Plasma exchanges in ANCA-associated vasculitis

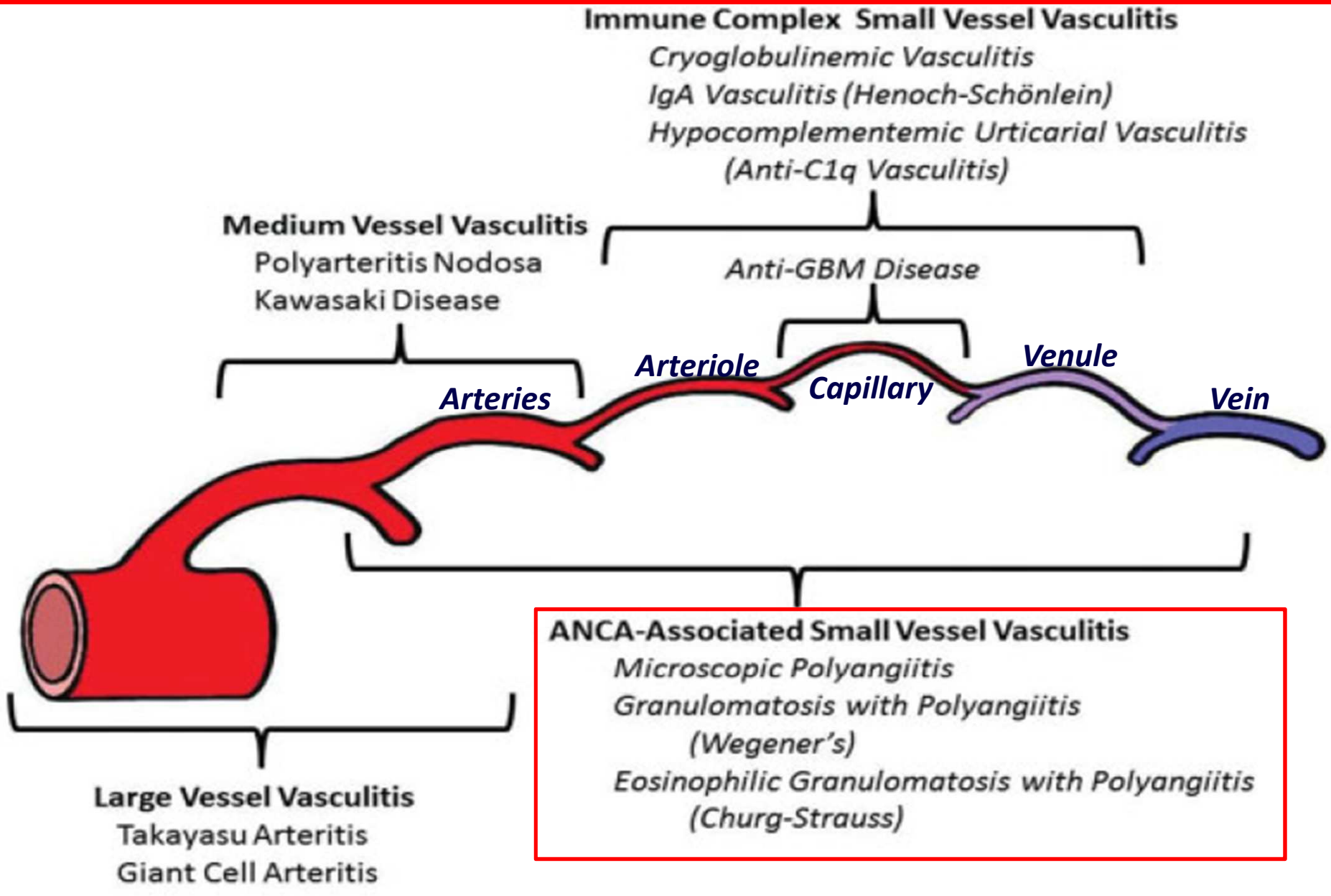
Xavier Puéchal, MD, PhD

Centre de Référence des
Maladies auto-immunes systémiques rares
d'Ile de France
Hôpital Cochin
Université Paris Descartes
http://www.vascularites.org

Plasma exchanges in ANCA-associated vasculitis

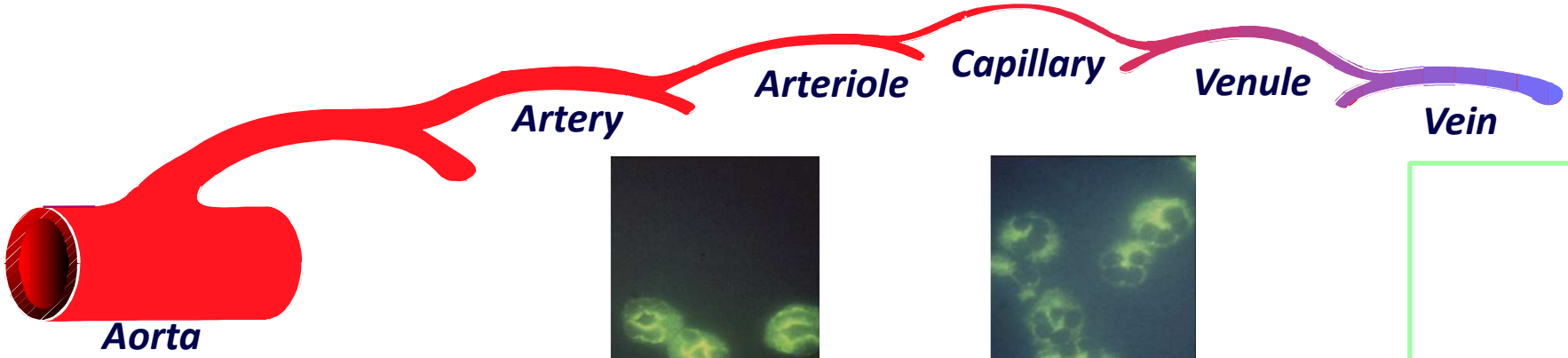
- ANCA-associated vasculitis
- History
- Several lines of evidence suggest that ANCA may be pathogenic
- PLEX Recommendations, KDIGO clinical practice guidelines for GN
- Non randomized data for use in lung haemorrhage
- Randomized controlled trials
- Meta analyses and Systematic Reviews
- PEXIVAS
- Questions to be answered

2012 Revised Chapel Hill Conference Nomenclature of Vasculitides



Jennette JC, Arthritis Rheum 2013

ANCA and clinical presentations in ANCA-associated vasculitides



pANCA : 60 %
8/10 anti-MPO

cANCA : 85 %
9/10 anti-PR3

pANCA : 30-40 %
¾ anti-MPO

Vasculitis with no granulomas or asthma

Vasculitis with granulomas and no asthma

Vasculitis with eosinophilia, granulomas and asthma

Microscopic Polyangiitis (MPA)

Granulomatosis with Polyangiitis (GPA, Wegener's)

Eosinophilic Granulomatosis with Polyangiitis (EGPA) (Churg-Strauss)

Jennette JC, Arthritis Rheum 2013

Plasma exchanges in ANCA-associated vasculitis

- ANCA-associated vasculitis
- History
- Several lines of evidence suggest that ANCA may be pathogenic
- PLEX Recommendations, KDIGO clinical practice guidelines for GN
- Non randomized data for use in lung haemorrhage
- Randomized controlled trials
- Meta analyses and Systematic Reviews
- PEXIVAS
- Questions to be answered

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).

Plasma exchanges in ANCA-associated vasculitis

- ANCA-associated vasculitis
- History
- Several lines of evidence suggest that ANCA may be pathogenic
- PLEX Recommendations, KDIGO clinical practice guidelines for GN
- Non randomized data for use in lung haemorrhage
- Randomized controlled trials
- Meta analyses and Systematic Reviews
- PEXIVAS
- Questions to be answered

Evidence suggests a pathogenic role for ANCA

- **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 death. 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

Plasma exchanges in ANCA-associated vasculitis

- ANCA-associated vasculitis
- History
- Several lines of evidence suggest that ANCA may be pathogenic
- PLEX Recommendations, KDIGO clinical practice guidelines for GN
- Non randomized data for use in lung haemorrhage
- Randomized controlled trials
- Meta analyses and Systematic Reviews
- PEXIVAS
- Questions to be answered

KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for Glomerulonephritis

13.2: Special Patient Populations

13.2.1: We recommend the addition of plasmapheresis for patients requiring dialysis or with rapidly increasing SCr. (*1C*)

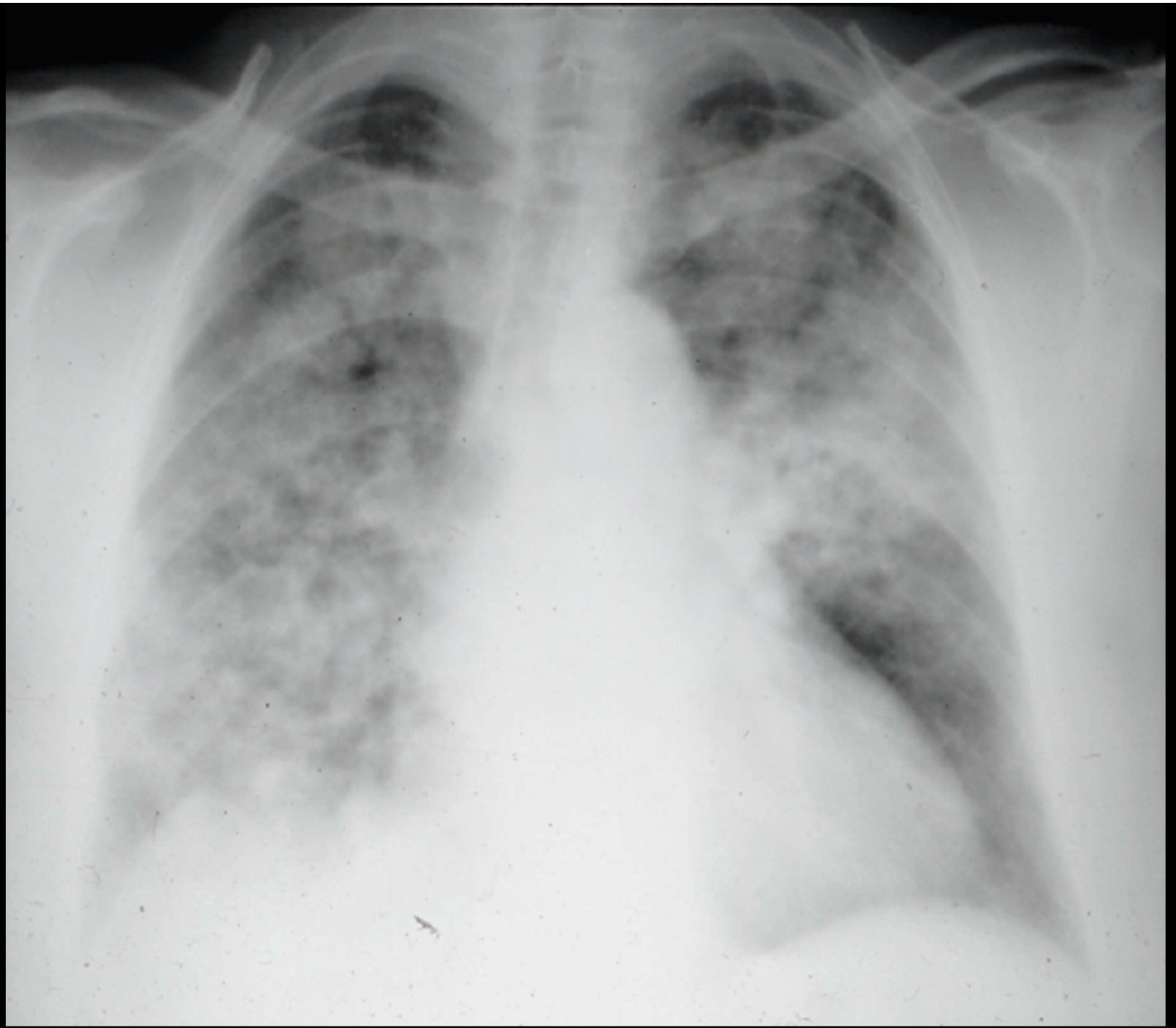
13.2.2: We suggest the addition of plasmapheresis for patients with diffuse pulmonary hemorrhage. (*2C*)

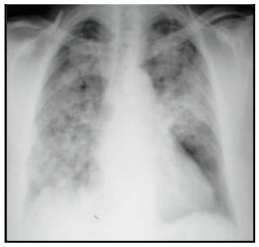
13.2.3: We suggest the addition of plasmapheresis for patients with overlap syndrome of ANCA vasculitis and anti-GBM GN, according to proposed criteria and regimen for anti-GBM GN (see Chapter 14). (*2D*)

Beck L, Am J Kidney Dis 2013

Plasma exchanges in ANCA-associated vasculitis

- ANCA-associated vasculitis
- History
- Several lines of evidence suggest that ANCA may be pathogenic
- PLEX Recommendations, KDIGO clinical practice guidelines for GN
- Non randomized data for use in lung haemorrhage
- Randomized controlled trials
- Meta analyses and Systematic Reviews
- PEXIVAS
- Questions to be answered





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:**

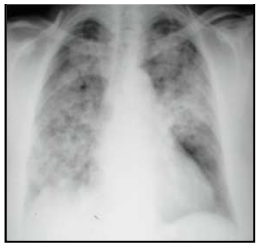
  - The use of PLEX in this setting is mostly based on a small uncontrolled retrospective study:
  - **20 patients received PLEX for lung haemorrhage**
    - **55% were not on mechanical ventilation**
    - **30% did not have renal involvement**

    => resolution of pulmonary symptoms in all 20 patients

    => 19 survived the initial disease episode.

French Vasculitis Study Group

Klemmer PJ, Am J Kidney Dis 2003



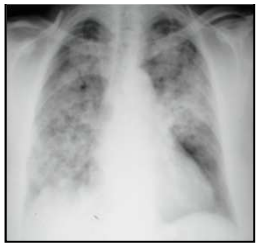
Non randomized data for use in lung haemorrhage

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.

French Vasculitis Study Group

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



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),

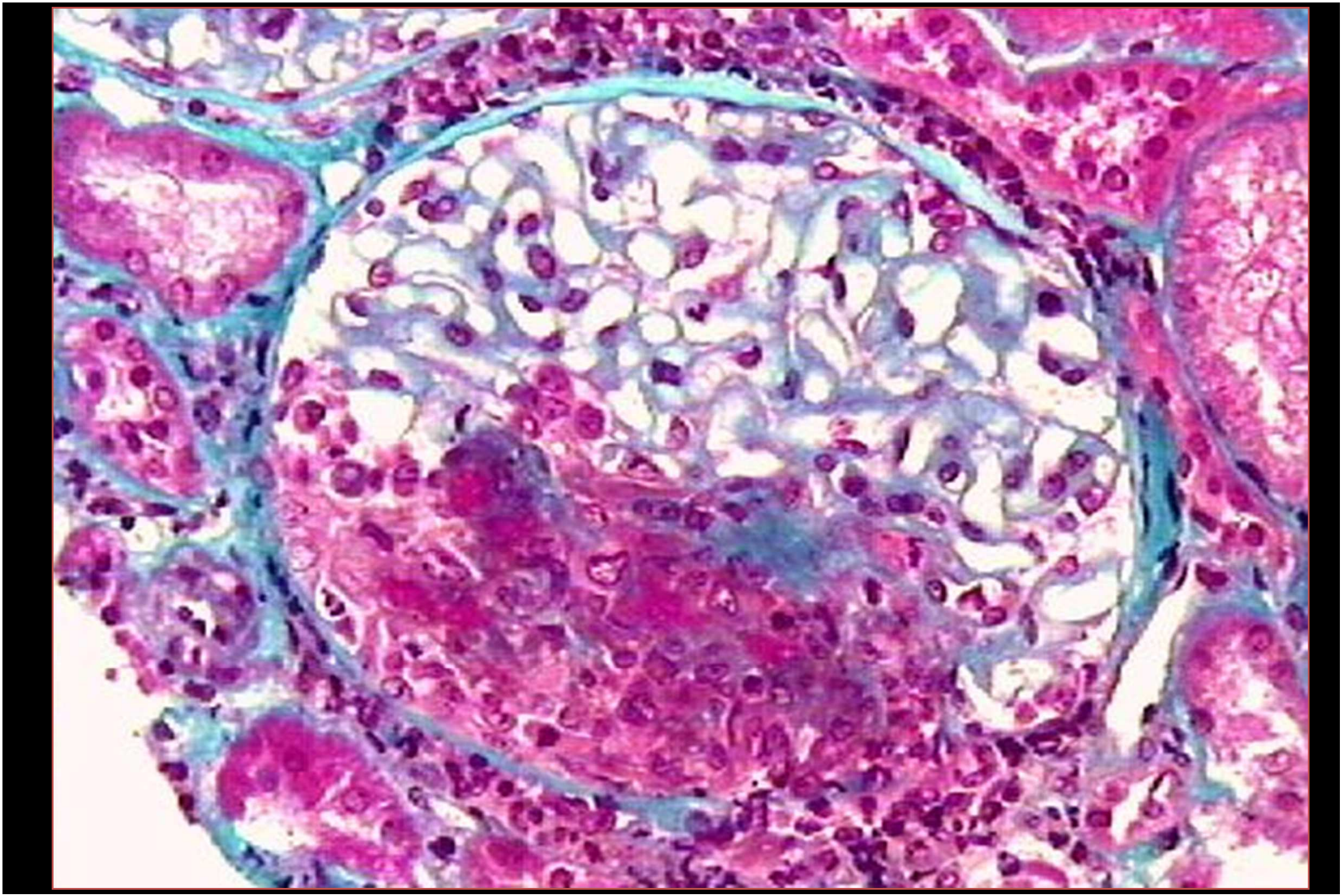
put great pressure on the physician to use PLEX
- in patients with ANCA-associated vasculitis and lung haemorrhage
- in the absence of clear data on its benefits.

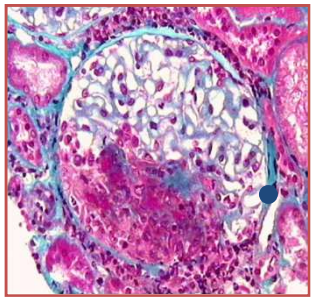
French Vasculitis Study Group

Walters G, Pediatr Nephrol 2016

Plasma exchanges in ANCA-associated vasculitis

- ANCA-associated vasculitis
- History
- Several lines of evidence suggest that ANCA may be pathogenic
- PLEX Recommendations, KDIGO clinical practice guidelines for GN
- Non randomized data for use in lung haemorrhage
- Randomized controlled trials
- Meta analyses and Systematic Reviews
- PEXIVAS
- Questions to be answered





Randomized controlled trials

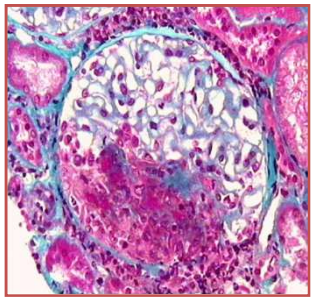
8 RCT with PLEX in ANCA-associated vasculitis

- **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



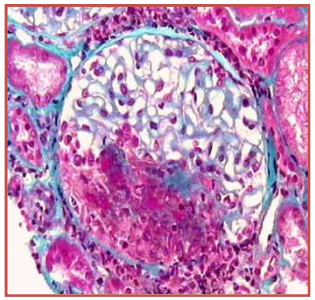
Randomized controlled trials

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 pts with creatinine above 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



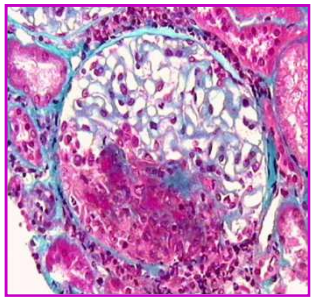
Randomized controlled trials

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 (3x1g) 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

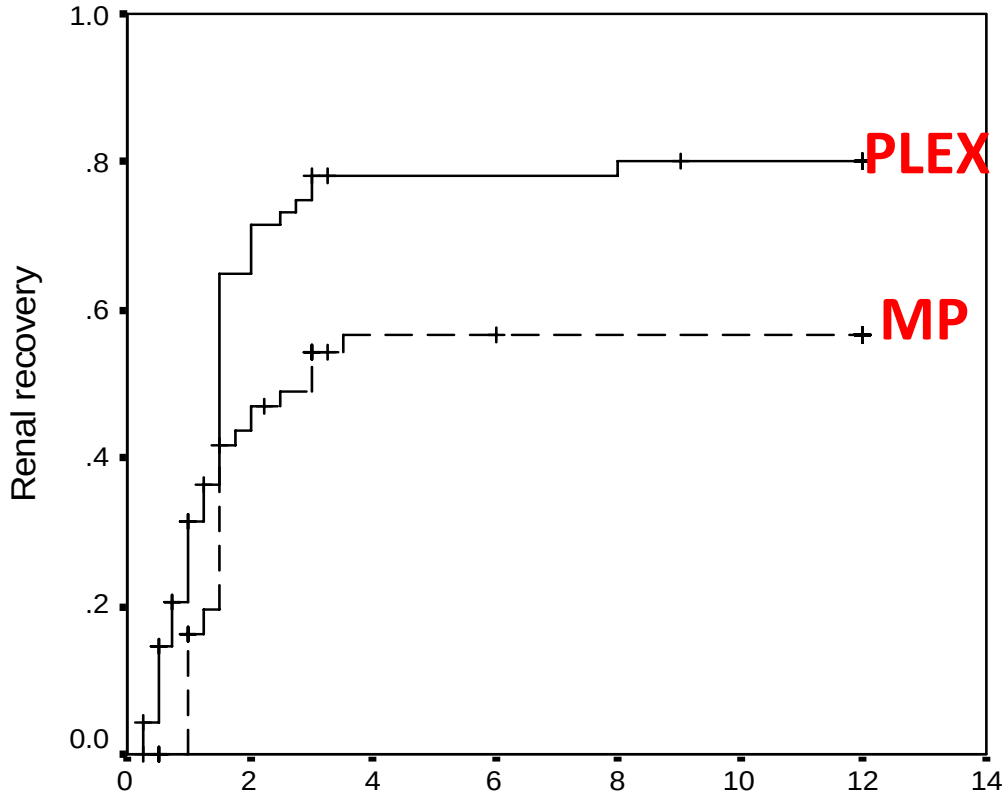


MEPEX Renal recovery

European Vasculitis Society EUVAS

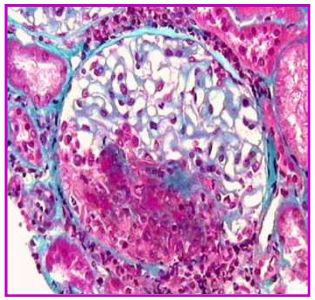
Increase by 20% in the number of patients alive and off dialysis

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

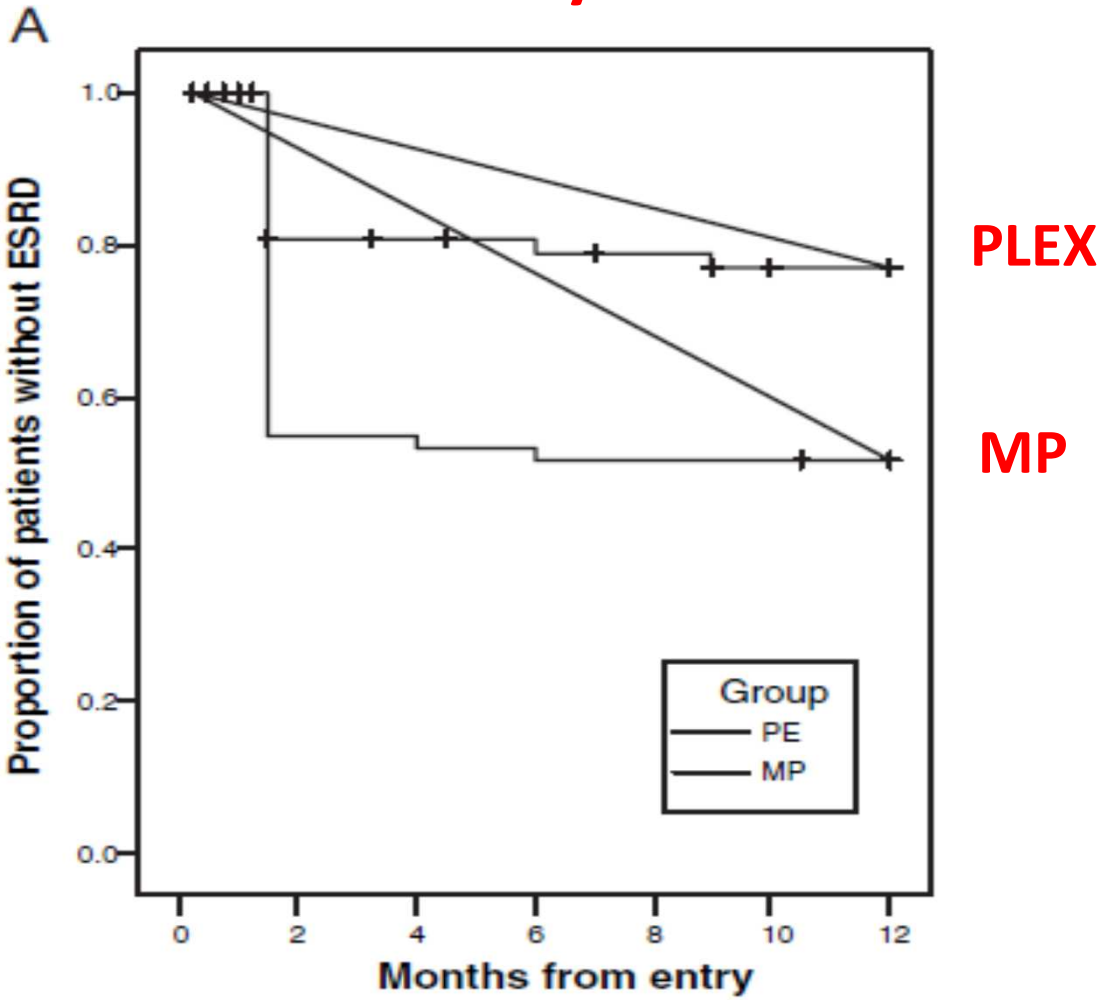
24% risk reduction in progression to ESRD at 1 year with PLEX

from 43% to 19%

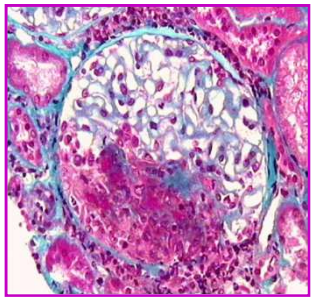
(95% CI: 6.1-41%)

for PLEX vs MP

(p=0.04)



Jayne DRW, J Am Soc Nephrol 2007

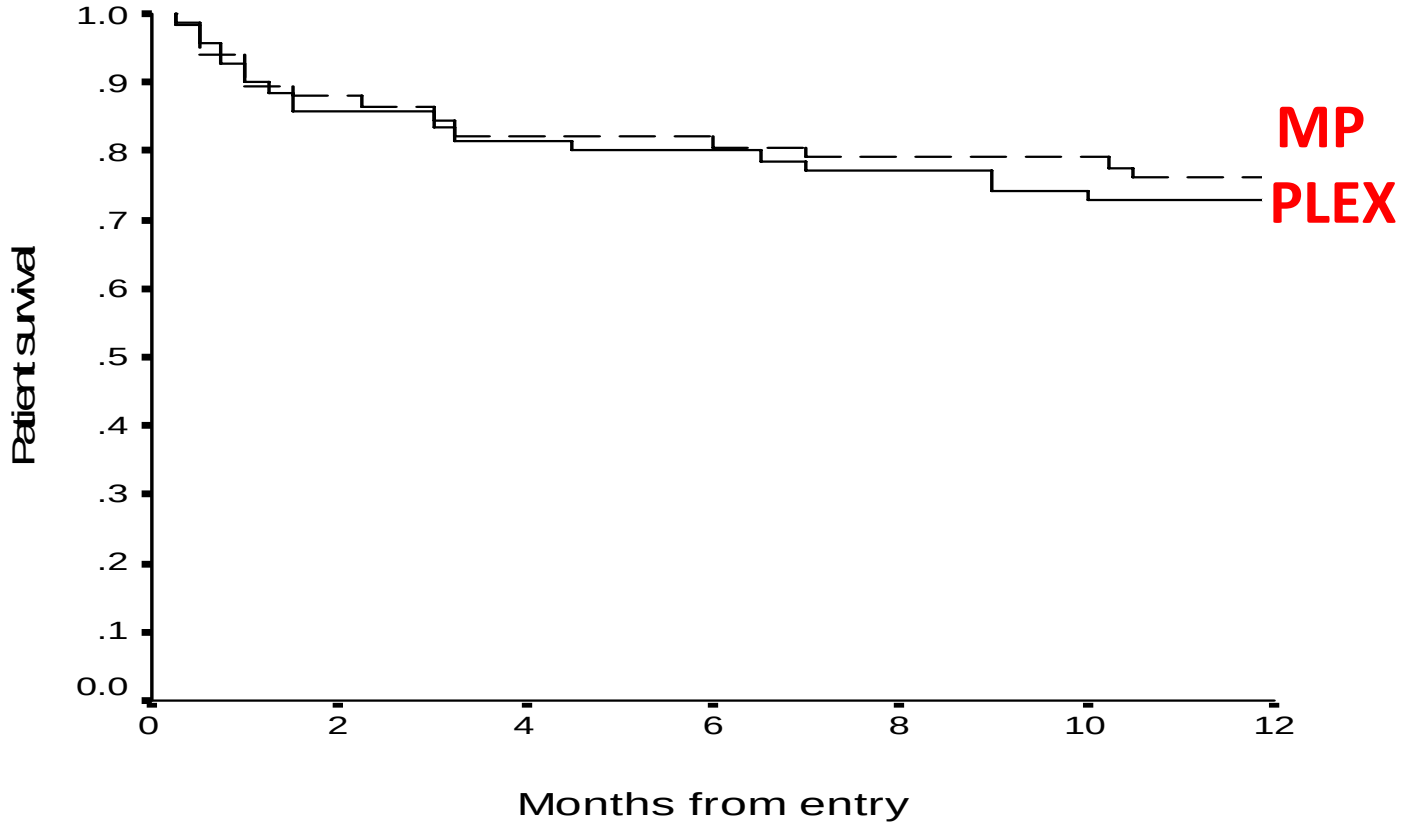


MEPEX Overall Survival

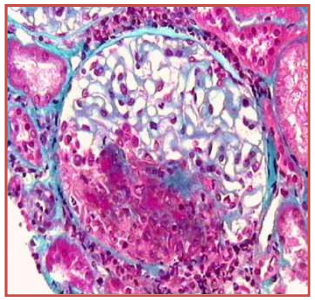
European Vasculitis Society EUVAS

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

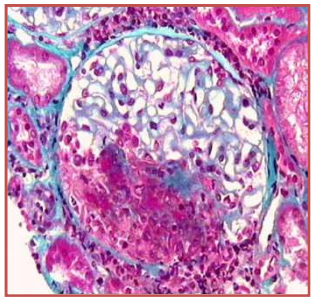
http://www.kidney-international.org

clinical trial

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

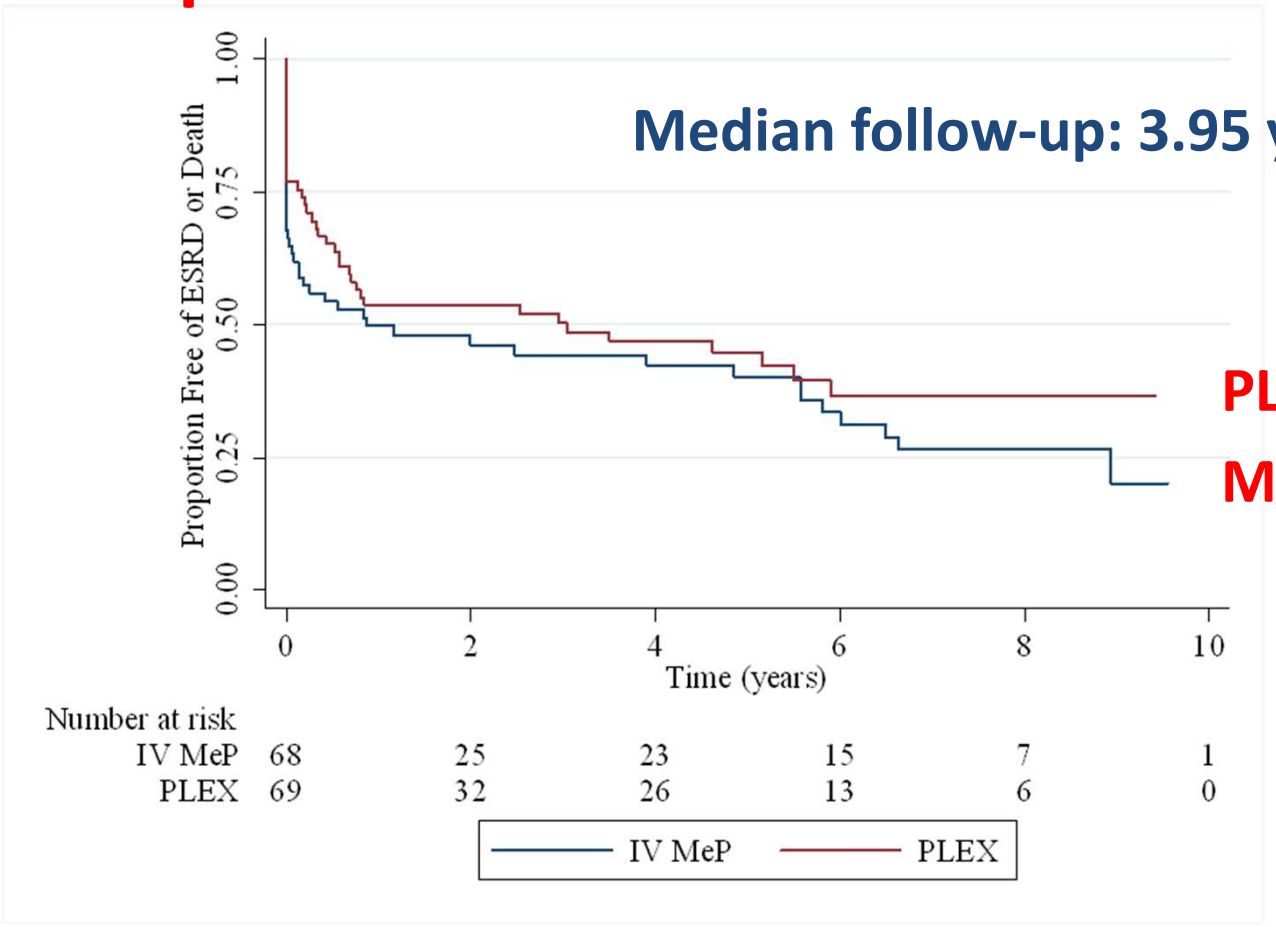
Michael Walsh[1], Alina Casian[2], Oliver Flossmann[3], Kerstin Westman[4], Peter Höglund[5], Charles Pusey[6] and David R.W. Jayne[2] on behalf of the European Vasculitis Study Group (EUVAS)

Walsh M, Kidney International 2013



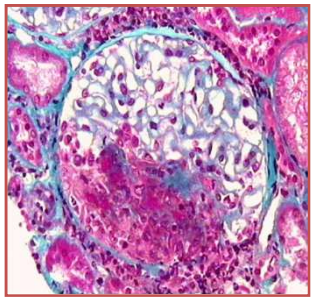
MEPEX Long-term outcomes

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

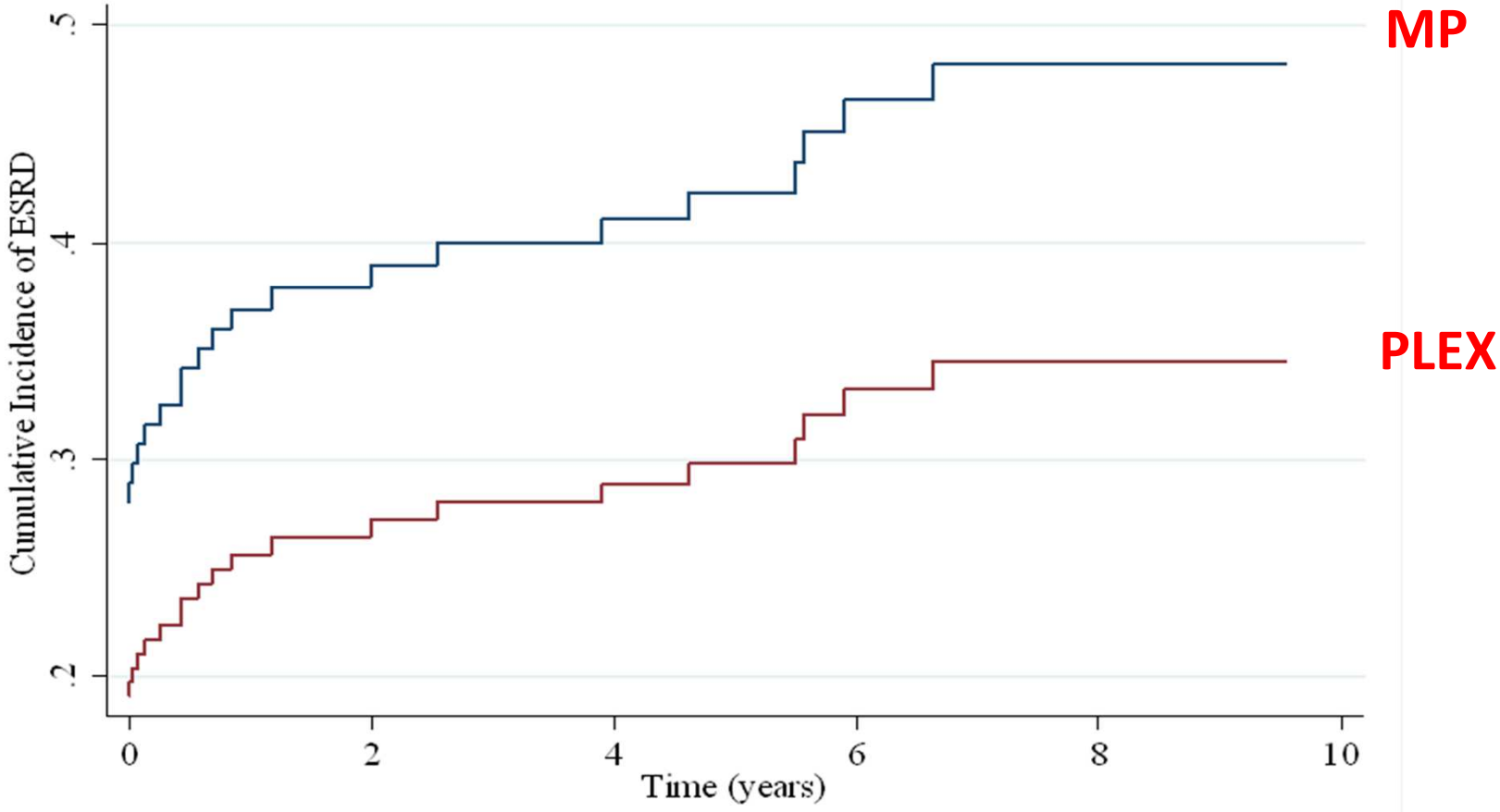
Walsh M, Kidney International 2013



MEPEX Long-term outcomes

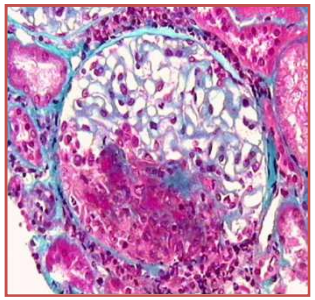
Cumulative incidence of ESRD

death is treated as competing risk



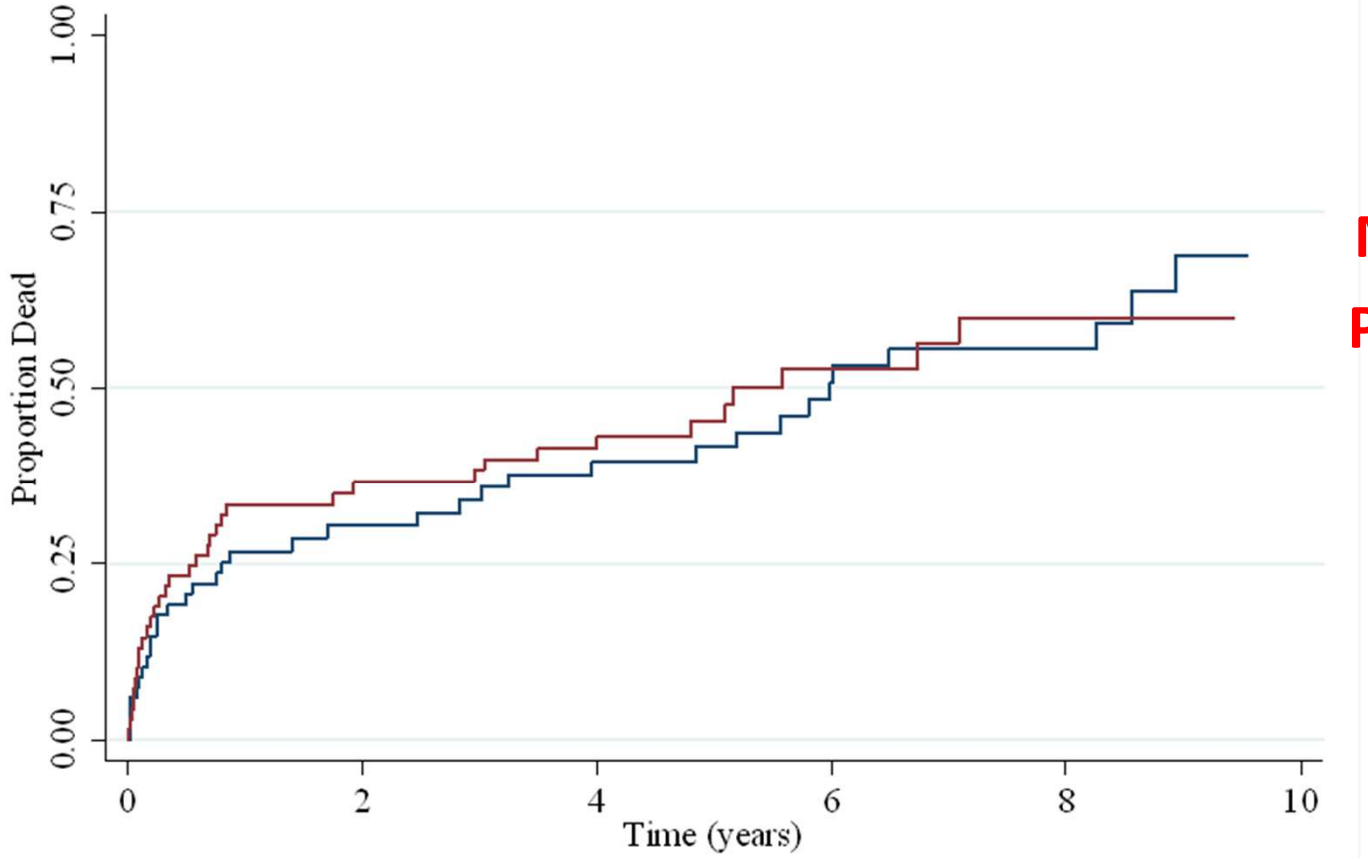
PLEX vs MP; HR 0.64, 95% CI 0.40-1.05; p=0.08

Walsh M, Kidney International 2013



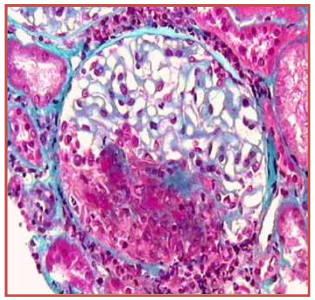
MEPEX Long-term outcomes

Proportion of Deaths



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

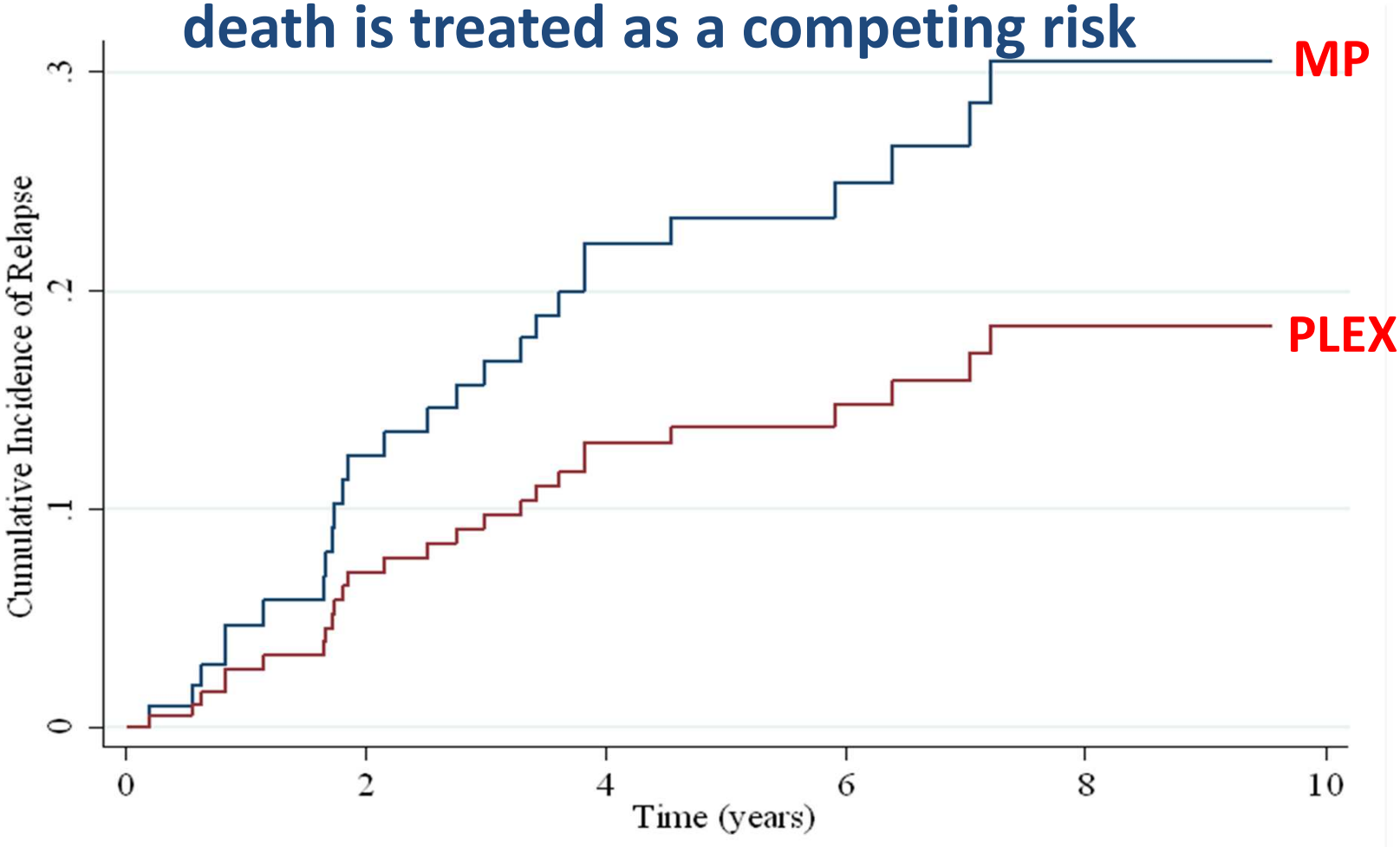
Walsh M, Kidney International 2013



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

Plasma exchanges in ANCA-associated vasculitis

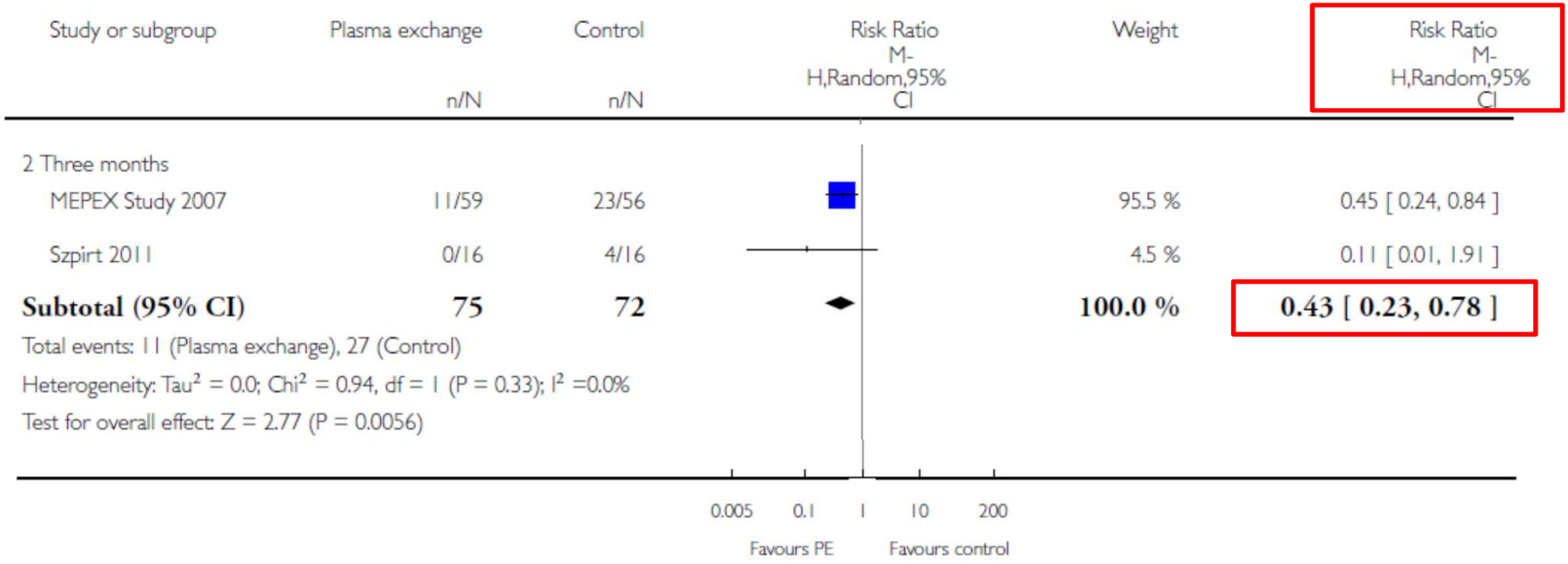
- ANCA-associated vasculitis
- History
- Several lines of evidence suggest that ANCA may be pathogenic
- PLEX Recommendations, KDIGO clinical practice guidelines for GN
- Non randomized data for use in lung haemorrhage
- Randomized controlled trials
- Meta analyses and Systematic Reviews
- PEXIVAS
- Questions to be answered

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.**

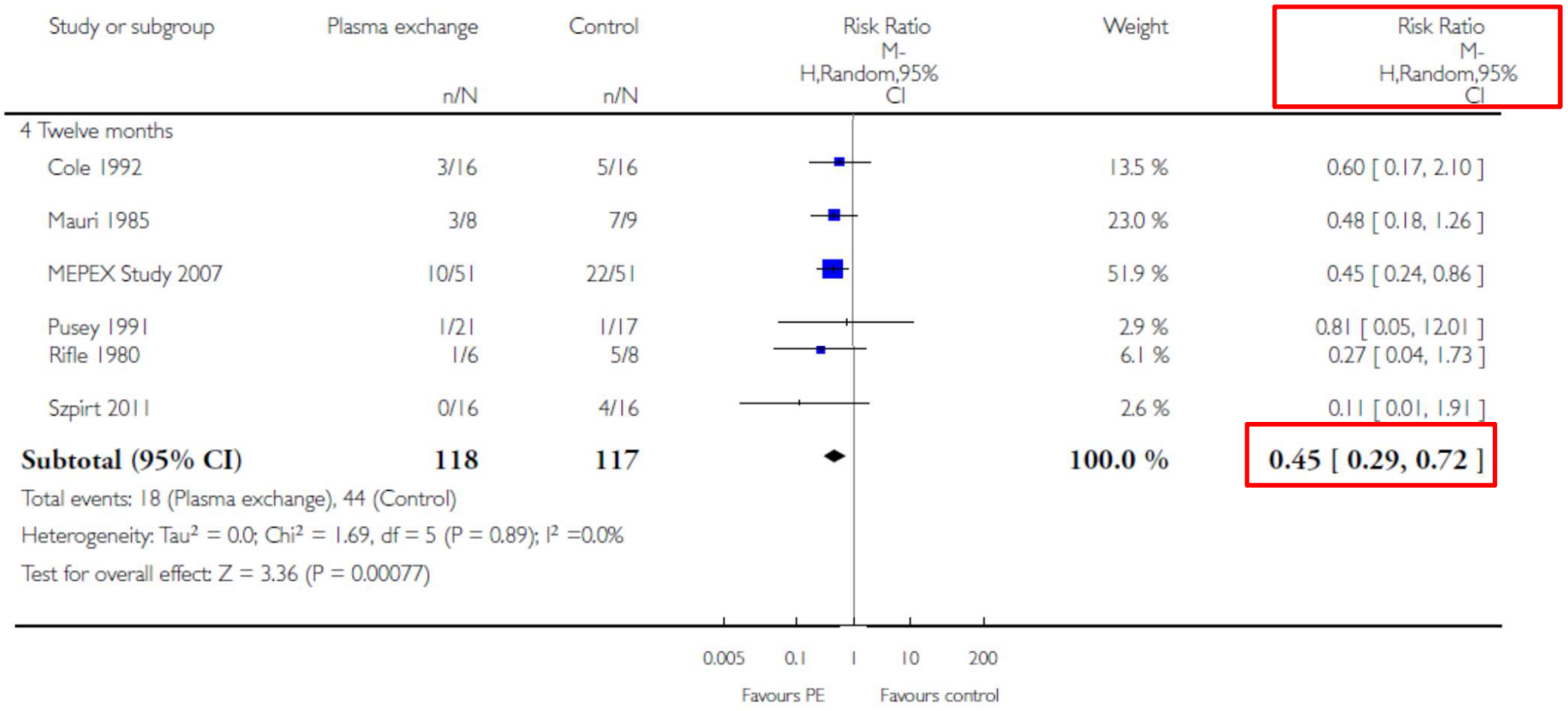
Walsh M, Am J Kid Dis 2010
Walters G, Cochrane Database of Systematic Reviews 2015

PLEX significantly reduced the risk of ESRD at 3 months



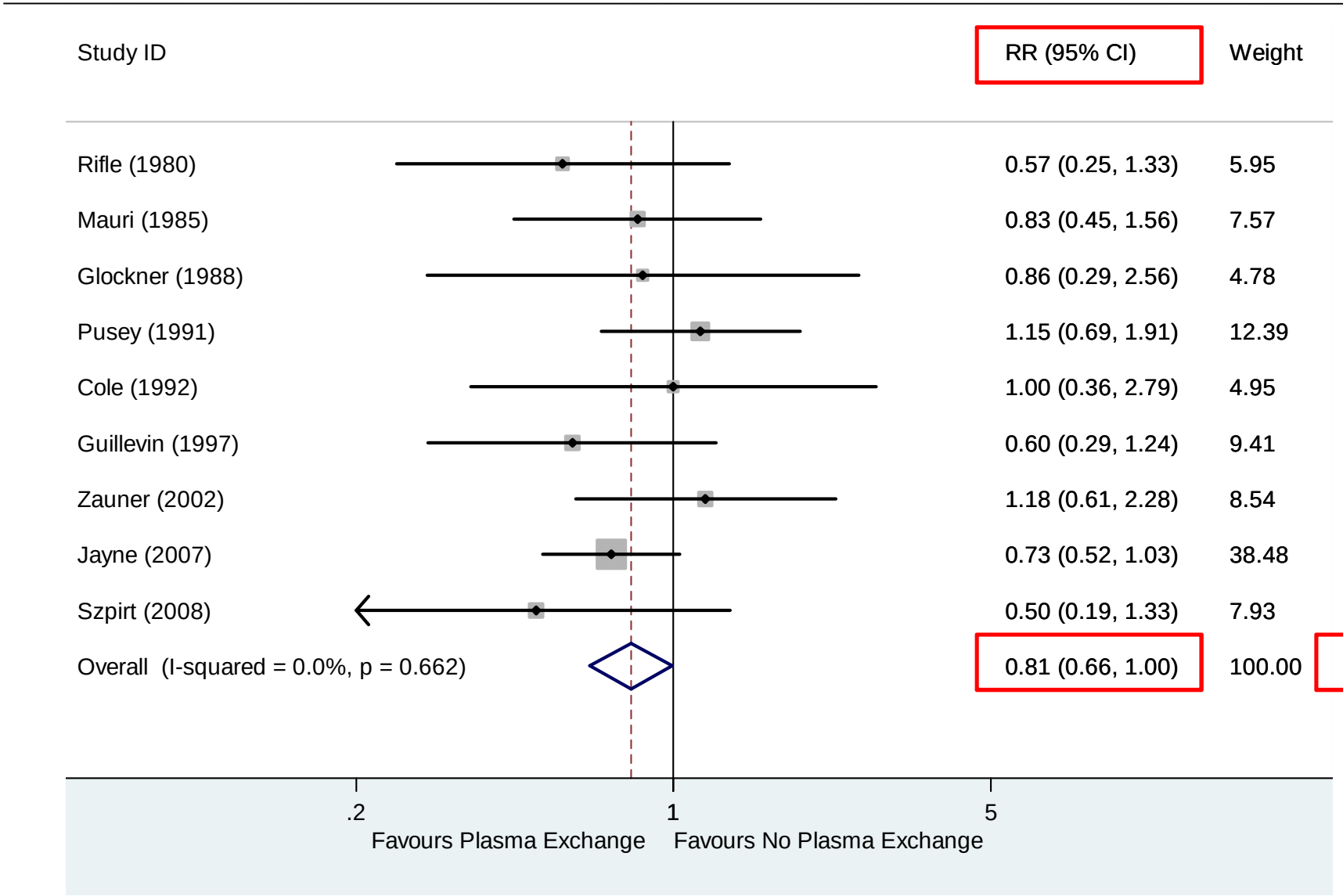
Walters G, Cochrane Database of Systematic Reviews 2015

PLEX significantly reduced the risk of ESRD at 12 months



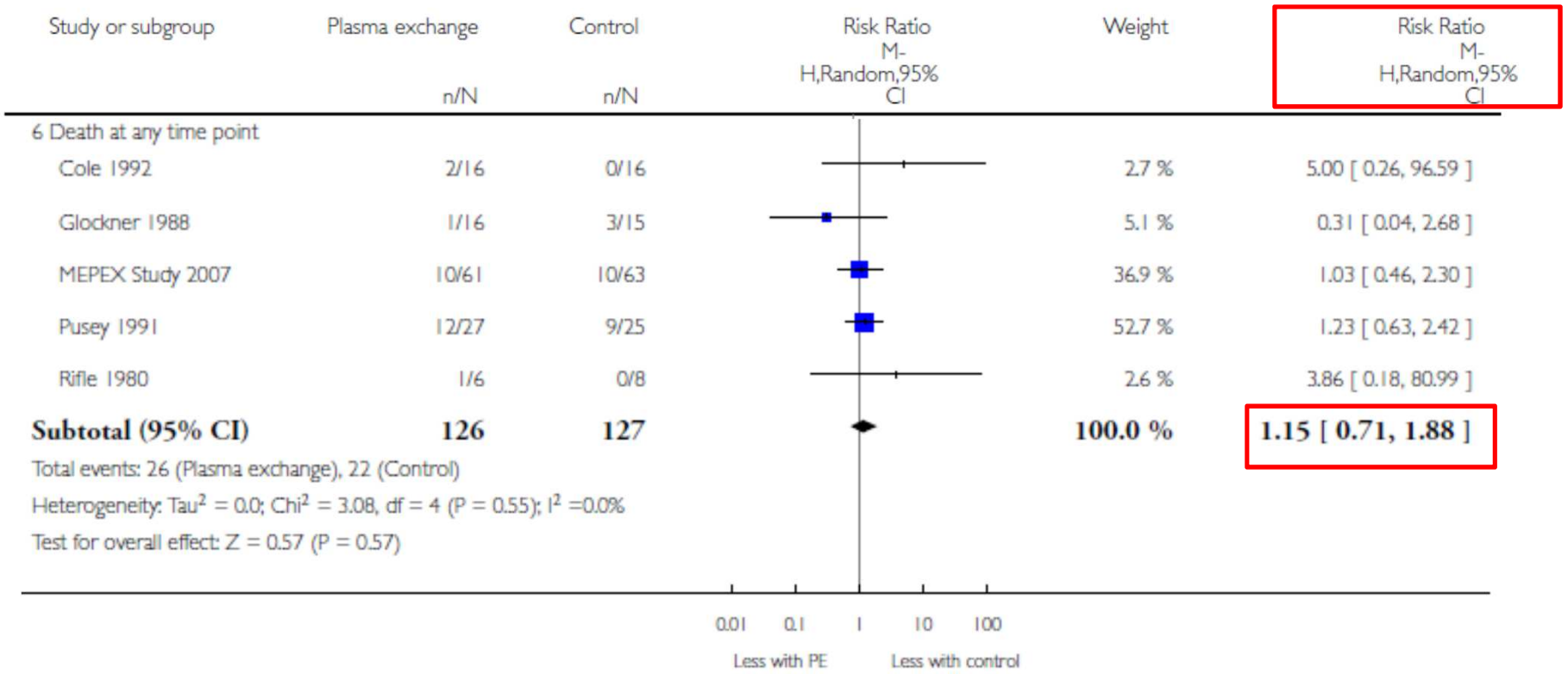
Walters G, Cochrane Database of Systematic Reviews 2015

PLEX significantly reduced the composite ESRD or Death



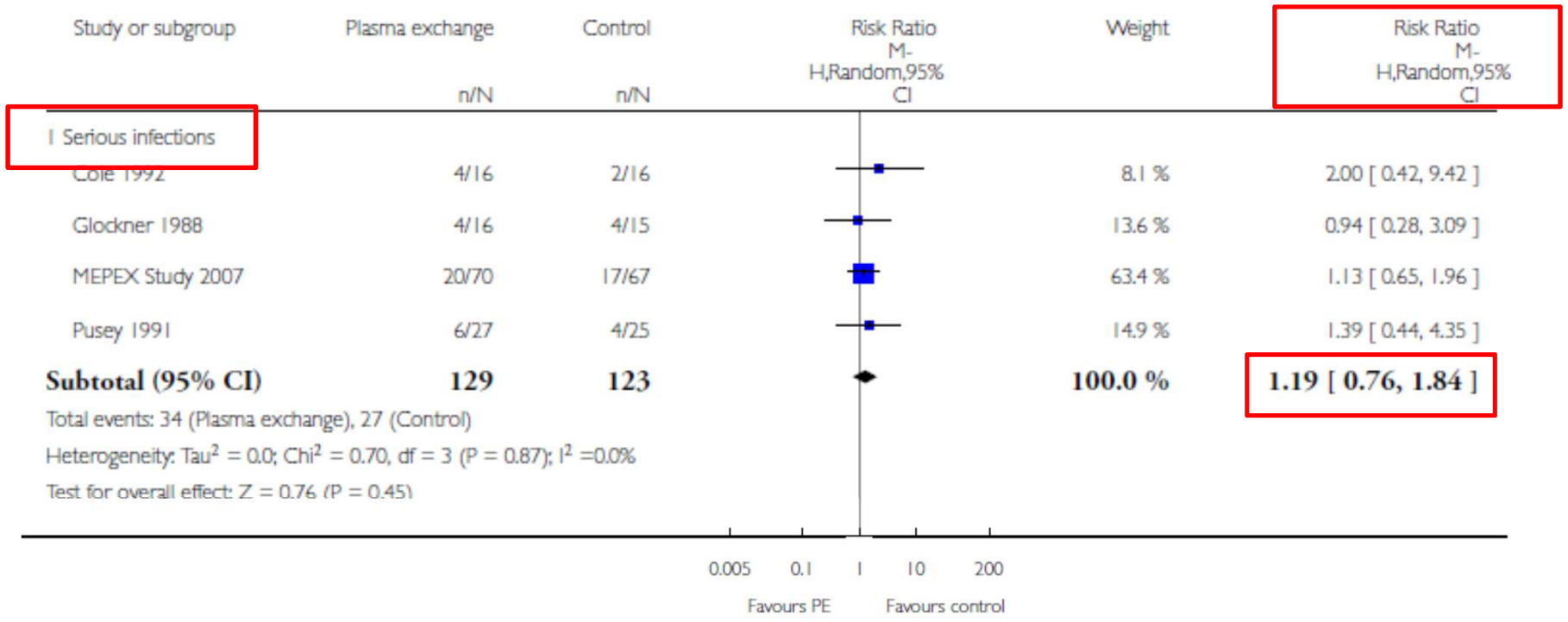
Walsh, Am J Kid Dis 2010

Mortality appears to be unchanged with PLEX



Walters G, Cochrane Database of Systematic Reviews 2015

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



Walters G, Cochrane Database of Systematic Reviews 2015

Plasma exchanges in ANCA-associated vasculitis

- ANCA-associated vasculitis
- History
- Several lines of evidence suggest that ANCA may be pathogenic
- PLEX Recommendations, KDIGO clinical practice guidelines for GN
- Non randomized data for use in lung haemorrhage
- Randomized controlled trials
- Meta analyses and Systematic Reviews
- PEXIVAS
- Questions to be answered

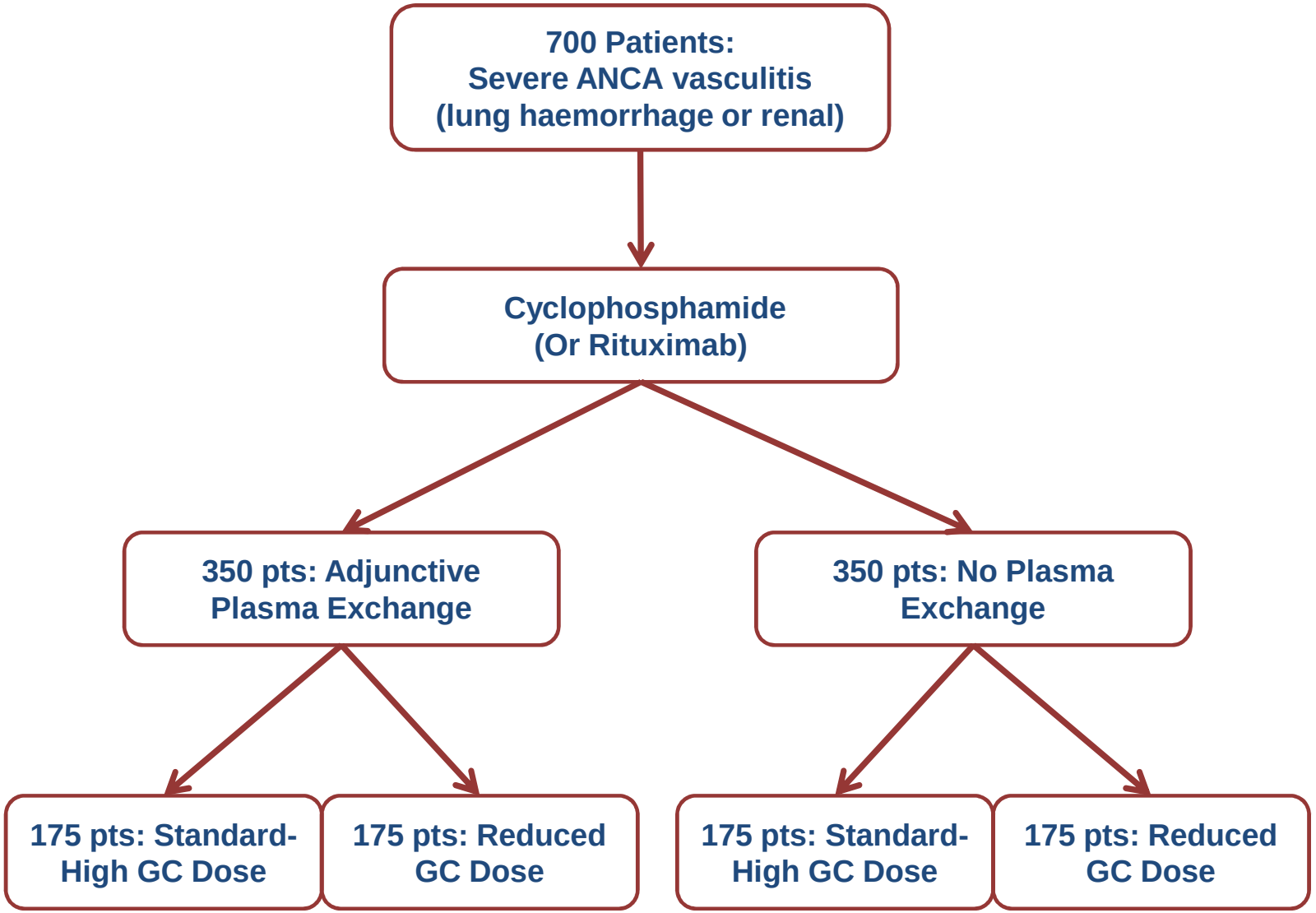
PEXIVAS

Hypothesis

1. PLEX increases the time to develop ESRD or death in severe ANCA-associated vasculitis
2. Reduced GC will not increase ESRD or death and will reduce adverse events (esp. infections)

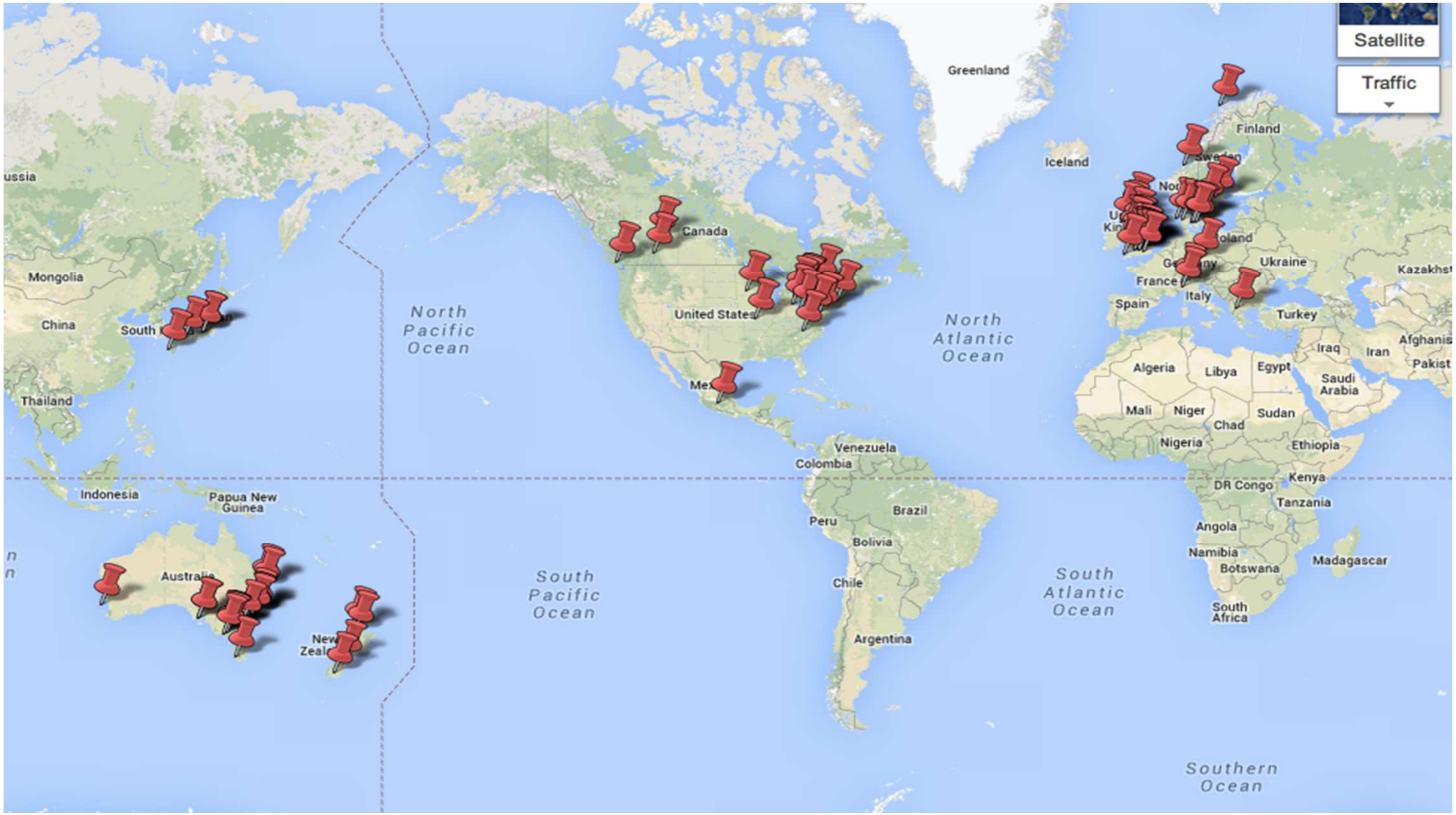
Walsh M, Trials 2013

Factorial design



Walsh M, Trials 2013

A global study, 108 centres, 4 continents, largest trial in AAV undertaken to date



52 inclus/ 704 dans 17 centres en France

Plasma exchanges in ANCA-associated vasculitis

- ANCA-associated vasculitis
- History
- Several lines of evidence suggest that ANCA may be pathogenic
- PLEX Recommendations, KDIGO clinical practice guidelines for GN
- Non randomized data for use in lung haemorrhage
- Randomized controlled trials
- Meta analyses and Systematic Reviews
- PEXIVAS
- Questions to be answered

Questions to be answered

- **Can PLEX be helpful in reducing immunosuppressive exposure?**
- **Can PLEX be helpful as a GC sparing procedure?**
- **What is the optimal PLEX dosing?**
- **What is the optimal type and dosing of concomitant medications?**
- **Can PLEX be useful in less severe renal involvement with serum creatinine level below 500 μmol/L?**
- **Can PLEX be useful in lung haemorrhage?**
- **Can selective apheresis techniques (immunoadsorption, cytapheresis) offer advantages in this setting?**

Szpirt WM, Nephrol Dial Transplant 2015
Walsh M, Am J Kid Dis 2010
Walters G, Cochrane Database of Systematic Reviews 2015

Conclusions

- PLEX confers a significant benefit to many patients with ANCA-associated vasculitis and RPGN by reducing the risk of ESRD at both 3 and 12 months from diagnosis.
- The 12 month RR of 0.45 suggests that the number of patients requiring dialysis may be halved by this intervention.
- A subgroup analysis showed a benefit for patients requiring dialysis at presentation (Pusey 1991).
- MEPEX trial showed a benefit in pts with creatinine >500 μmol/L
- The benefit at 5-year follow-up is controversial (Szpirt 2011 ≠ MEPEX)
- It is also still unclear whether PLEX would have an impact on pts whose kidney failure is not severe or with lung haemorrhage.
- The PEXIVAS trial will help to answer these questions.

French Vasculitis Study Group

www.vascularites.org

Hôpital Cochin, Paris, France