Echanges plasmatiques dans les vascularites associées aux ANCA

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Echanges plasmatiques dans les VAA

- Vascularites associées aux ANCA
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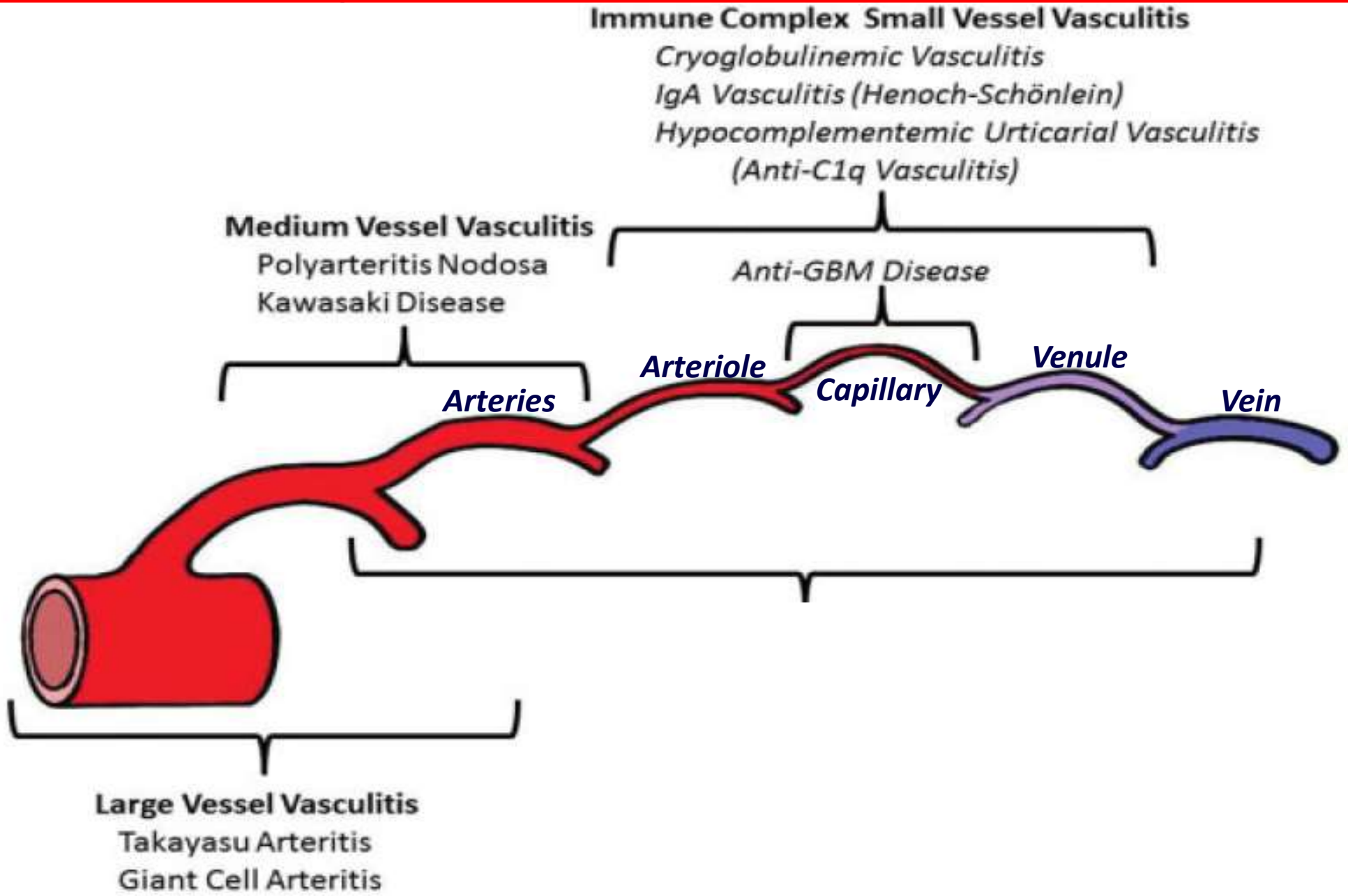
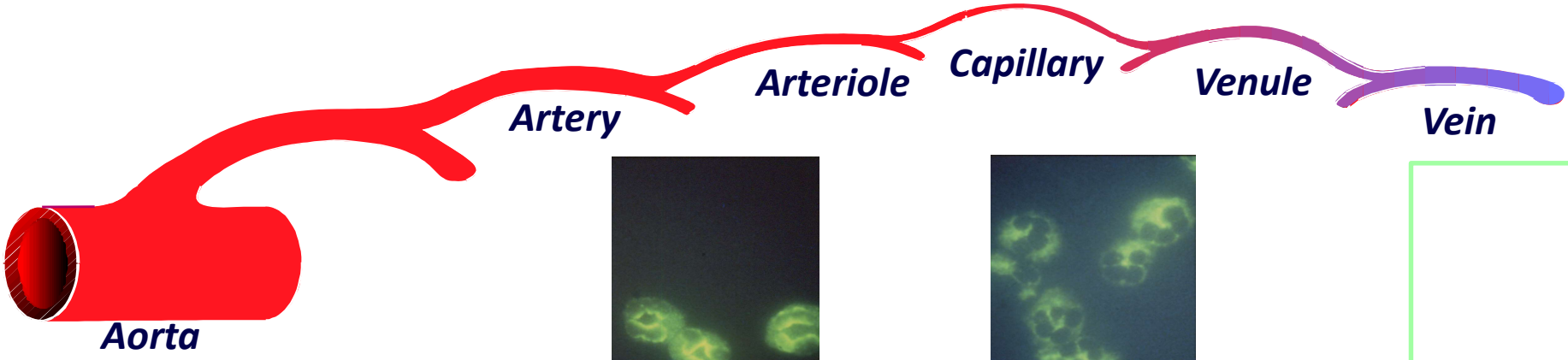
2012 Revised Chapel Hill Conference Nomenclature of Vasculitides



Jennette JC, Arthritis Rheum 2013

Nomenclature de Chapell Hill des vascularites associées aux ANCA



pANCA : 60 %
8/10 anti-MPO

cANCA : 85 %
9/10 anti-PR3

pANCA : 40 %
¾ anti-MPO

Vascularite sans granulome ni asthme → Polyangéite microscopique (PAM)

Vascularite avec granulome sans asthme → Granulomatose avec polyangéite (GPA, Wegener)

Vascularite avec asthme éosinophilique et granulome → Granulomatose éosinophilique avec polyangéite (GEPA, Churg-Strauss)

Jennette JC, Arthritis Rheum 2013

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History

- **The use of PLEX in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis is still controversial.**
- **1975: Lockwood reported treating Goodpasture's (anti–glomerular basement membrane [GBM]) disease with PLEX as an adjunct to immunosuppression:**
  - **rapid reduction in anti-GBM antibody levels**
  - **followed by a reduction in serum creatinine level.**

  Lockwood CM, BMJ 1975
- **1977: Lockwood published the first report describing the use of PLEX in 9 patients with crescentic glomerulonephritis (GN)**
  - **5 rapidly recovered renal function** *Lockwood CM, Lancet 1977*

  => use of PLEX in the treatment of crescentic GN without anti-GBM antibodies before the discovery of ANCA (1982).

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Evidence suggests a pathogenic role for ANCA

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- **Primed neutrophils release ANCA antigens at the cell surface, where they interact with ANCA, leading to activation of PMNs**

  => adhesion to endothelial cells

  => respiratory burst and degranulation with the release of toxic products and finally, accelerated neutrophils dysregulated apoptosis and impaired clearance by macrophages

  => endothelial cell damage. *Jennette JC, Nat Rev Rheumatol 2014*

- **Animal models of anti-MPO ANCA-associated disease**

  - Anti-MPO Ab generation by immunizing an MPO-/- mouse with murine MPO and transferred into wild-type mice

  => sufficient for the mice to develop GN ≈ to that in human disease.

  Xiao H, J Clin Invest 2002

- **A case of transplacental transfer of ANCAs from mother to child**

  => neonatal GN and pulmonary haemorrhage, which was treated successfully using GC and PLEX *Bansal PJ, Ann Allergy Asthma Immunol 2004*

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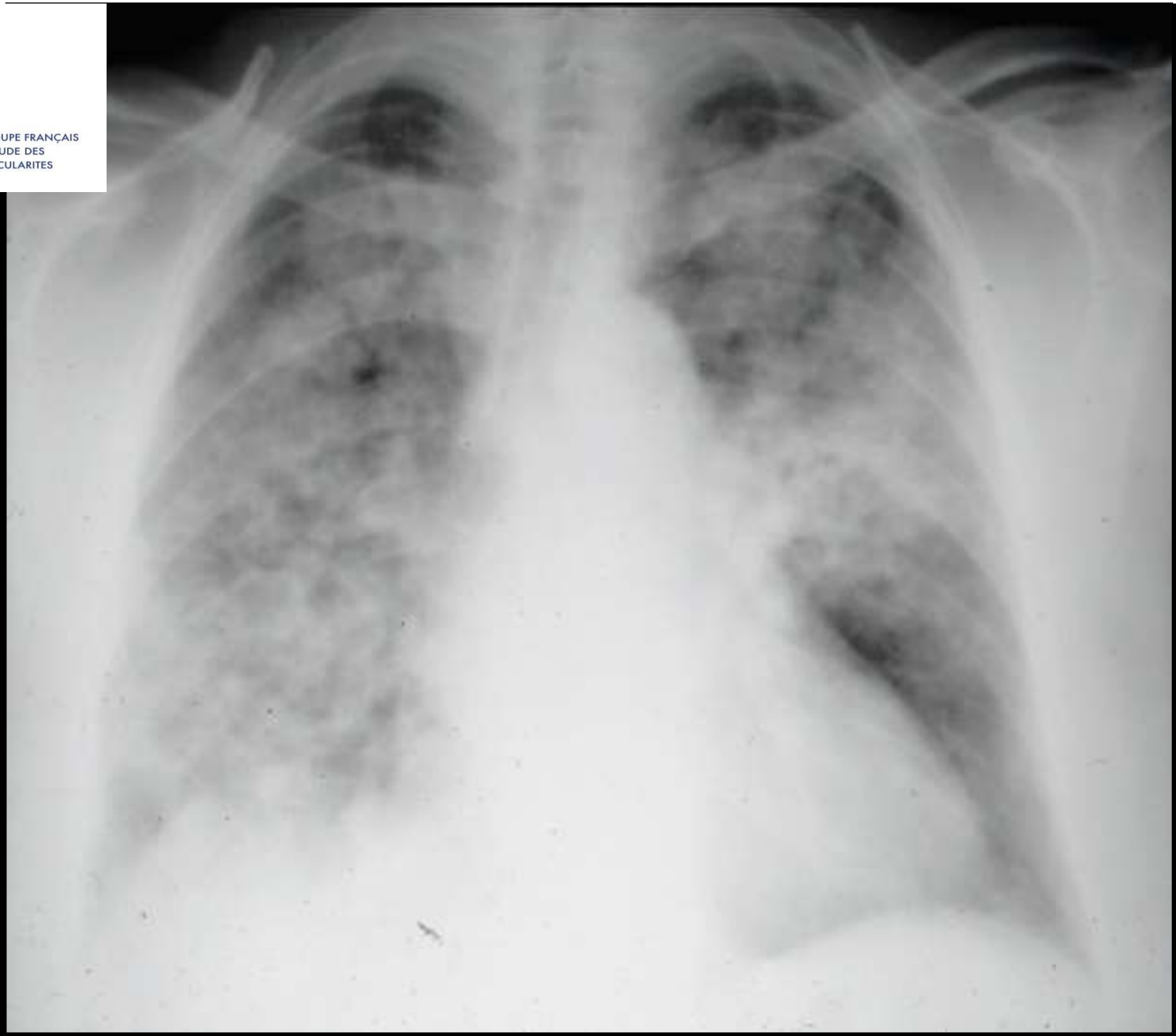

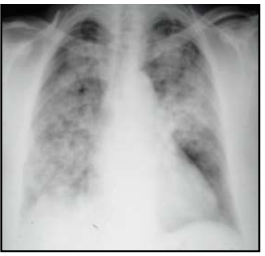

Non randomized data for use in lung haemorrhage

- **The use of PLEX in ANCA-associated vasculitis lung haemorrhage is not currently supported by randomized data.**
- **There have been several non-randomized studies, some of which strongly advocated its use as standard of care.**
- **Pros:**

  - The use of PLEX in this setting is mostly based on a small uncontrolled retrospective study:
  - **20 patients received PLEX for lung haemorrhage**
    - **55% were not on mechanical ventilation**
    - **30% did not have renal involvement**

    => resolution of pulmonary symptoms in all 20 patients

    => 19 survived the initial disease episode.

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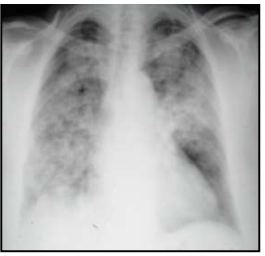
Klemmer PJ, Am J Kidney Dis 2003



Non randomized data for use in lung haemorrhage

Cons:

- This study was uncontrolled and referred to historical cases of lung haemorrhage. However, there is a spectrum of severity in lung haemorrhage from asymptomatic disease to ventilator-dependent disease.
- The cause of death in AAV patients with lung haemorrhage is commonly related to infection and PLEX removing Igs indiscriminately may increase the risk of severe infection.
- Incomplete restoration of clotting factors may ↑bleeding.
- More recent cohorts have not found compelling evidence that PLEX alters outcome in patients with either severe or nonsevere lung haemorrhage.

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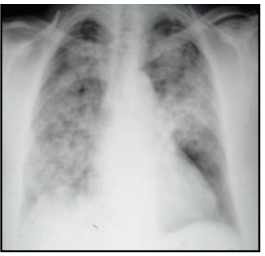
Walsh M, Curr Opin Nephrol Hypertens 2004
Cybulsky AV, Am J Kidney Dis 2014
Cartin-Ceba, Arthritis Rheumatology 2016



Non randomized data for use in lung haemorrhage

- These retrospective data,
- The logic of removing ANCA from the circulation,
- The frequently severe condition of the patient with lung haemorrhage
- The probable similar pathogenic basis of lung haemorrhage and of the associated rapidly progressive GN (may be improved by the same treatment),

put great pressure on the physician to use PLEX
- in patients with ANCA-associated vasculitis and lung haemorrhage
- in the absence of clear data on its benefits.

Walters G, Pediatr Nephrol 2016

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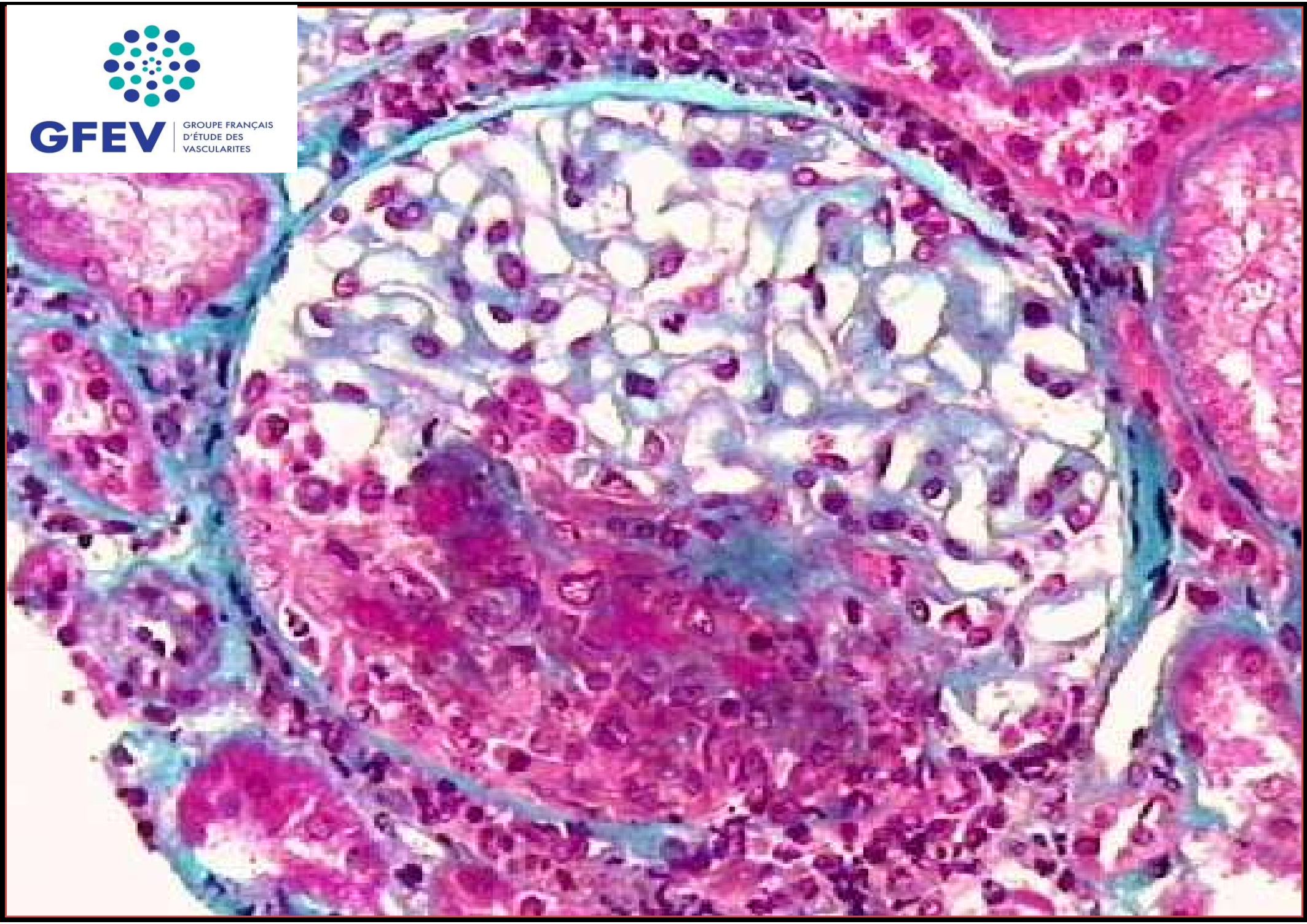

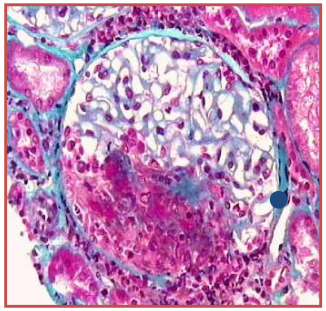

Randomized controlled trials

10 RCT with PLEX in renal ANCA-associated vasculitis

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- **1991:** 48 patients with 23 GPA, 20 MPA or 5 idiopathic RPGN
  - Stratified into 3 groups depending on renal function
  - 19 dialysis-dependent patients
  - Heavy course of immunosuppression for all: GC + AZA + CYC for 2 months +/- PLEX then AZA for maintenance

=> beneficial effect of PLEX at Month 1 in 10/11 dialysis-dependent pts vs. 3/8 dialysis-dependent controls (p=0.04)

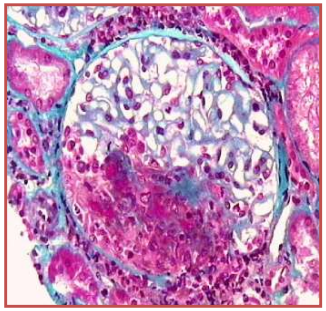
=> no outcome difference was shown for pts with milder renal deterioration (creatinine > ou < 500 µmol/L)

=> any early advantage from PLEX appeared to make little difference to the M12 outcomes

=> high mortality in both PLEX and non-PLEX groups

➢ **Benefit of PLEX for patients requiring dialysis at presentation**

Pusey CD, Kidney Int 1991



Randomized controlled trials

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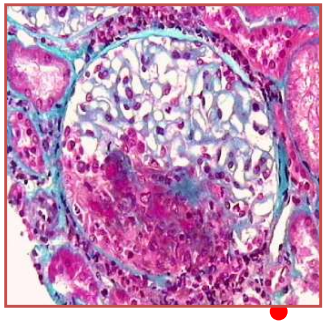
PLEX is not commonly performed for ANCA-associated vasculitis, if the serum creatinine is < 500 μmol/L.

- **2011: Only one RCT included 32 newly-diagnosed GPA patients with moderate renal impairment (median serum creatinine 240 μmol/L; range, 70-930).**
  => PLEX improved renal survival in patients with creatinine > 250 μmol/L (p<0.01)
  - **at 1 month, 3 months, 12 months**
  - **and 5 years**
  - **with no effect on mortality or vasculitis relapse rate.**

➢ **Benefit of PLEX that may persist 5 years in patients with moderate renal impairement.**

Szpirt WM, Nephrol Dial Transplant 2011



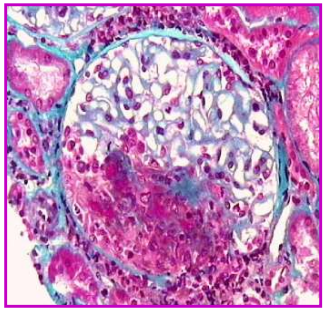
Randomized controlled trials

European Vasculitis Society
EUVAS

2007 : MEPEX study from the EUVAS

- 137 pts with newly-diagnosed ANCA-associated vasculitis
- no anti-GBM Ab or linear staining of GBM on histology
- Biopsy-proven necrotizing GN
- acute severe renal failure (creatinine level >500 μmol/L)
- All received CYC PO 6 months and GC then AZA
- Randomization: 7 PLEX sessions within 2 weeks vs. pulse MP (3 x 1g) as initial adjuvant therapy
- Primary endpoint: dialysis independence at 3 months
- Secondary endpoints included renal and patient survival at 1 year.

Jayne DRW, J Am Soc Nephrol 2007

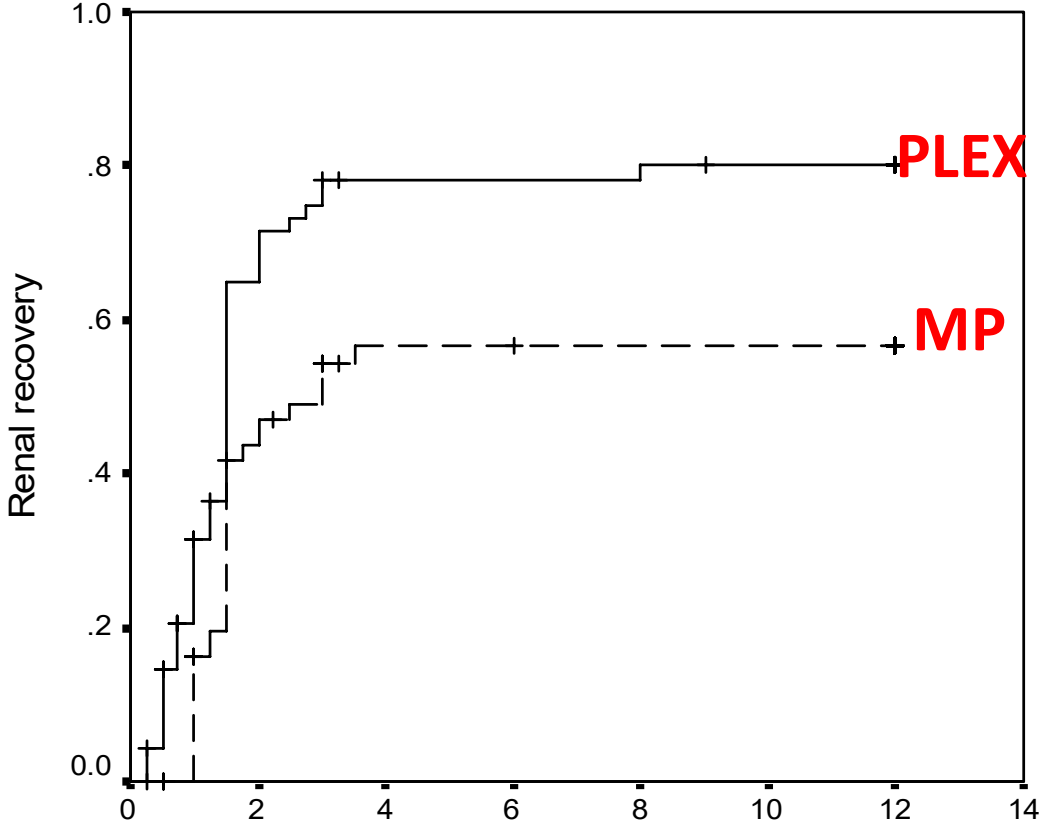


MEPEX Renal recovery

European Vasculitis Society EUVAS

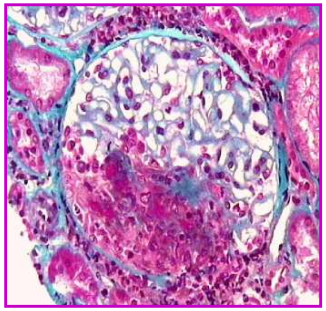
Increase by 20% in the number of patients alive and off dialysis

at 3 months: 46% vs 69% (95% CI for the difference, 18-25%) (p=0.02)



at 12 months: 43% vs 59% (p=0.008)

Jayne DRW, J Am Soc Nephrol 2007



MEPEX Renal survival

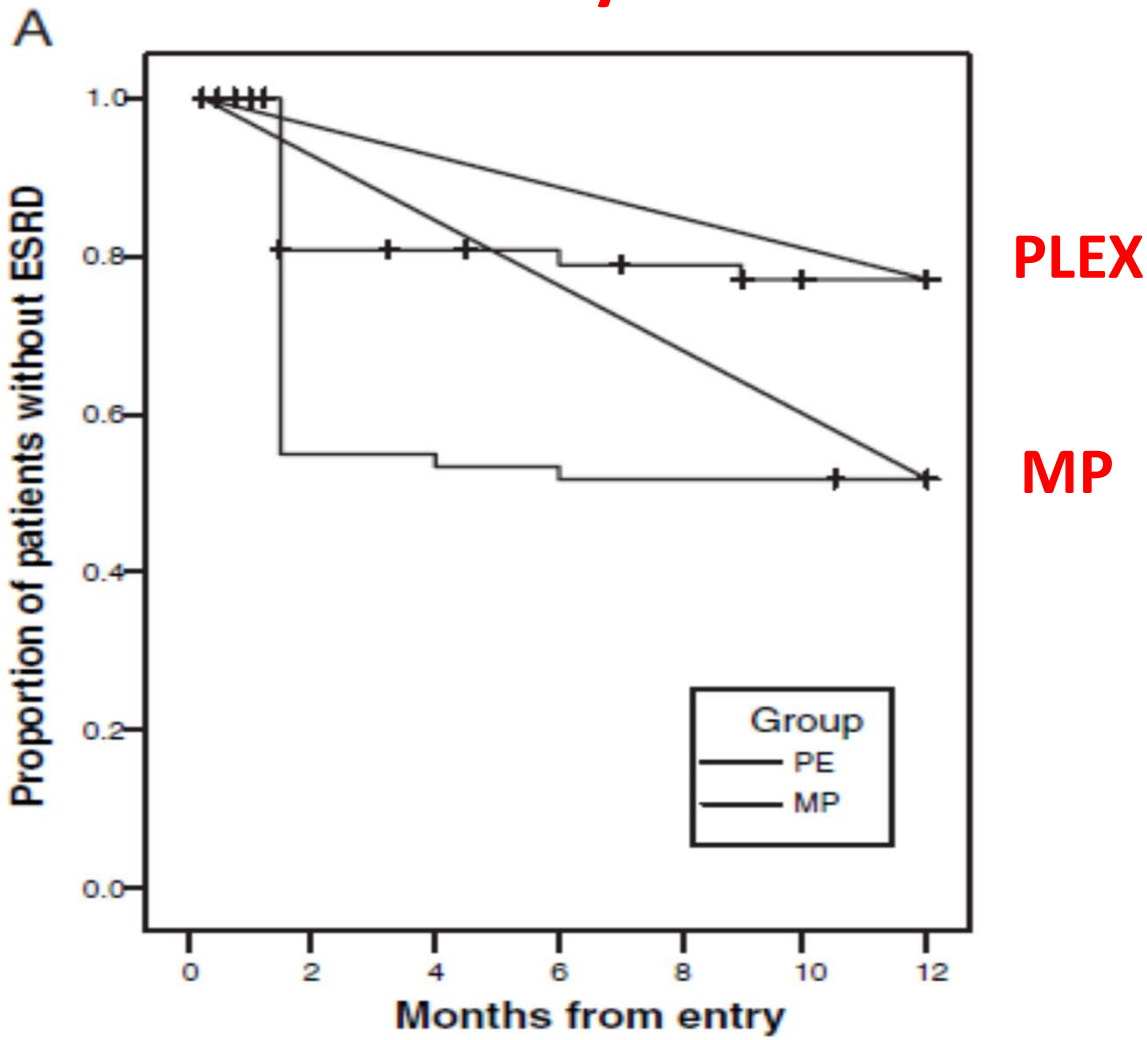
24% risk reduction in progression to ESRD at 1 year with PLEX

from 43% to 19%

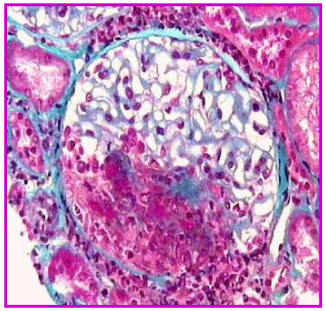
(95% CI: 6.1-41%)

for PLEX vs MP

(p=0.04)



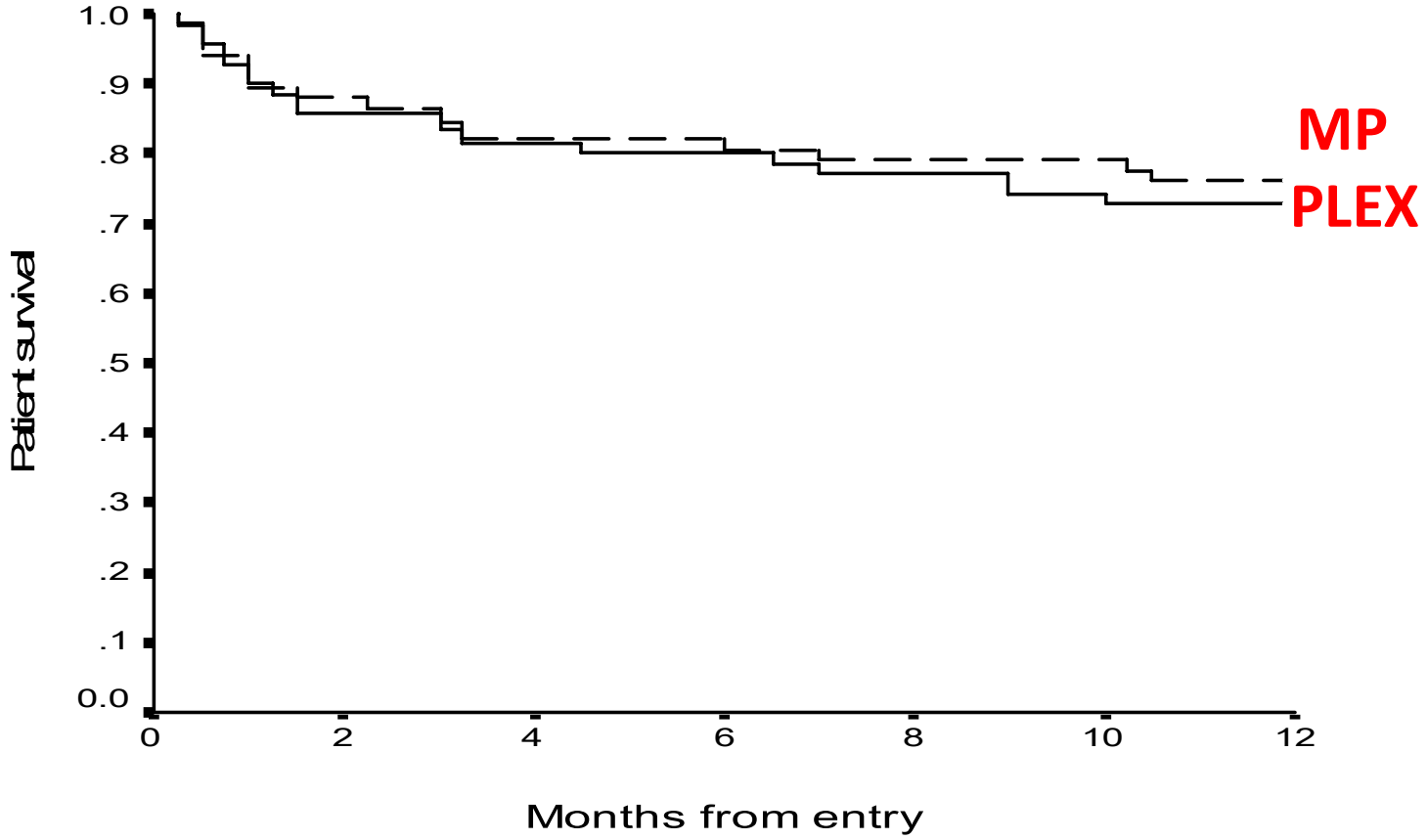
Jayne DRW, J Am Soc Nephrol 2007



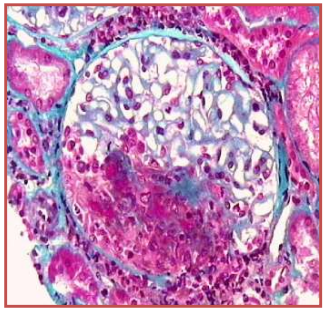
MEPEX Overall Survival

No PLEX impact on mortality at 1 year: 76% vs 73%

High mortality rate of 26% at 3 months



Jayne DRW, J Am Soc Nephrol 2007



MEPEX Long-term outcomes

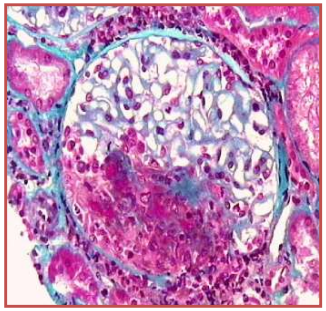
http://www.kidney-international.org

clinical trial

Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear

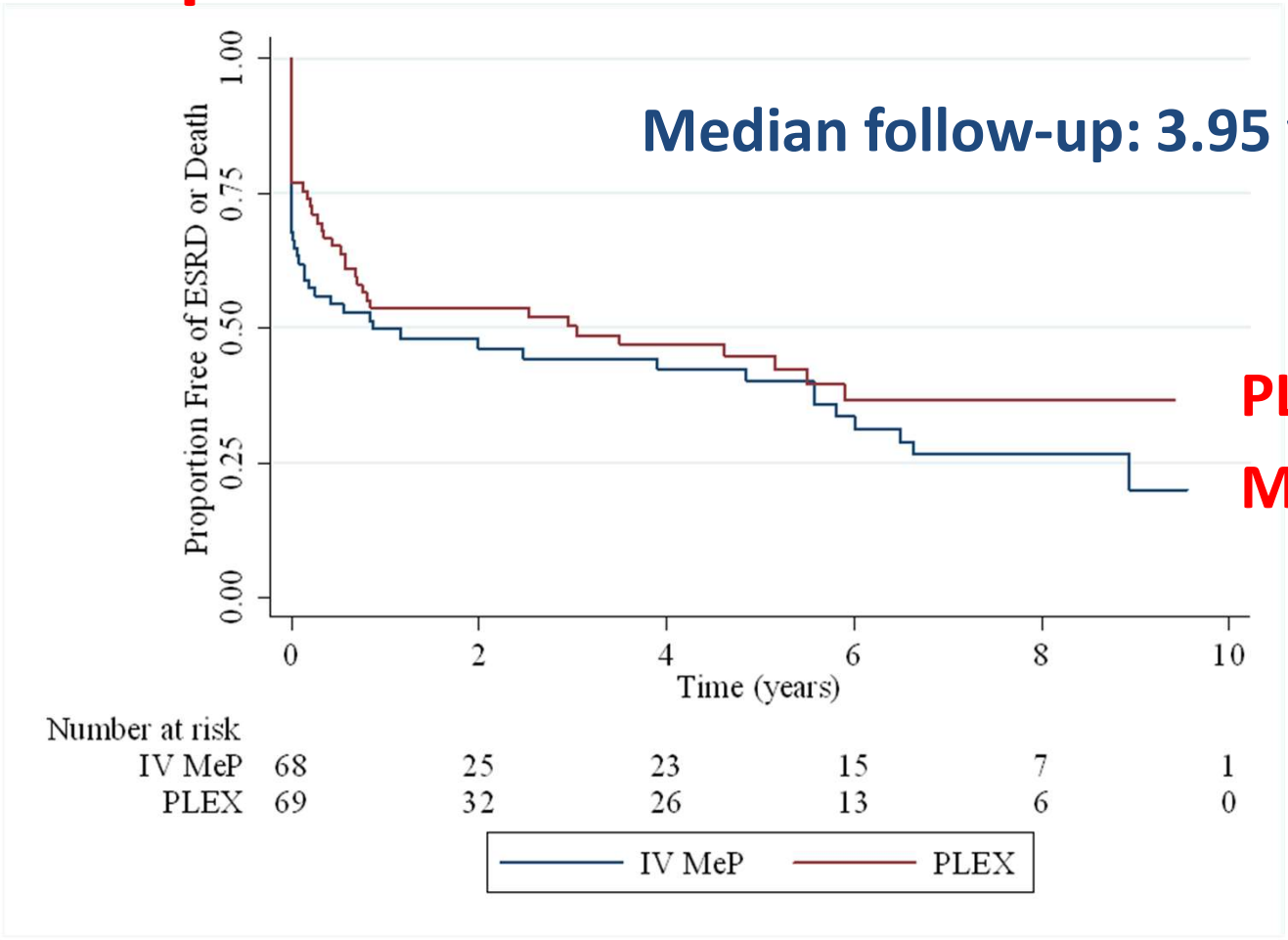
Michael Walsh[1], Alina Casian[2], Oliver Flossmann[3], Kerstin Westman[4], Peter Höglund[5], Charles Pusey[6] and David R.W. Jayne[2] on behalf of the European Vasculitis Study Group (EUVAS)

Walsh M, Kidney International 2013



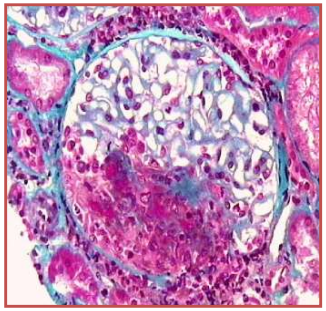
MEPEX Long-term outcomes

Proportion free of ESRD or Death



PLEX vs MP; HR 0.81, 95% CI 0.53-1.23; p=0.32
competing risk regression model

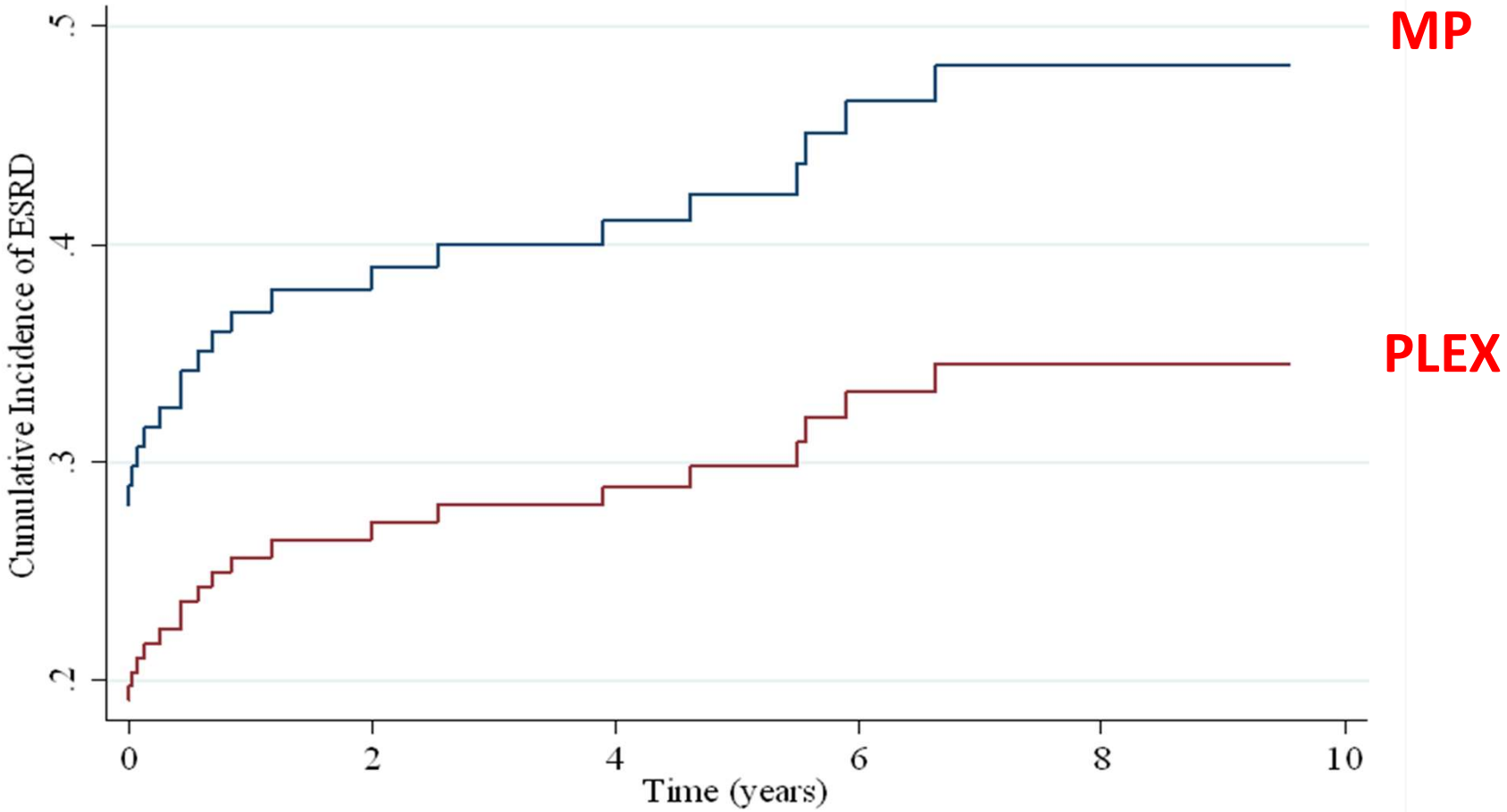
Walsh M, Kidney International 2013



MEPEX Long-term outcomes

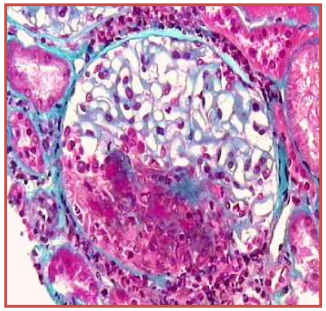
Cumulative incidence of ESRD

death is treated as competing risk



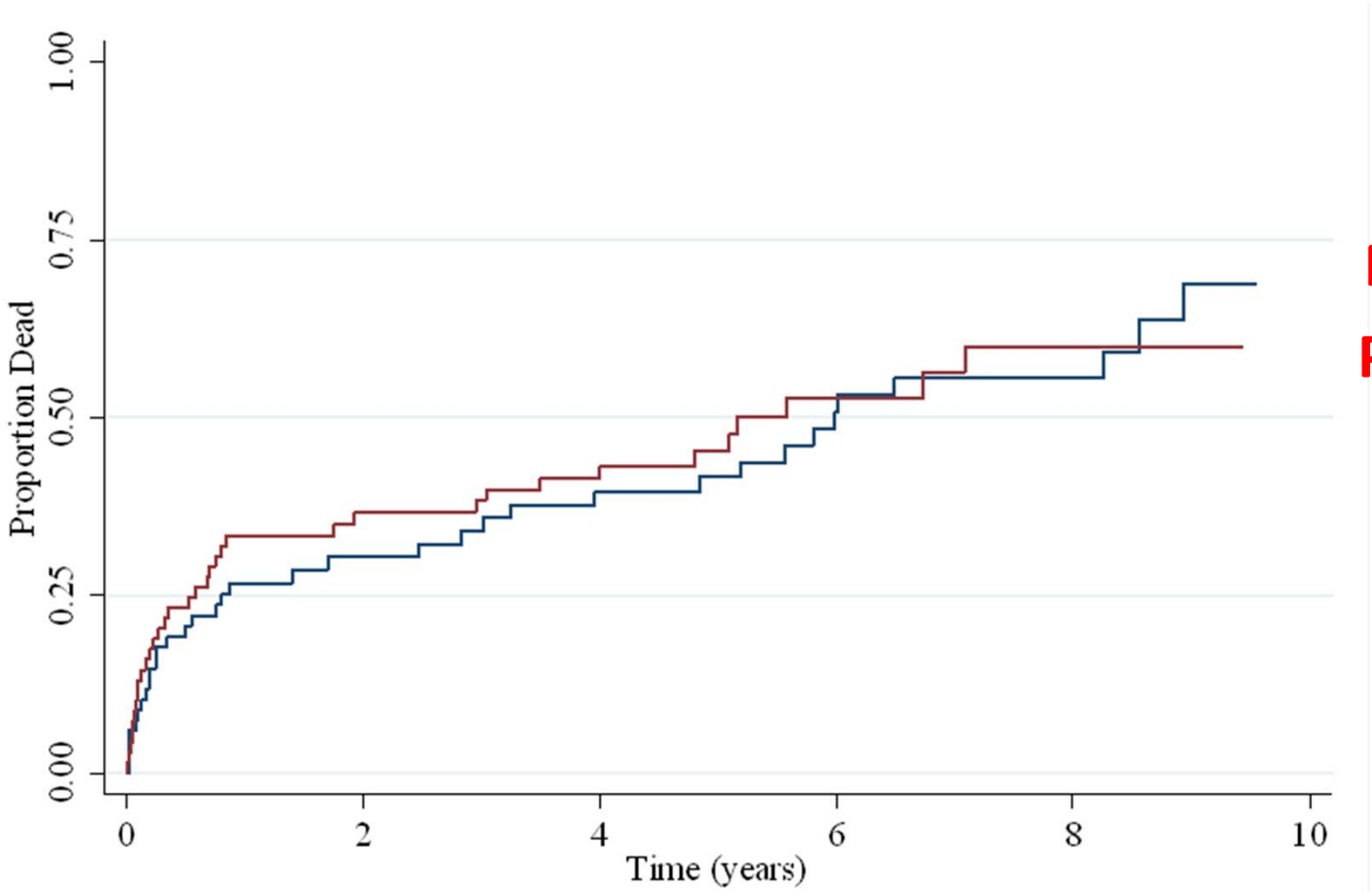
PLEX vs MP; HR 0.64, 95% CI 0.40-1.05; p=0.08

Walsh M, Kidney International 2013



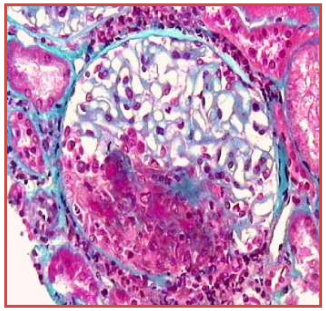
MEPEX Long-term outcomes

Proportion of Deaths



PLEX vs MP; HR 1.08, 95% CI 0.67-1.73; p=0.75

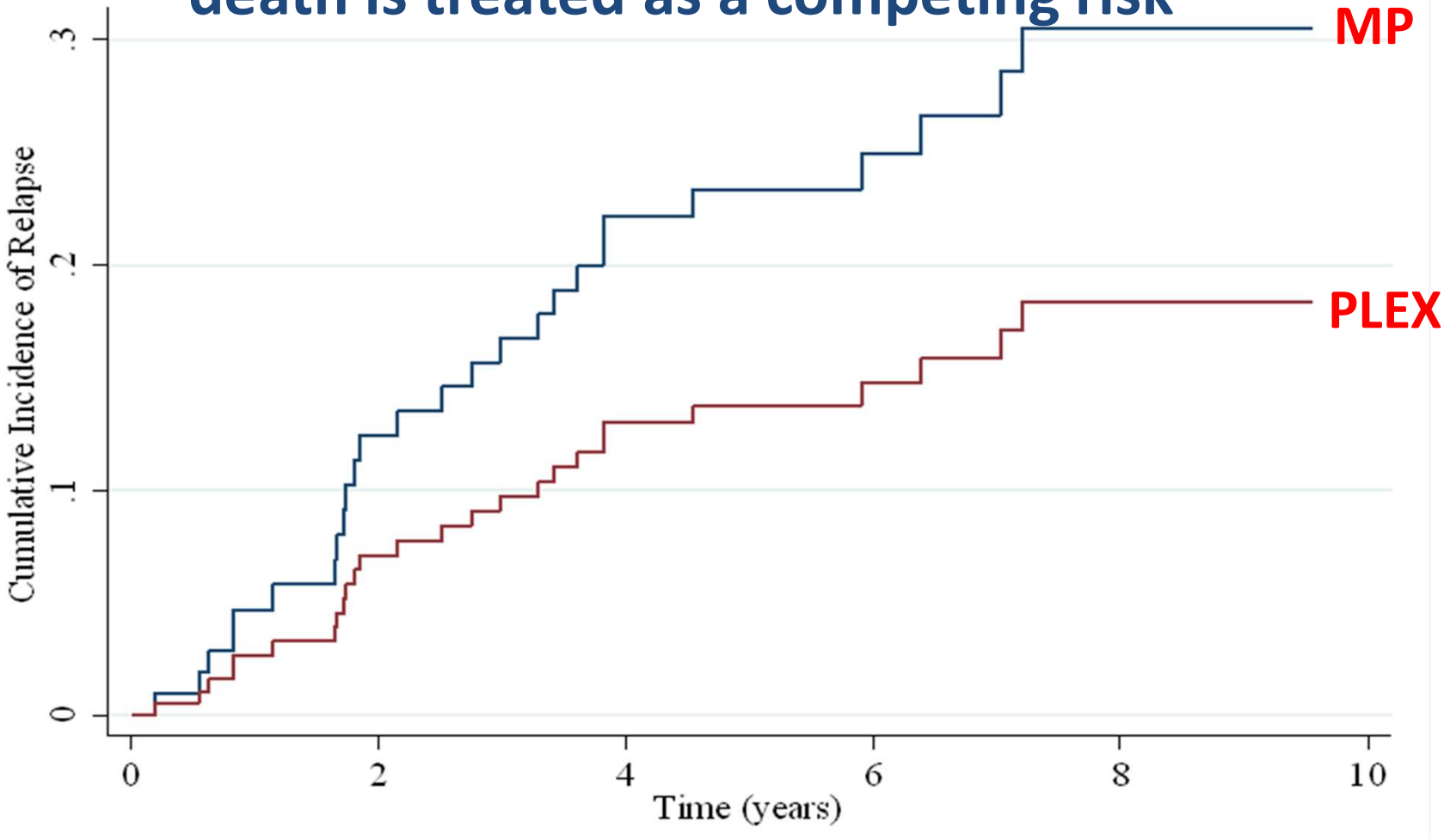
Walsh M, Kidney International 2013



MEPEX Long-term outcomes

Cumulative Incidence of Relapse

death is treated as a competing risk



MP vs PLEX; HR 0.56, 95% CI 0.26 to 1.21; p=0.14

Walsh M, Kidney International 2013

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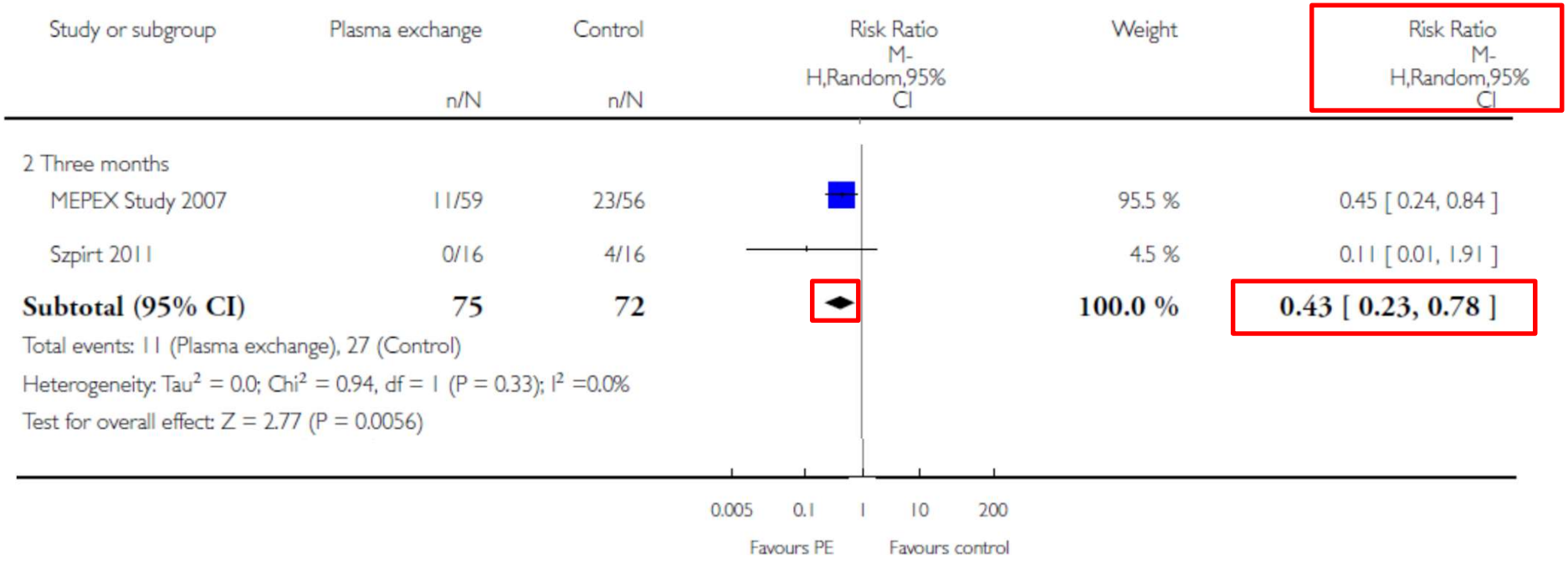
Meta analyses and Systematic Reviews

- **Two meta-analyses on PLEX in ANCA-associated vasculitis for renal vasculitis have been published with similar results.**
- **Low level of heterogeneity => overall result likely to be valid**
- **PLEX significantly reduced the risk of ESRD**
  - **at 3 months**
  - **at 12 months**
- **PLEX significantly reduced the composite ESRD or death**
- **Mortality appears to be unchanged**
- **There were no other demonstrable differences between groups in terms of renal function or adverse events.**

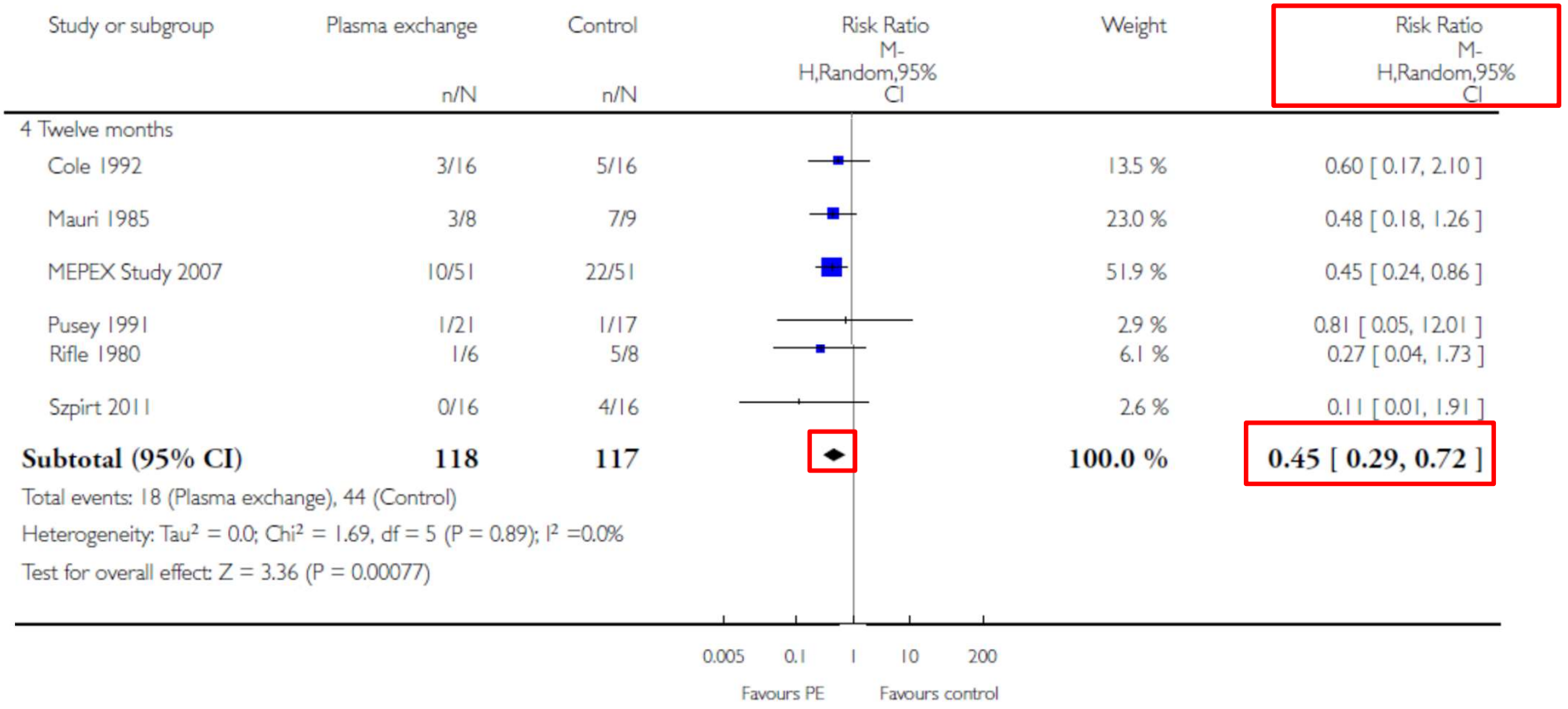
Walsh M, Am J Kid Dis 2010
Walters G, Cochrane Database of Systematic Reviews 2015

PLEX significantly reduced the risk of ESRD at 3 months



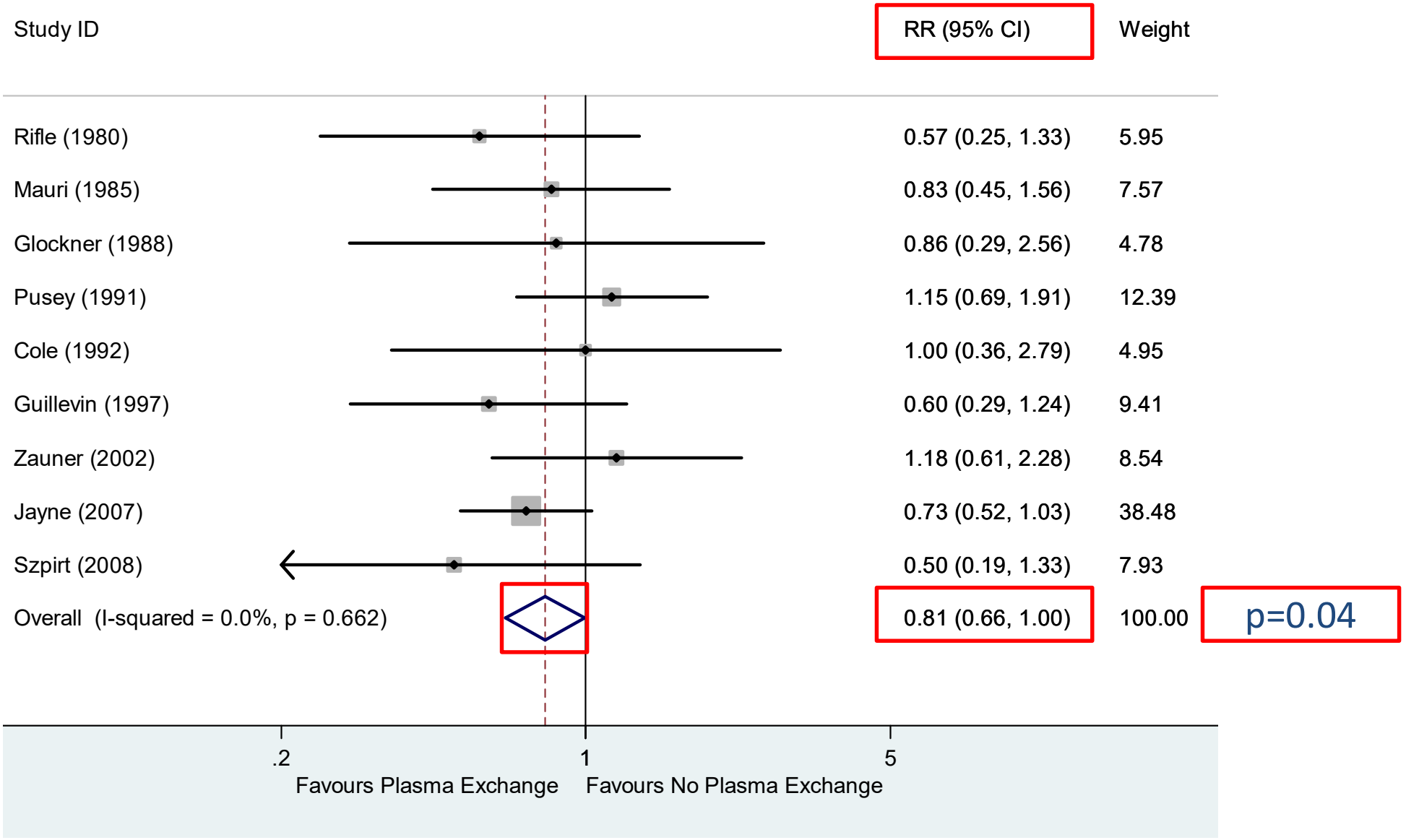
Walters G, Cochrane Database of Systematic Reviews 2015

PLEX significantly reduced the risk of ESRD at 12 months



Walters G, Cochrane Database of Systematic Reviews 2015

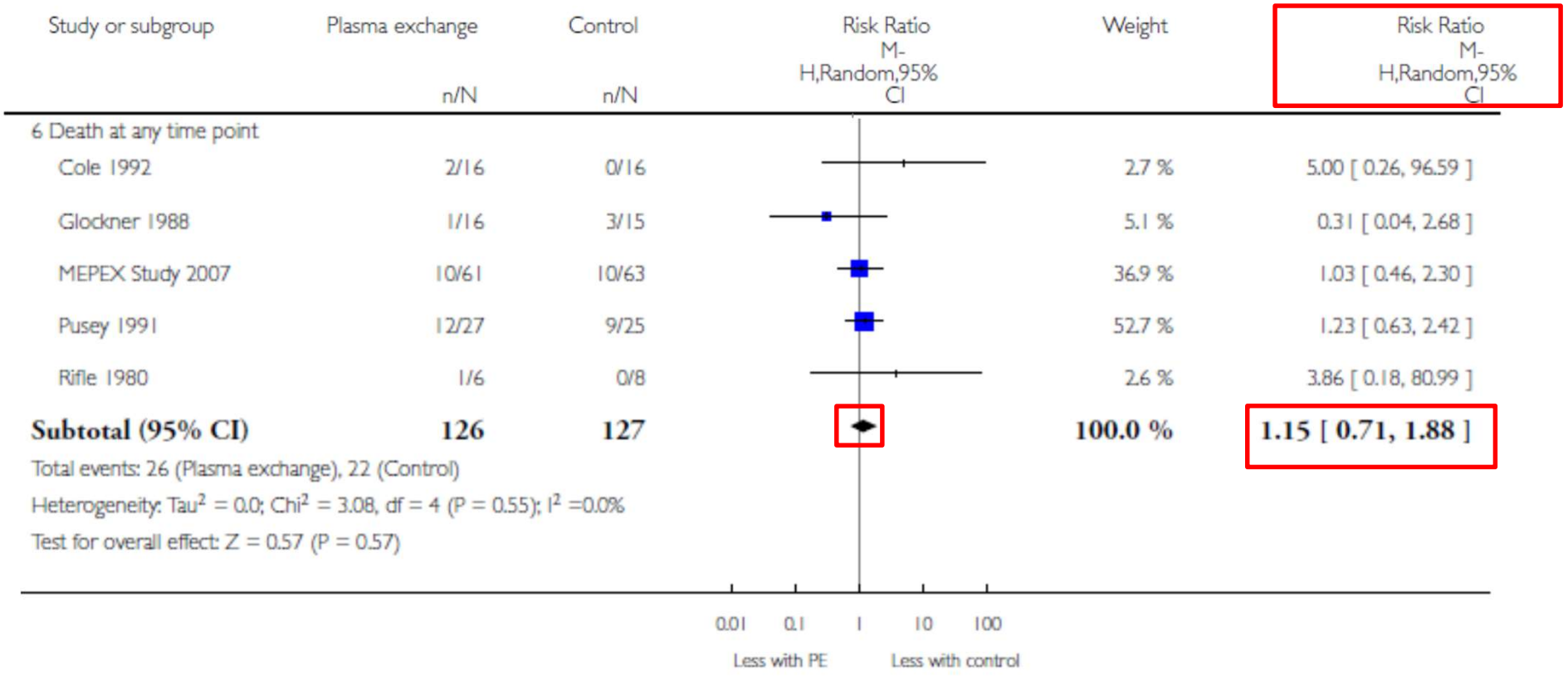
PLEX significantly reduced the composite ESRD or Death



Walsh, Am J Kid Dis 2010

Cochrane Library

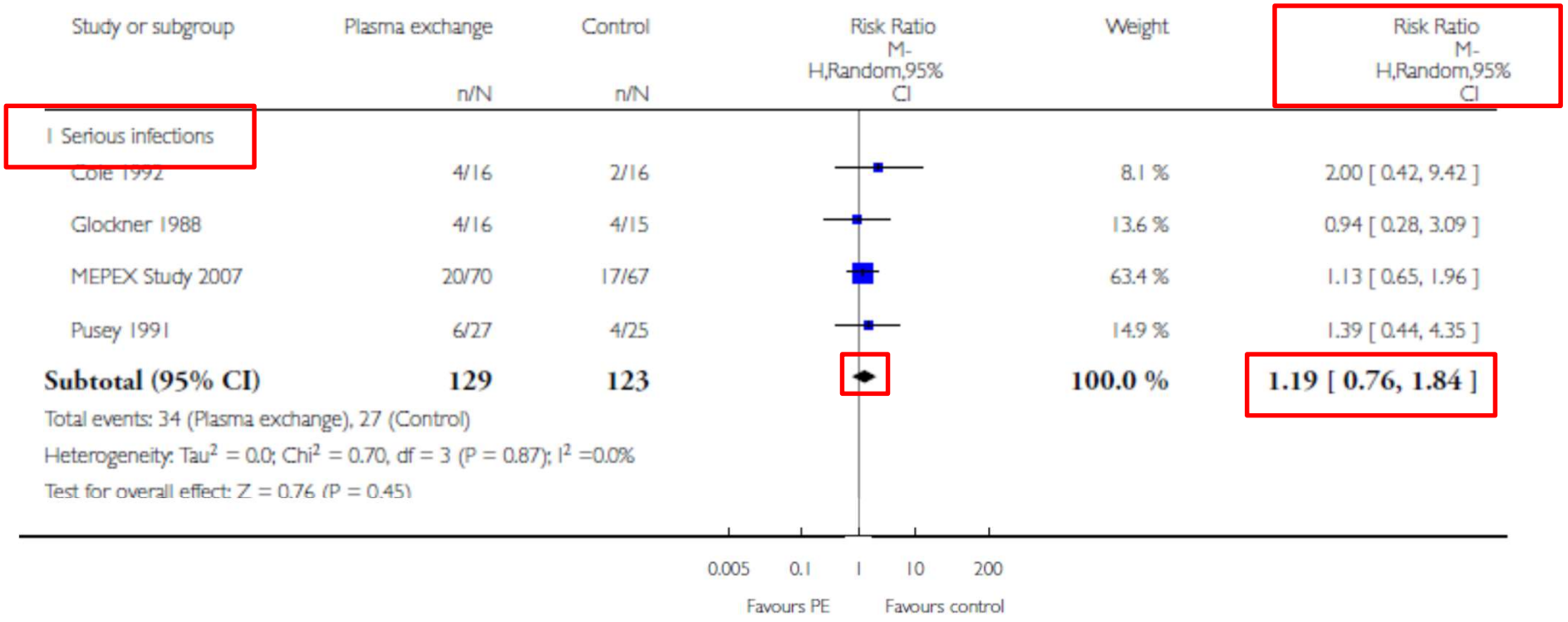
Mortality appears to be unchanged with PLEX



Walters G, Cochrane Database of Systematic Reviews 2015

Cochrane Library

There were no other between groups differences in terms of AEs, including serious infections



Walters G, Cochrane Database of Systematic Reviews 2015

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PEXIVAS : EP et corticothérapie réduite d'induction dans les VAA sévères

Rationale

- Plasma exchange
  - Rapidly reduce autoantibodies to limit organ damage
  - Low adverse effect rates
- Reduced glucocorticoids
  - Reduce risk of infection
  - Risk of less effective disease control
  - No accepted standard of care

PEXIVAS : EP et corticothérapie réduite d'induction dans les VAA sévères

Questions

1. Does plasma exchange reduce death from any cause or end-stage renal disease?

2. Is a "reduced" dose oral glucocorticoid regimen non-inferior to a "standard" dose regimen in terms of death from any cause or end-stage renal disease?

Objectifs et Critères de jugement

Objectif Principal

- Démontrer la supériorité des EP en adjonction aux CS et aux IS
- Démontrer la non-infériorité d'une dose réduite de CS

Critère de Jugement Principal

- Critère composite :

mortalité ou insuffisance rénale terminale

Design

700 Patients:
Severe ANCA vasculitis
(lung haemorrhage or renal = eGFR <50 ml/min)

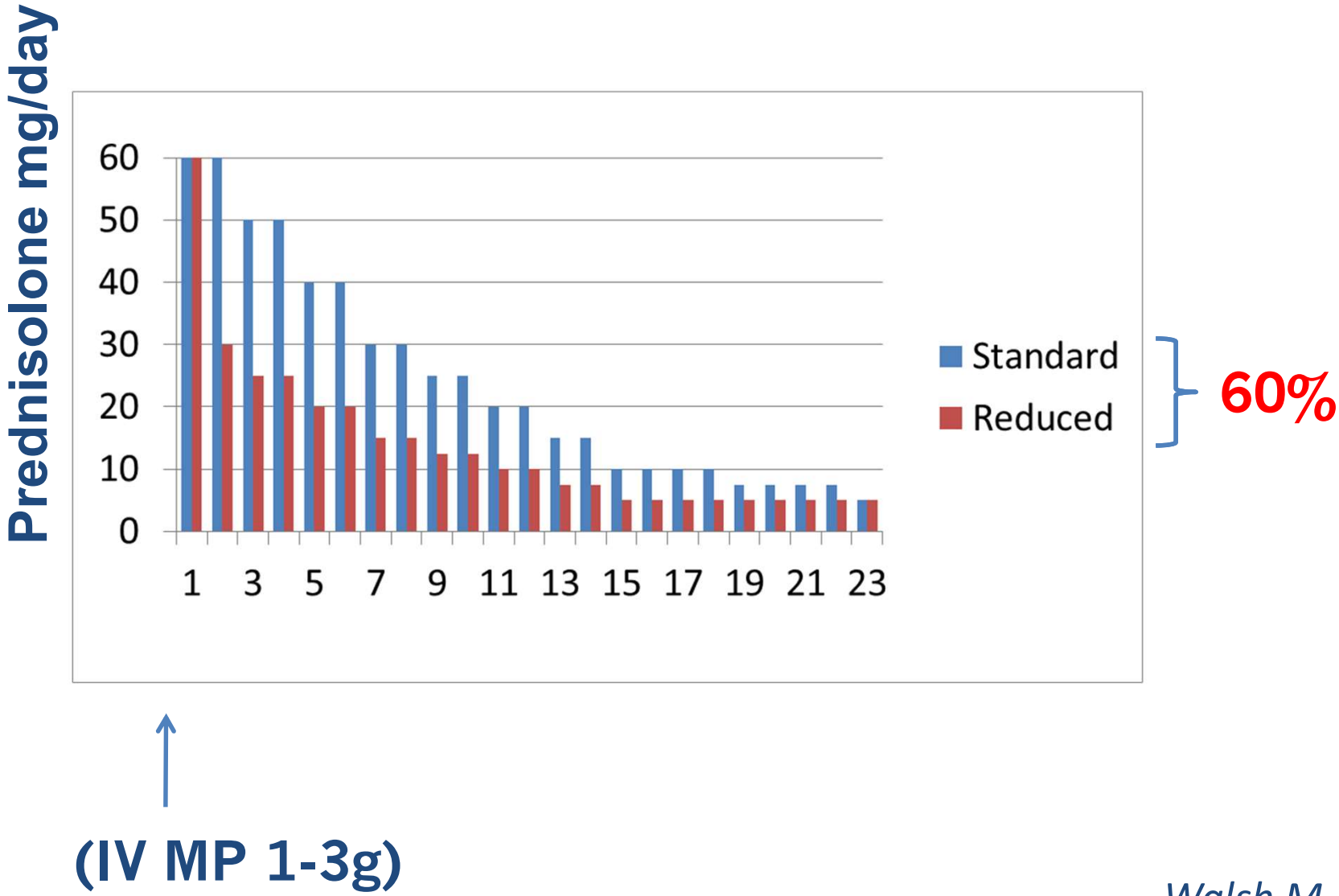
Walsh M, Trials 2013

Schéma de décroissance des glucocorticoïdes

Semaine	Groupe standard			Groupe dose réduite		
	<50 kg	50-75 kg	>75 kg	<50 kg	50-75 kg	>75 kg
	bolus	bolus	bolus	bolus	bolus	bolus
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	Pratiques du centre			Pratiques du centre		

Objectifs GC : 10 mg/j à 3 mois, 5 mg/j avant 5 mois => 1 an

Glucocorticoid Dosing



Walsh M, Trials 2013

Methods: Plasma Exchange

- 7 exchanges within 14 days of randomization
  - Filter separation or centrifugation
  - 60 ml/kg exchange volumes
  - Albumin replacement fluid (plasma if bleeding)
- Access and anticoagulation left to local practice

Walsh M, Trials 2013

Overall Methods: Outcomes

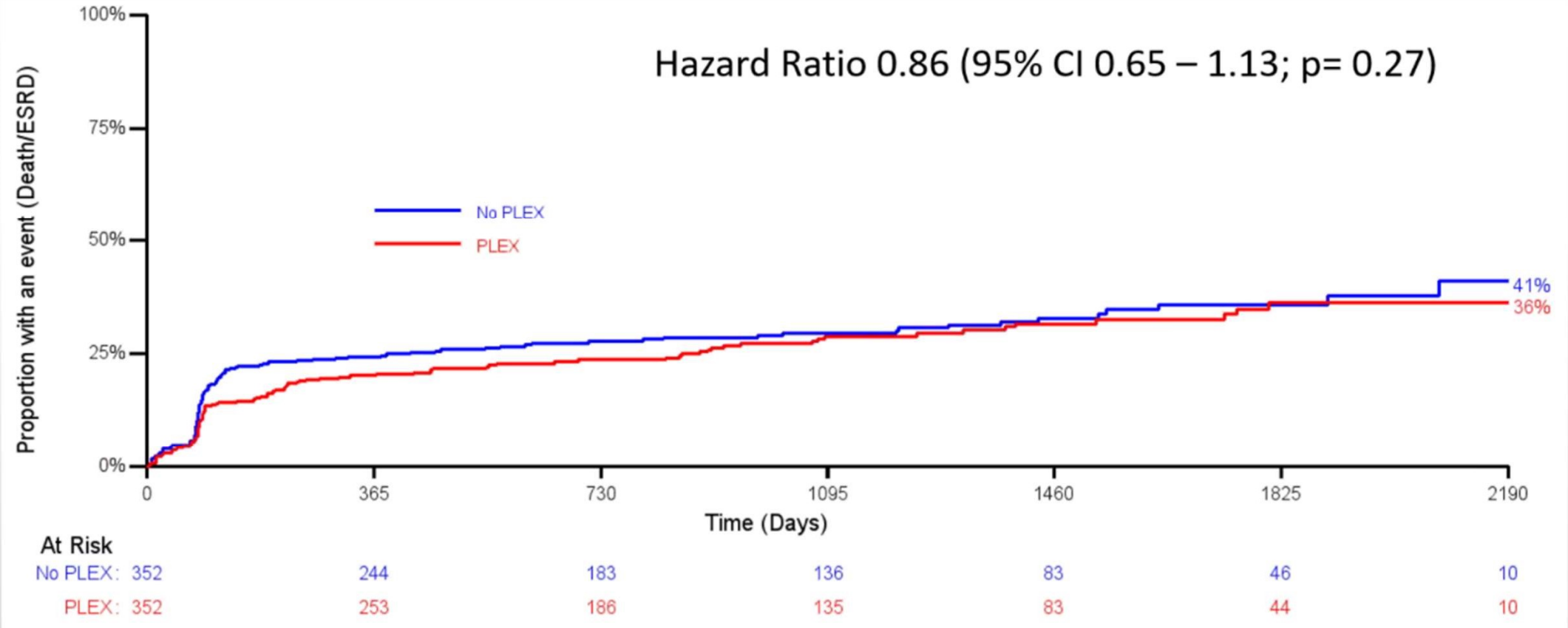
- Primary
  - Composite of death from any cause or end-stage renal disease
- Secondary
  - Death from any cause
  - End-stage renal disease
  - Sustained remission
  - Overall serious adverse events
  - Serious infections
  - Health related quality of life

Plasma Exchange

Results: Participants

Characteristic	PLEX (n=352)	Control (n=352)
Mean age, years (SD)	62.8 (14.4)	63.5 (13.7)
Female, n (%)	149 (42.3)	158 (44.9
Dominant ANCA, n (%)		
PR3+	143 (40.6)	143 (40.6)
MPO+	209 (59.4)	209 (59.4)
Lung Hemorrhage, n (%)		
Any	95 (27.0)	96 (27.3)
Severe	31 (8.8)	30 (8.5)
Creatinine		
Median (25^{th} - 75^{th})	327 (206 – 491)	335.9 (209 – 495)
>500 umol/L, n (%)	101 (28.7)	104 (29.5)
On Dialysis, n (%)	66 (18.8)	74 (21)
Immunosuppression, n(%)		
IV Cyclophos.	177 (50.3)	177 (50.3)
Oral Cyclophos.	120 (34.1)	121 (34.3)
Rituximab	55 (15.6)	54 (15.4)

Results: PLEX – Primary Composite



Results: PLEX – Primary Composite

Analysis	Hazard Ratio (95% CI)	P-value
Unadjusted	0.89 (0.68 – 1.17)	0.42
Per protocol population	0.85 (0.66 – 1.16)	0.35
Censored at 12 months	0.77 (0.56 – 1.06)	0.11
Subgroups		Interaction P-value
< 60 years ≥ 60 years	1.20 (0.73 – 1.97) 0.75 (0.54 – 1.04)	0.13
Creatinine ≥ 500 umol/L Creatinine < 500 umol/L	0.98 (0.65 – 1.48) 0.77 (0.53 – 1.11)	0.38
PR3-ANCA MPO-ANCA	0.84 (0.51 – 1.36) 0.84 (0.62 – 1.21)	0.91
No lung hemorrhage Mild lung hemorrhage Severe lung hemorrhage	0.95 (0.69 – 1.31) 0.64 (0.33 – 1.24) 0.67 (0.28 – 1.64)	0.49
IV cyclophosphamide Oral cyclophosphamide Rituximab	0.79 (0.55 – 1.14) 0.98 (0.61 – 1.57) 0.87 (0.38 – 1.96)	0.79

Results: PLEX – Secondary Outcomes

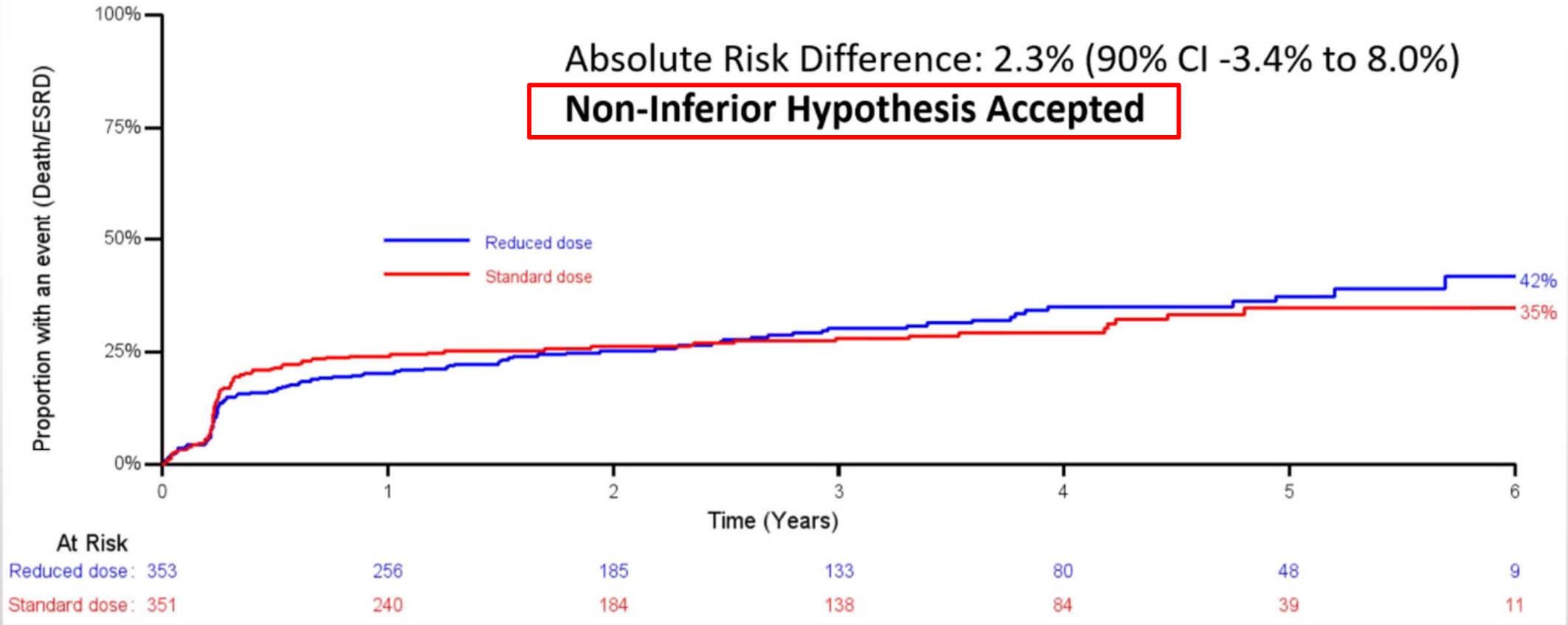
Outcome	PLEX	Control	Hazard Ratio (95% CI)	P-value
Death, n (%)	46 (13)	53 (15)	0.87 (0.58 – 1.29)	0.86
ESRD, n (%)	67 (19)	71 (20)	0.81 (0.57 – 1.13)	0.65
Sustained Remission, n (%)	200 (57)	197 (56)	1.01 (0.89 – 1.15)	0.48
SAEs, n (%)	224 (64)	225 (64)	1.00 (0.90 – 1.12)	0.99
			Incidence Rate Ratio (95% CI)	
Serious Infections, n (%)	119 (34)	93 (26)	1.16 (0.86 – 1.56)	0.34
			Difference in Score (95% CI)	
EQ-5D Index Score			0.008 (-0.003 – 0.02)	0.14

Glucocorticoids

Results: Participants

Characteristic	Reduced Dose (n=353)	Standard Dose (n=351)
Mean age, years (SD)	63.3 (14.2)	63.1 (13.9)
Female, n (%)	156 (44.2)	151 (43.0)
Dominant ANCA, n (%)		
PR3+	143 (40.5)	143 (40.7)
MPO+	210 (59.5)	208 (59.3)
Lung Hemorrhage, n (%)		
Any	96 (27.2)	95 (27.0)
Severe	31 (8.8)	30 (8.5)
Creatinine		
Median (25^{th} - 75^{th})	320 (190 – 480)	335 (219 – 502)
>500 umol/L, n (%)	102 (28.9)	103 (29.3)
On Dialysis, n (%)	67 (19)	73 (20.8)
Immunosuppression, n(%)		
IV Cyclophos.	179 (50.7)	175 (49.9)
Oral Cyclophos.	120 (34.0)	121 (34.5)
Rituximab	54 (15.3)	55 (15.6)

Results: GC – Primary Composite



Results: GC – Primary Composite

Analysis	Hazard Ratio (95% CI)	
Intent-to-treat population	1.00 (0.76 – 1.31)	
Censored at 12 months	0.80 (0.58 – 1.10)	
Subgroups		Interaction P-value
< 60 years ≥ 60 years	0.86 (0.52 – 1.41) 1.06 (0.76 – 1.48)	0.49
Creatinine ≥ 500 umol/L Creatinine < 500 umol/L	1.24 (0.82 – 1.88) 0.85 (0.59 – 1.22)	0.17
PR3-ANCA MPO-ANCA	0.82 (0.50 – 1.34) 1.10 (0.79 – 1.53)	0.33
No lung hemorrhage Mild lung hemorrhage Severe lung hemorrhage	0.94 (0.68 – 1.29) 1.16 (0.60 – 2.26) 1.25 (0.52 – 3.03)	0.74
IV cyclophosphamide Oral cyclophosphamide Rituximab	0.84 (0.58 – 1.21) 1.08 (0.67 – 1.73) 1.86 (0.83 – 4.14)	0.20

Results: GC – Secondary Outcomes

Outcome	Reduced	Standard	Hazard Ratio (95% CI)	P-value
Death, n (%)	46 (13)	53 (15)	0.78 (0.53 – 1.17)	0.23
ESRD, n (%)	70 (20)	68 (19)	0.96 (0.68 – 1.34)	0.65
Sustained Remission, n (%)	204 (58)	193 (55)	1.04 (0.92 – 1.19)	0.48
SAEs, n (%)	231 (65)	218 (62)	1.05 (0.94 – 1.17)	0.20
			Incidence Rate Ratio (95% CI)	
Serious Infections, n (%)	96 (27)	116 (33)	0.70 (0.52 – 0.94)	0.02

Limitations

- Open label
  - Reasonable adherence
  - Objective, easily ascertained outcomes
- Powered for moderate-large effects
  - Largest trial in this disease to date
- Long-term follow-up may result in dilution of acute treatment effects

Conclusions

- In patients with severe AAV:
  - PLEX did not reduce the composite of mortality or ESRD
  - A reduced dose of GC was non-inferior to a “standard” dose and resulted in fewer serious infections

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Echanges plasmatiques dans les VAA

- Vascularites associées aux ANCA
- Historique
- Rôle pathogène des ANCA
- Essais non randomisés dans les hémorragies alvéolaires
- Essais randomisés contrôlés
- Meta analyses et Revues Systématiques
- PEXIVAS
- Avis du conseil scientifique du GFEV

Avis du Conseil Scientifique du GFEV sur les échanges plasmatiques

L'utilisation des EP doit désormais être réduite.

On ne peut exclure leur intérêt chez certains patients, après discussion au cas par cas, en particulier :

- **Patients ayant une hémorragie alvéolaire sévère**
- **Patients ayant une aggravation persistante de leur insuffisance rénale malgré le traitement conventionnel par corticoïdes associées au cyclophosphamide ou au rituximab**
- **Patients se présentant avec une glomérulonéphrite rapidement progressive et/ou une hémorragie alvéolaire sans diagnostic de certitude, au moins jusqu'au résultat de la recherche d'anticorps anti-MBG et/ou du diagnostic de certitude (avec un éventuel arrêt une fois le diagnostic de VAA posé).**

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