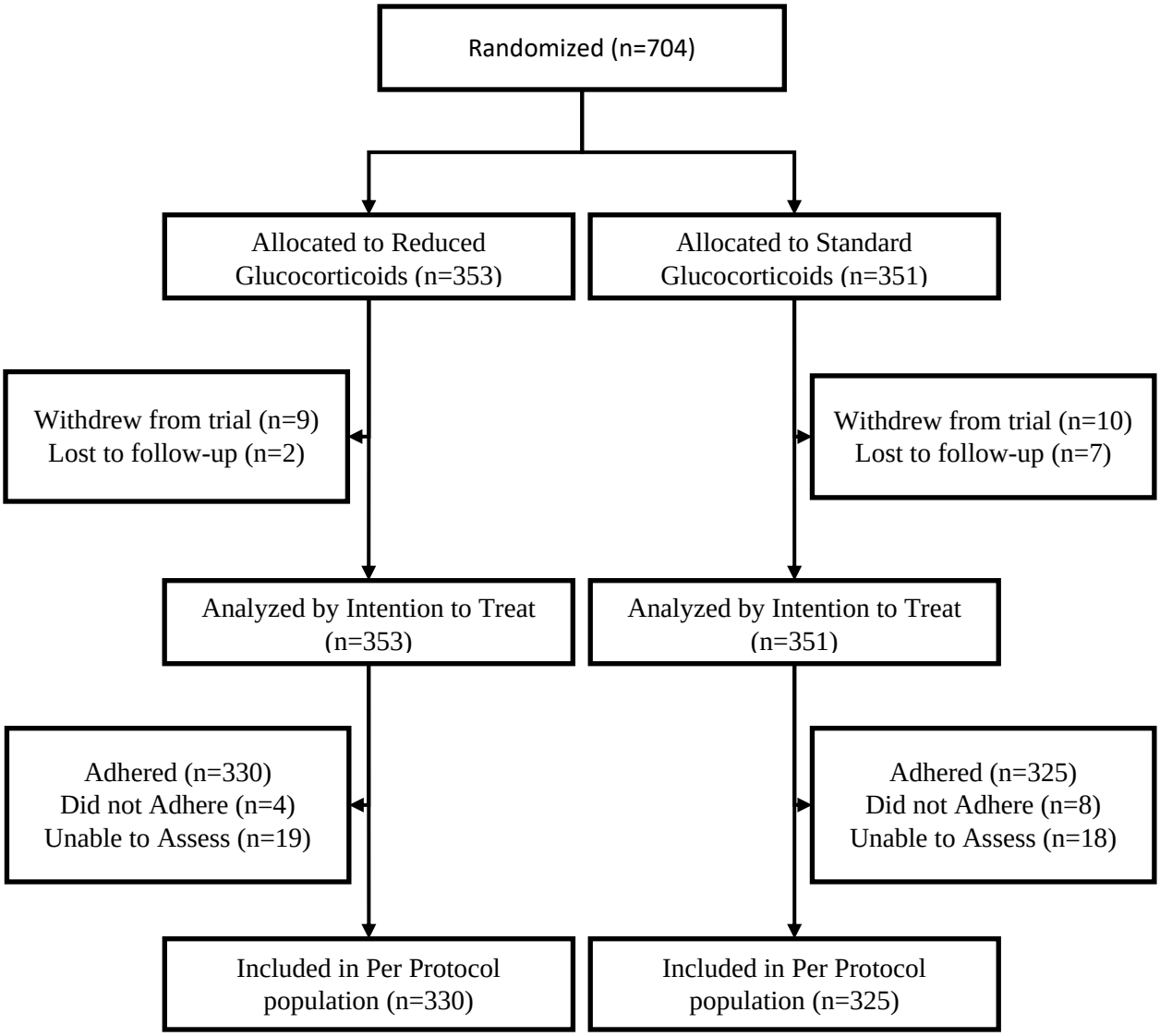

Figure S2. Glucocorticoid dosing participants

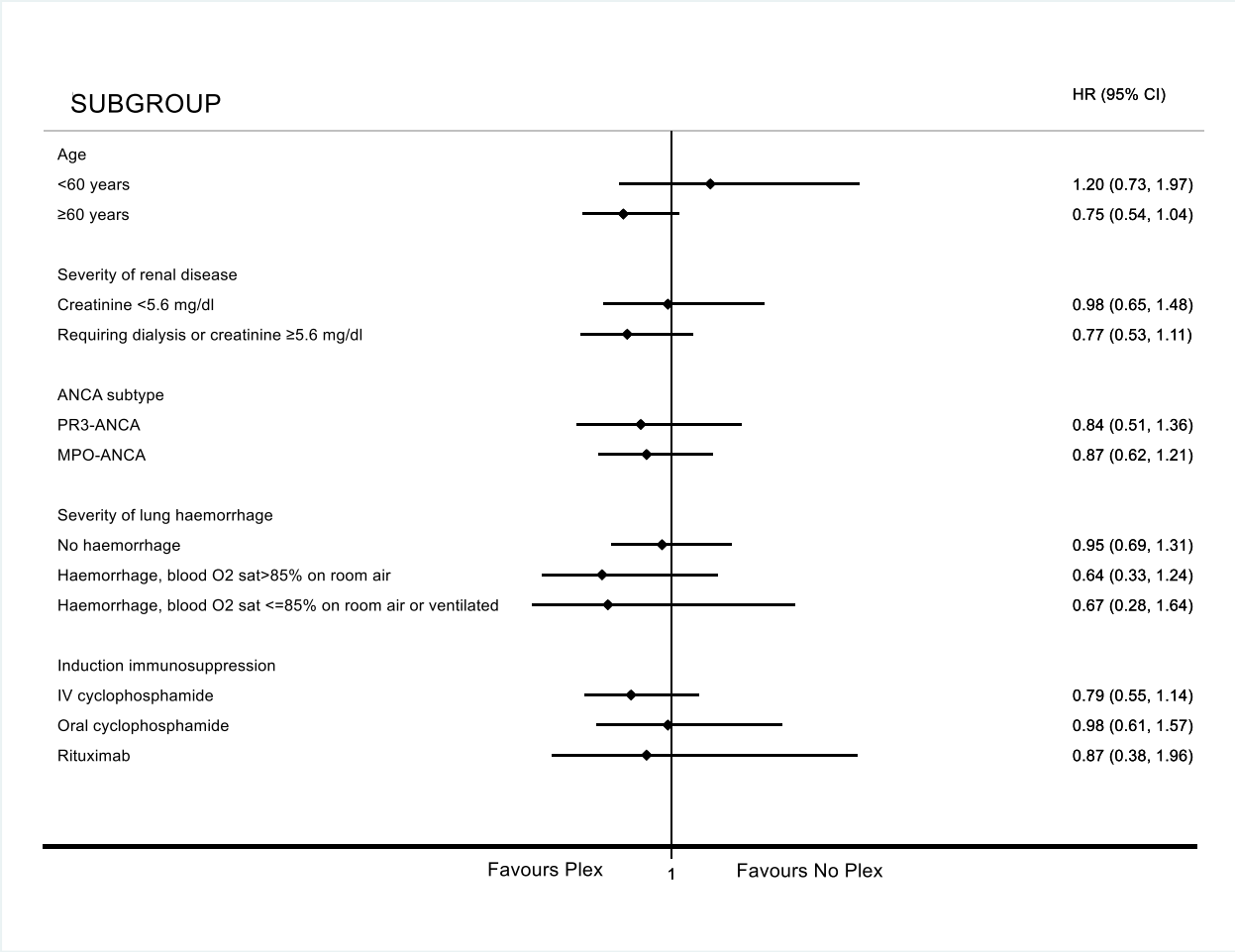

Figure S3. Results of subgroup analyses of the effect of plasma exchange on the primary outcome of death from any cause or end-stage kidney disease.
CI = confidence interval; ANCA = anti-neutrophil cytoplasmic antibody; PR3 = anti-proteinase antibody; MPO = anti-myeloperoxidase antibody; IV = intravenous; 500 µmol/L = 5.6 mg/dL; Plex = Plasma Exchange

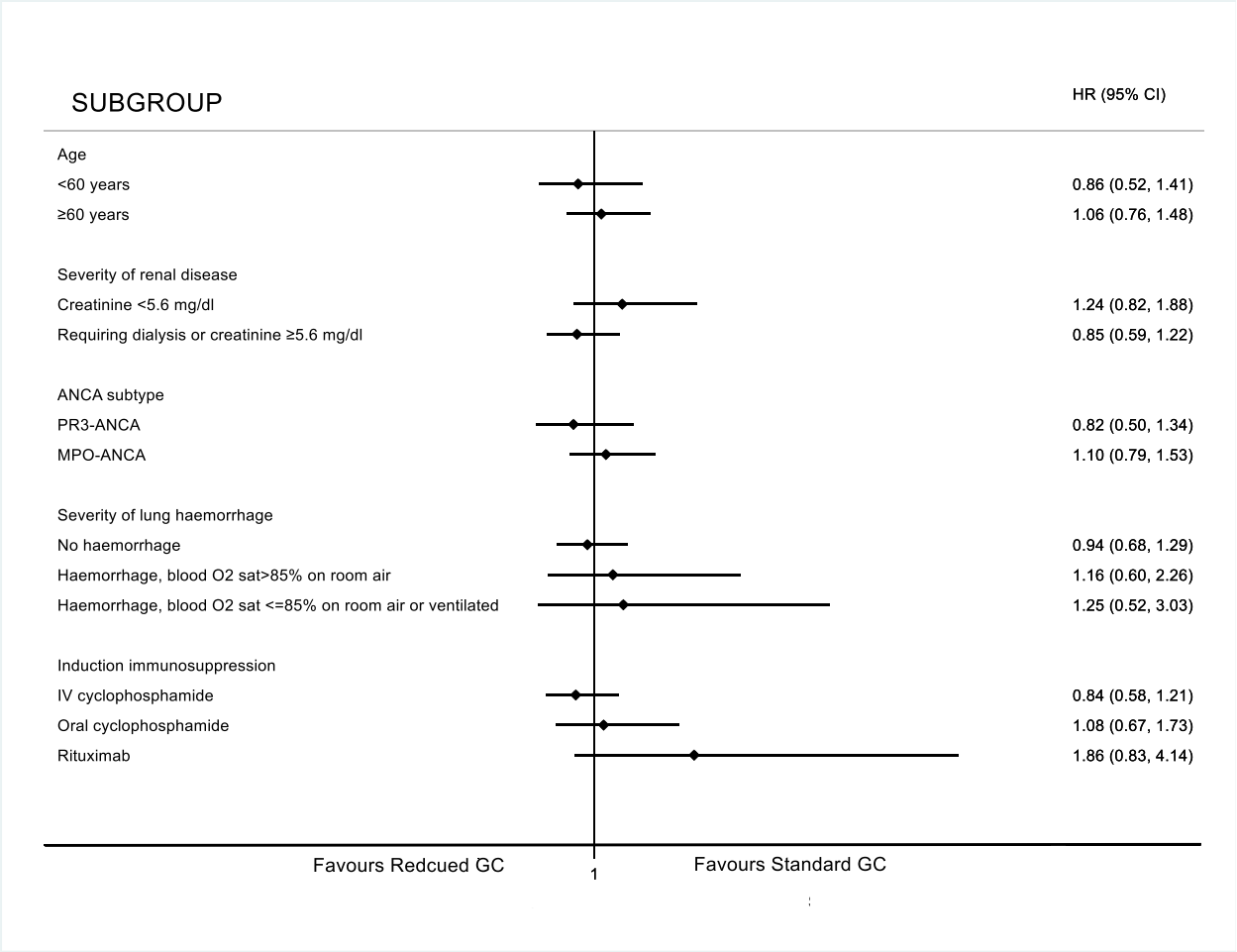

Figure S4. Results of subgroup analyses of the effect of a reduced-dose regimen of oral glucocorticoids on the primary outcome of death from any cause or end-stage kidney disease.

CI = confidence interval; ANCA = anti-neutrophil cytoplasmic antibody; PR3 = anti-proteinase antibody; MPO = anti-myeloperoxidase antibody; O2 sat = oxygen saturation; IV = intravenous; 500 µmol/L = 5.6 mg/dL; GC = glucocorticoids

Table S1. Pulse intravenous cyclophosphamide schedule. Doses may be modified for age and renal function. After week 13, patients in remission may be transitioned to remission-maintenance therapy.

Time (weeks)	Pulse number	Dose
0	1	15 mg/kg
2	2	15 mg/kg
4	3	15 mg/kg
7	4	15 mg/kg
10	5	15 mg/kg
13	6	15 mg/kg
16	7	15 mg/kg
19	8	15 mg/kg
22	9	15 mg/kg
25	10	15 mg/kg

Table S2. Oral and intravenous cyclophosphamide dose adjustments (mg/kg) for age and renal impairment.

	Oral Cyclophosphamide eGFR (ml/min/1.73 m^2)		IV Cyclophosphamide eGFR (ml/min/1.73 m^2)	
Age	>30	≤30	>30	≤30
<60	2	1.5	15	12.5
60-70	1.5	1.25	12.5	10
>70	1.25	1	10	7.5

NOTE: dose reductions for renal impairment should reflect renal function at the time the dose is given rather than baseline renal function

Table S3. Dosing for oral Glucocorticoids in the standard and reduced-dose limbs from trial start.

Week	Standard			Reduced-dose		
	<50 kg	**50-75 kg**	**>75 kg**	**<50 kg**	**50-75 kg**	**>75 kg**
	pulse	pulse	pulse	pulse	pulse	pulse
1	50	60	75	50	60	75
2	50	60	75	25	30	40
3-4	40	50	60	20	25	30
5-6	30	40	50	15	20	25
7-8	25	30	40	12.5	15	20
9-10	20	25	30	10	12.5	15
11-12	15	20	25	7.5	10	12.5
13-14	12.5	15	20	6	7.5	10
15-16	10	10	15	5	5	7.5
17-18	10	10	15	5	5	7.5
19-20	7.5	7.5	10	5	5	5
21-22	7.5	7.5	7.5	5	5	5
23-52	5	5	5	5	5	5
>52	Investigators' Local Practice			Investigators' Local Practice		

Table S4. Health related quality of life 12 months after randomization. For all scores, higher scores indicate better health related quality of life. Commonly accepted minimally important differences for the SF-36 are at least 5 points, for the EQ-5D Index is at least 0.03 points, and for the EQ-5D Thermometer is at least 5 points.

Score	PLEX	No PLEX	Mean Difference (95% CI)	Reduced-Dose Glucocorticoids	Standard-Dose Glucocorticoids	Mean Difference (95% CI)
SF-36 PCS	39.04	37.96	1.07 (-0.46 to 2.61)	39.13	37.84	1.29 (-0.26 to 2.84)
SF-36 MCS	51.94	51.40	0.55 (-0.67 to 1.76)	52.16	51.19	0.97 (-0.24 to 2.18)
EQ-5D Index	0.79	0.77	0.02 (-0.01 to 0.05)	0.79	0.77	0.02 (-0.01 to 0.05)
EQ-5D Thermometer	72.13	71.10	1.04 (-1.09 to 3.16)	72.11	71.07	1.04 (-1.09 to 3.17)

PLEX = plasma exchange; SF-36 = short form 36; PCS = physical component score; MCS = mental component score; EQ = EuroQol

Table S5. Number of patients experiencing serious adverse events.

Serious Adverse Event Type	PLEX (N=352)	No PLEX (n=352)	Relative Risk (95% CI)	Reduced-Dose Glucocorticoids (N=353)	Standard-Dose Glucocorticoids (n=351)	Unadjusted Relative Risk (95% CI)
Cardiovascular	69 (20%)	55 (16%)	1.25 (0.91 to 1.73)	68 (19%)	56 (16%)	1.21 (0.88 to 1.66)
Endocrine	9 (3%)	3 (1%)	3.00 (0.82 to 11.0)	4 (1%)	8 (2%)	0.50 (0.15 to 1.64)
Gastrointestinal	34 (10%)	39 (11%)	0.87 (0.56 to 1.35)	43 (12%)	30 (9%)	1.43 (0.92 to 2.22)
Hematologic	25 (7%)	16 (5%)	1.56 (0.85 to 2.88)	22 (6%)	19 (5%)	1.15 (0.63 to 2.09)
Infection	136 (39%)	114 (32%)	1.19 (0.98 to 1.46)	119 (34%)	131 (37%)	0.90 (0.74 to 1.10)
Kidney/Urinary	41 (12%)	36 (10%)	1.14 (0.75 to 1.74)	50 (14%)	27 (8%)	1.84 (1.18 to 2.87)
Surgery	16 (5%)	13 (4%)	1.23 (0.60 to 2.52)	14 (4%)	15 (4%)	0.93 (0.45 to 1.89)
Vasculitis relapse	23 (7%)	32 (9%)	0.72 (0.43 to 1.20)	32 (9%)	23 (7%)	1.38 (0.83 to 2.32)
Other	89 (25%)	79 (22%)	1.13 (0.86 to 1.47)	91 (26%)	77 (22%)	1.18 (0.90 to 1.53)

PLEX = plasma exchange; CI = confidence interval