Rheumatologist

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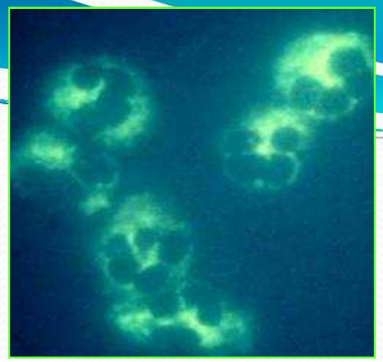
CASE 1

- 55 year old Japanese-Canadian
- 09/2008 creatinine 169, 3 g/l protein, 3+ blood, 3 cellular casts, BP 160/100 - **RF 28** (<20), CRP 0.5, ESR 14, **ANA 1:80** homogeneous, ANCA negative, cryoglobulins negative
- Prednisone Jan 2009 → October 2009
- 09/2011, creatinine 302 → 800, 3+ blood, casts; **C-ANCA at 1/10,000 in one lab then p-ANCA positive >8 and c-ANCA negative**, anti-GBM Ab negative

- Not responsive to Solumedrol, Cyclophosphamide and plasmapheresis x 6

ANCA as surrogate markers



	PR3-ANCA	MPO-ANCA
MPA	5-20%	> 50% (75)
GPA	75-90%	5-15%
EGPA	<5%	30-40%

Sensitivity and Specificity of ANCA

Sensitivity

- **The IIF assay is more sensitive than the ELISA**
- **A positive IIF assay should ALWAYS be confirmed by an ELISA**
- **The sensitivity of ANCA by IIF and/or ELISA is as high as 90% in active generalized GPA (Wegener's) but as low as 60% in limited disease**

Specificity

- **Compared to disease controls, specificities are:**
- **- cANCA = 95%**
- **- pANCA = 81%**
- **- anti-PR3 = 87%**
- **- anti-MPO = 91%**
- **The specificity of the combination of pANCA + anti-PR3 OR pANCA + anti-MPO is as high as 99%**

ANCA, anti-neutrophil cytoplasmic antibody; cANCA, cytoplasmic-ANCA; ELISA, Enzyme-linked immunoabsorbent assay; GPA (Wegener's), granulomatosis with polyangiitis; IIF, indirect immunofluorescence; pANCA, perinuclear-ANCA

Hagen et al. *Kidney Int.* 1998;53:743-53; Hagen and van Gurp. *Arthritis Care Res.* 2000;13:341-2

Conditions associated with ANCA

IIF	ELISA	Diseases/conditions
cANCA	**PR3**	**GPA (Wegener's), MPA (CSS)** **Endocarditis, Tuberculosis, amoebiasis**
	BPI (bacterial permeability increasing protein)	**Cystic fibrosis** **Infections**
pANCA	**MPO**	**MPA, GNRP, CSS (GPA (Wegener's))** **Felty's syndrome (RA)** **Drugs (propylthiouracil +)**
pANCA or atypical ANCA	**Cathepsine G**	**Ulcerative colitis** **Primary sclerosing cholangitis**
	Lactoferrin	**RA, ulcerative colitis**
	Elastase (or PR3)	**Cocaine-induced vasculopathy**
	Other or unindentified	**Infections** **RA, SLE** **Ulcerative colitis, AI Liver disease** **Drugs**

ANCA, anti-neutrophil cytoplasmic antibody; cANCA/pANCA, ANCA with cytoplasmic/perinuclear fluorescence labelling pattern in IIF; CSS, Churg-Strauss syndrome; ELISA, enzyme linked immunosorbent assay; GNRP, rapidly progressive glomerulonephritis; GPA (Wegener's), granulomatosis with polyangiitis; IIF, indirect immunofluorescence; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus

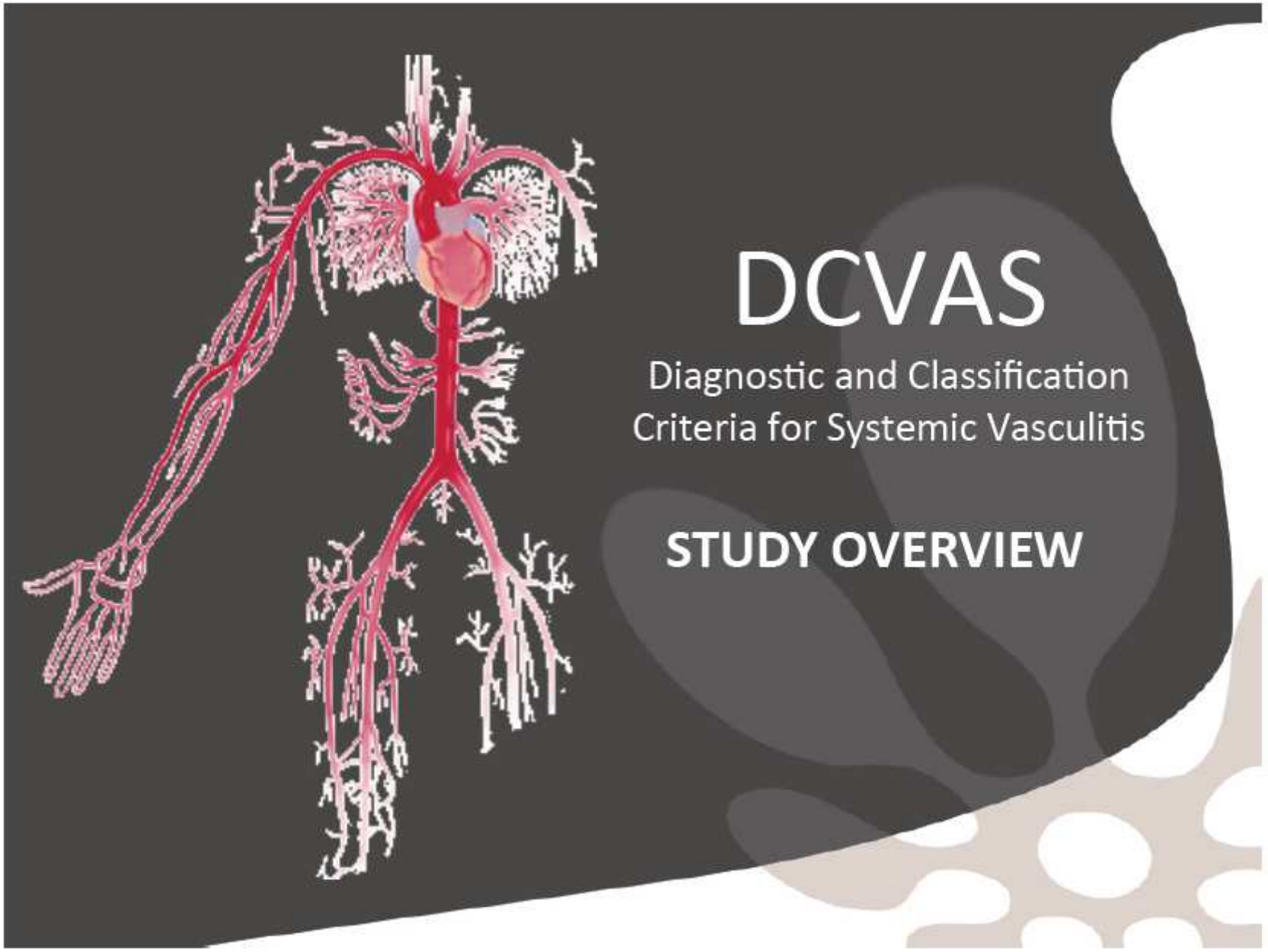
CASE 2 - Diagnosis, 1998

- 1998 Wegener's Granulomatosis (GPA)
- Manifestations:
  - C-ANCA positive
  - Crescentic GN, Creat 120-130 after treatment
  - Lung nodules, hemoptysis
  - Supracellar mass -> Diabetes Insipidus
  - Recurrent otitis media, sinusitis and nasal ulcers
  - Purpuric rash
  - Constitutional symptoms

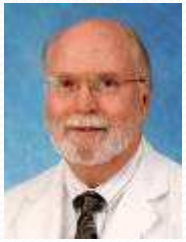
1990 ACR Classification criteria

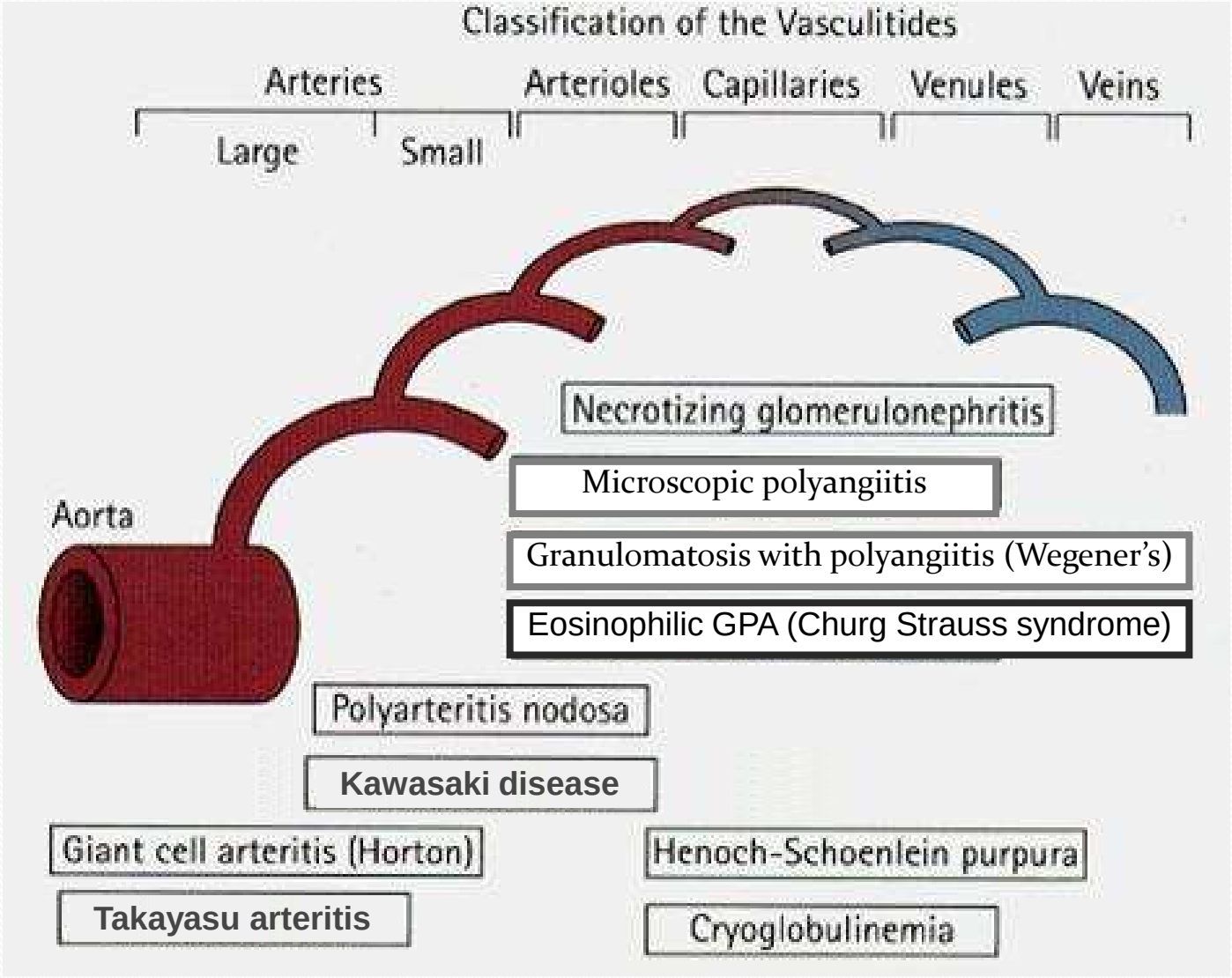
- Nasal or oral inflammation: oral ulcers or purulent or bloody nasal discharge
- Abnormal chest radiograph: nodules, fixed infiltrates, or cavities
- Abnormal urinary sediment: microhematuria (>5 RBC/HPF) or casts
- Granulomatous inflammation on biopsy: within the vessel wall or perivascular or extravascular

2 criteria → Sp 92% Se 88%

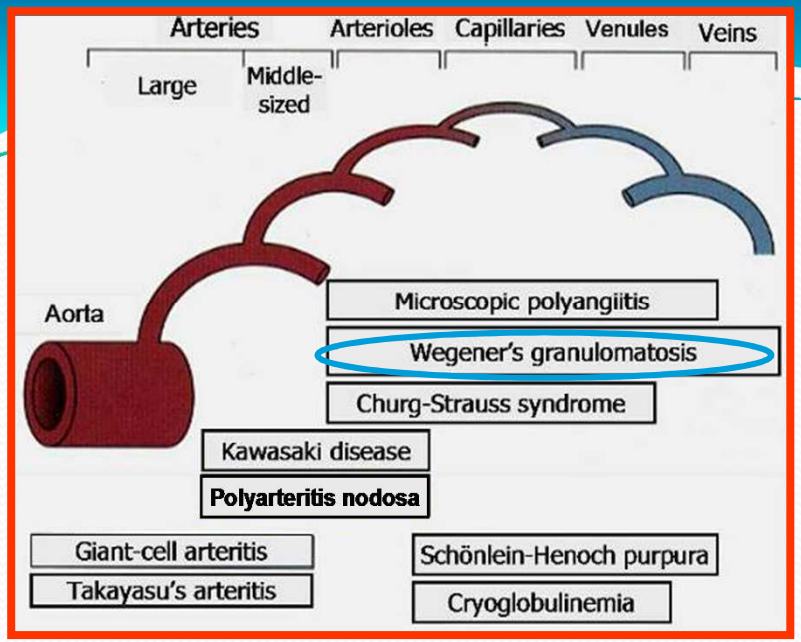

DCVAS
Diagnostic and Classification
Criteria for Systemic Vasculitis
STUDY OVERVIEW

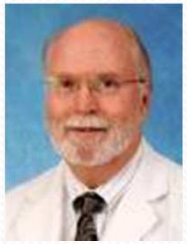
AMERICAN COLLEGE OF
RHEUMATOLOGY





Jennette et al. Arthritis Rheum 1994;37:187-92
Falk et al. Arthritis Rheum 2011 Apr;63(4):863-4





Jennette et al., Arthritis Rheum 1994

- Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels, e. g. capillaries, venules, arterioles and arteries.

- *Necrotizing glomerulonephritis is common.*
- *Frequently associated with ANCA*

2012 revised Chapel hill nomenclature

- **Large Vessel Vasculitis (LVV):** Takayasu Arteritis (TAK) and Giant Cell Arteritis (GCA)
- **Medium Vessel Vasculitis (MVV):** Polyarteritis Nodosa (PAN) and Kawasaki Disease (KD)
- **Small Vessel Vasculitis (SVV):**
  - *ANCA-Associated Vasculitis (AAV)* including: Microscopic Polyangiitis (MPA), Granulomatosis with Polyangiitis (Wegener's) (GPA) and Eosinophilic Granulomatosis with Polyangiitis (Churg Strauss) (EGPA)
  - *Immune Complex SVV including:* Anti-GBM Disease, Cryoglobulinemic Vasculitis, IgA Vasculitis (Henoch-Schönlein) (IgAV) and Hypocomplementemic Urticarial Vasculitis (Anti-C1q Vasculitis) (HUV).
- **Variable Vessel Vasculitis (VVV):** Behçet's Disease (BD) and Cogan's Syndrome (CS).
- **Single Organ Vasculitis (SOV):** Cutaneous Leukocytoclastic Angiitis, Cutaneous Arteritis, Primary CNS Vasculitis and Isolated Aortitis.
- **Vasculitis Associated with Systemic Disease:** Lupus Vasculitis, Rheumatoid Vasculitis and Sarcoid Vasculitis.
- **Vasculitis Associated with Probable Etiology:** Hepatitis C Virus-Associated Cryoglobulinemic Vasculitis, Hepatitis B Virus-Associated Vasculitis, Syphilis-Associated Aortitis, Serum Sickness-Associated Immune Complex Vasculitis, Drug-Associated Immune Complex Vasculitis, Drug-Associated ANCA-Associated Vasculitis and Cancer-Associated Vasculitis.

Treatment and natural history

- Initial flare 1998
  - Cyclophosphamide for 3-6 months then
  - Azathioprine

Treatment of severe GPA/MPA

CYCLOPHOSPHAMIDE

15 mg/kg (d1,14,28 then q3wk)

2 mg/kg/d

+ Corticosteroids

3 - 6 months

INDUCTION

+ adjuvant/prophylactic measures: cotrimoxazole, osteoporosis treatment, etc

CYCLOPS

- Open label RCT
- 149 AASV (40% GPA)
- All with renal disease
- No Iº hypothesis
- Pulse (IV or oral) vs continuous oral CYC
- Remission <u>at 9 mo</u>

Pulse 88.1%

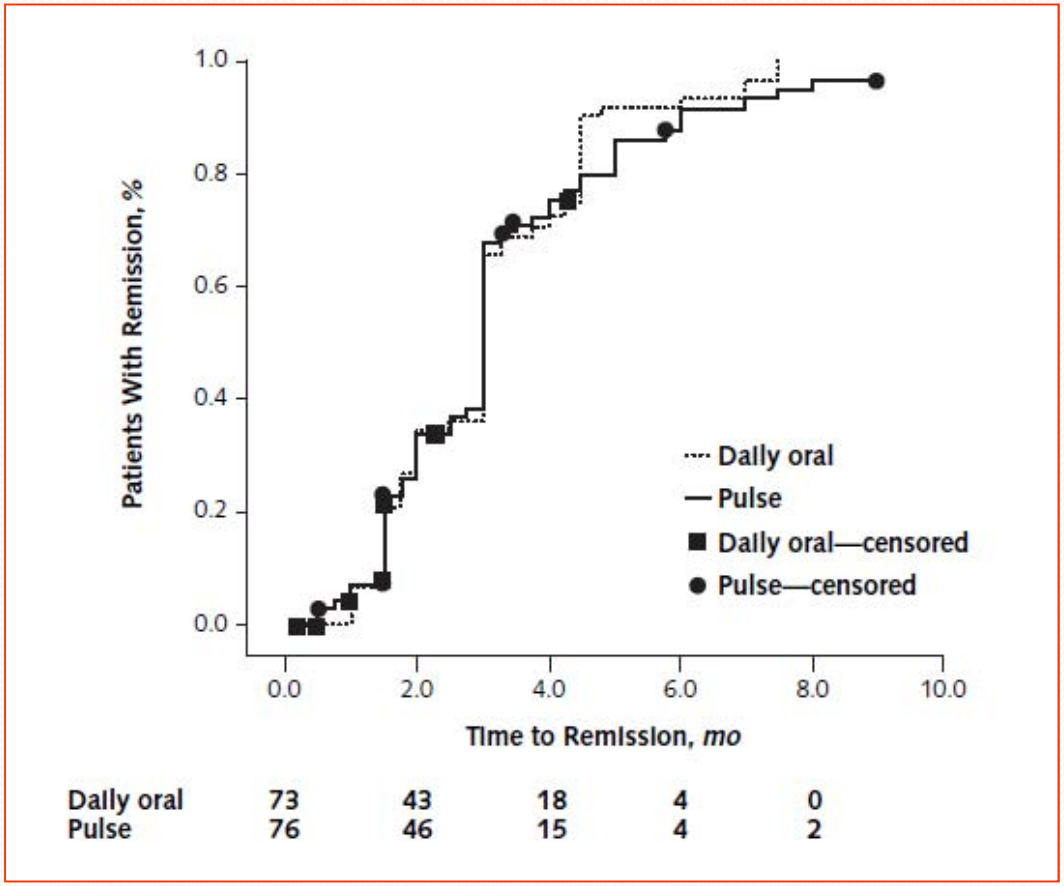
Continuous 87.7%

- DO = higher rate of leukopenia

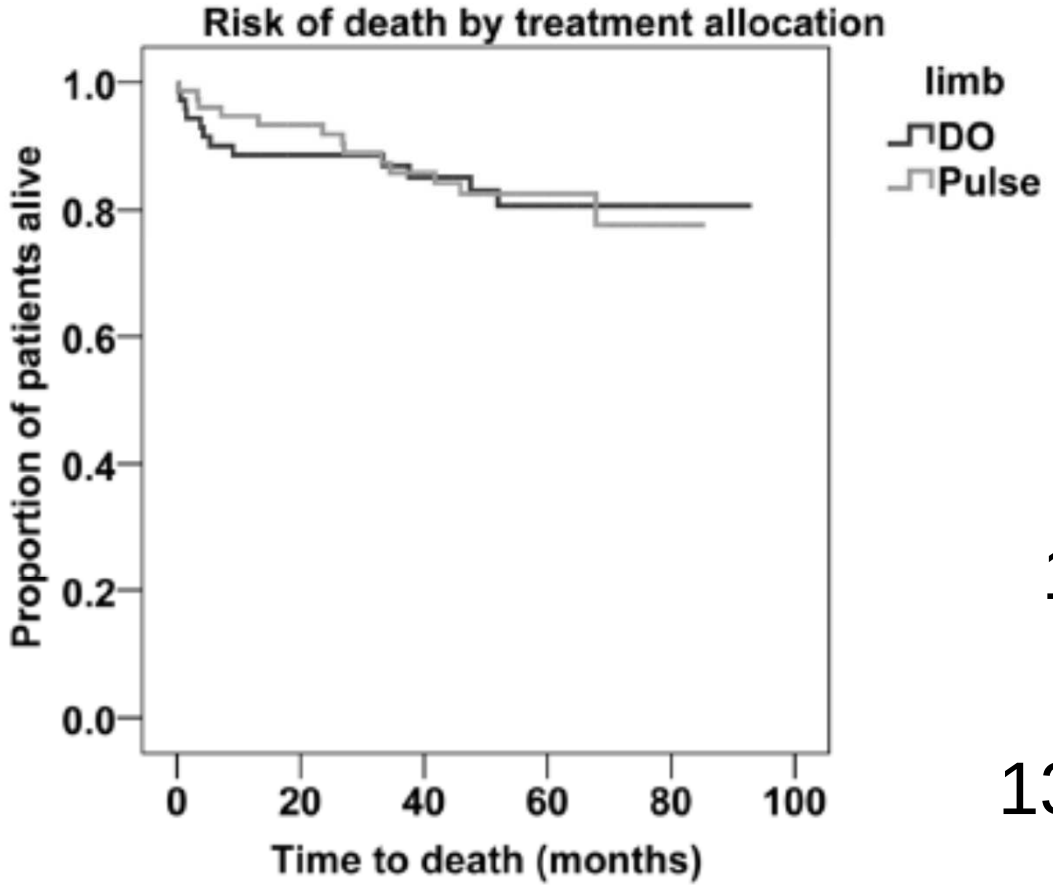
- <u>At 18 mo:</u>

14.5% relapsed

(18.8% IV vs. 9.4% PO)



de Groot et al, Ann Intern Med 2009;150:670-680



Time (months)	0	20	40	60	80
DO (n)	72	55	46	26	2
Pulse (n)	76	64	54	24	3

Figure 1. Patient survival according to treatment allocation. There was no significant difference in mortality risk between patients randomised to pulse cyclophsophamide or daily oral (DO) treatment.

Median duration of follow-up of **4.3 yrs**

DEATHS

12 patients in DO

vs.

13 in IV pulse group

(NS)

Harper et al. Ann Rheum Dis. 2011 Nov 29. [Epub ahead of print]

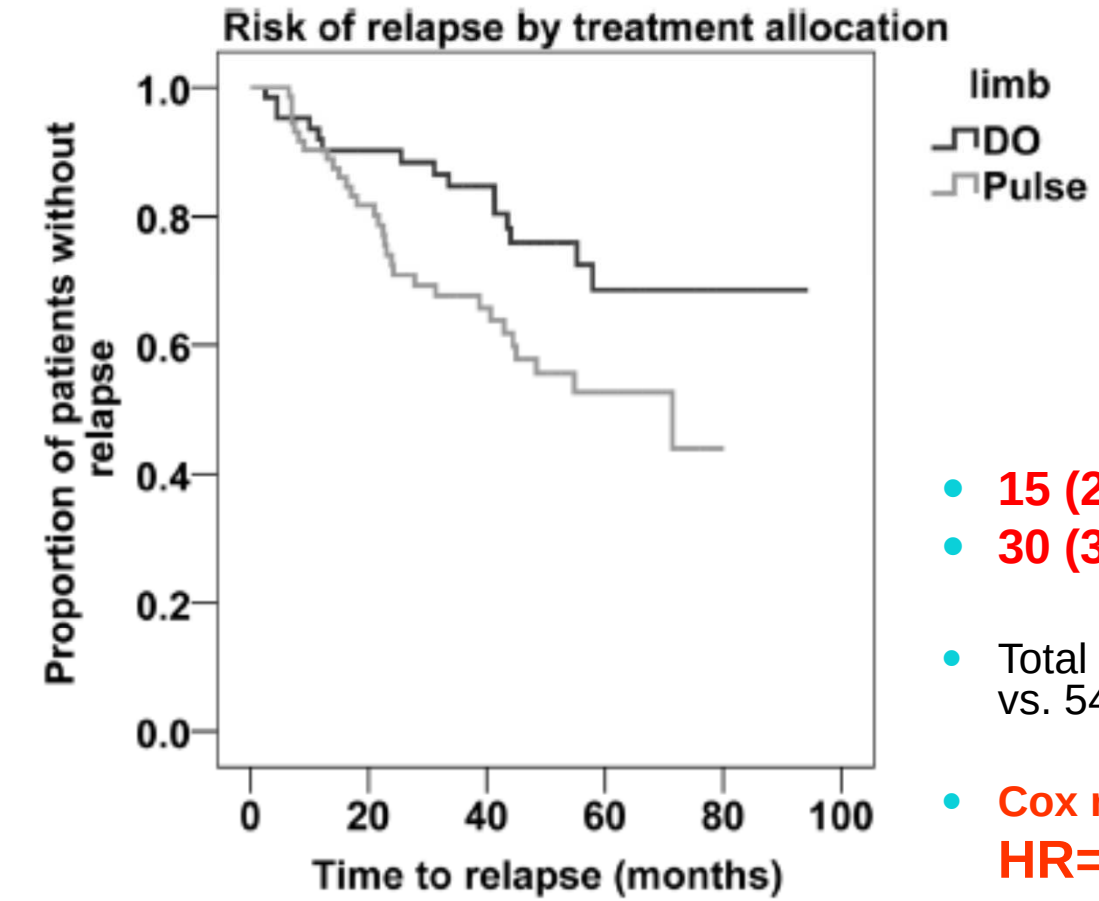


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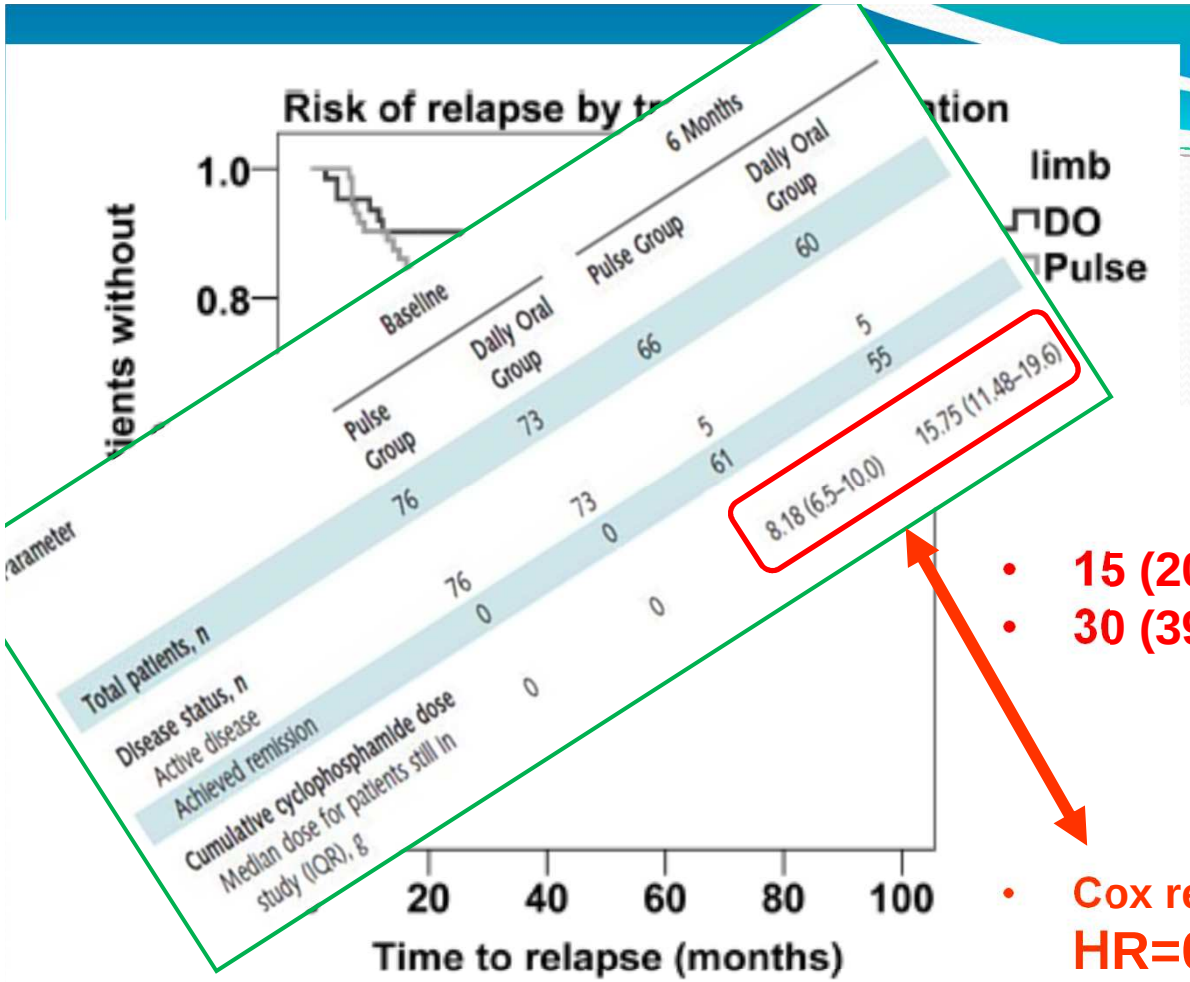
Figure 2. Relapse-free survival in the two treatment arms. Using Kaplan–Meier survival analysis, there was a significantly increased risk of relapse during follow-up in patients randomised to pulse cyclophsophamide rather than daily oral (DO) treatment (p=0.029).

RELAPSES

- **15 (20.8%) DO**
- **30 (39.5%) pulse had ≥1 relapse**

- Total of 21 relapses (10 renal) in the DO vs. 54 (12 renal) in the pulse limb

- **Cox regression analysis**
  HR=0.50, 95% (CI, 0.26-0.93); p=0.029



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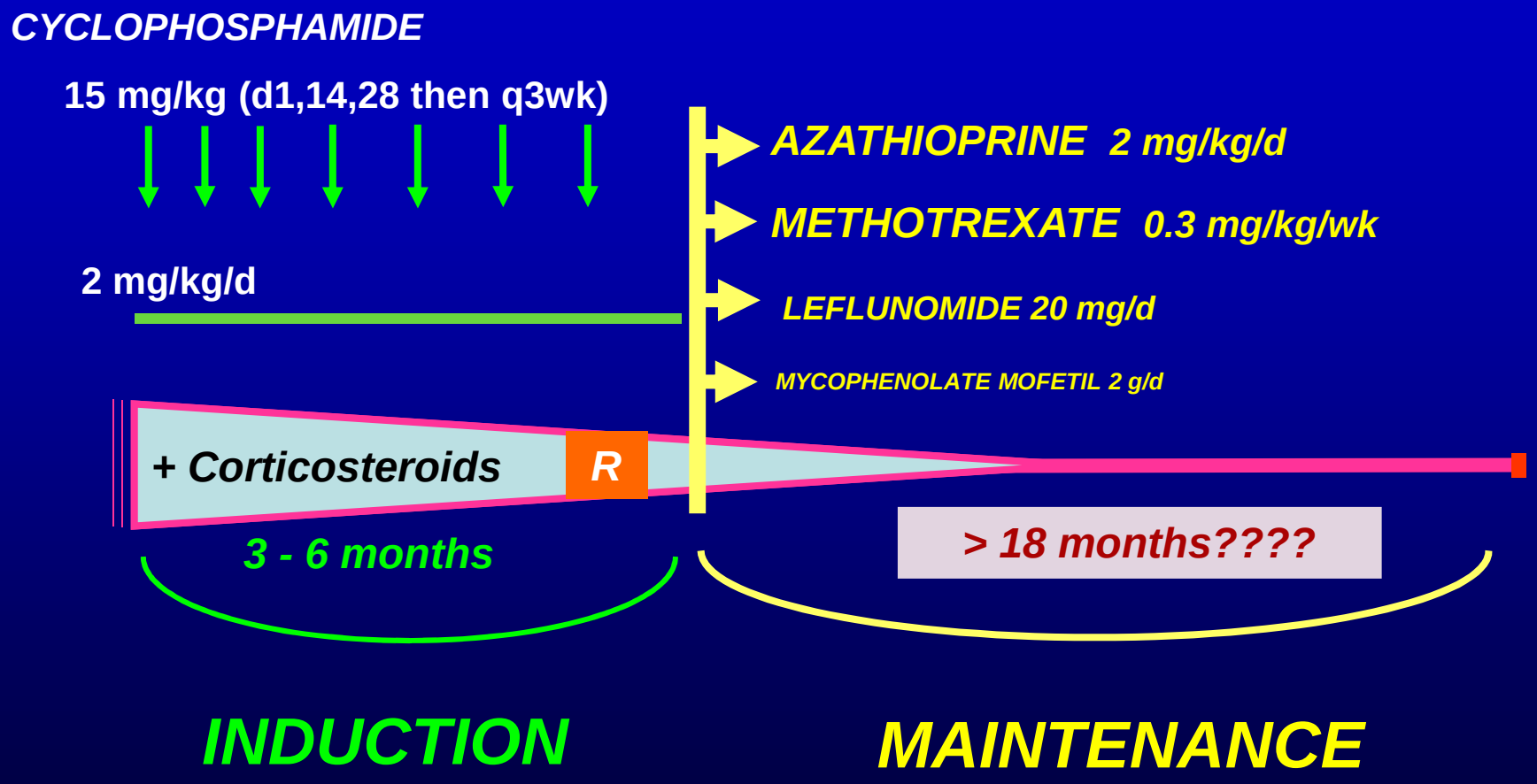
Treatment of severe GPA/MPA



+ adjuvant/prophylactic measures: cotrimoxazole, osteoporosis treatment, etc

Frequent relapses…

	Patients		Follow-up from Dg	Relapse rate	p
CYCAZAREM NEJM, 2003	WG, MPA	144	18 mo	AZA 15,5% vs. CYC 13,7%	NS
WGET NEJM, 2005	WG	180	27 mo	MTX 32,8% vs MTX/ETN 30,6%	NS
Langford Am J Med, 2003	WG	42	35 mo	52%	
WEGENT **Pagnoux, NEJM, 2009**	WG, MPA	126	37,3 mo	AZA 36,5% vs MTX 33,3%	NS
Sanders NEJM, 2003	WG, MPA	136	→ 5 yrs	AZA 42.3% vs. CYC 57.4%	NS

At 7 years, relapse rate 63.9% → 51.2% (445 patients)

Holle et al. Arthritis Rheum 2011 Jan;63(1):257-66

Mild relapses, 2007 and 2012…

- Mild flare, 2007
  - Treated with Azathioprine until 2009
- Mild flare, January 2012
  - Anorrhexia, malaise, chills, weight loss
  - Cough, hemoptysis

Optimal maintenance Rx?

GPA
antiPR3+

ENT?
Lung (nodules)??

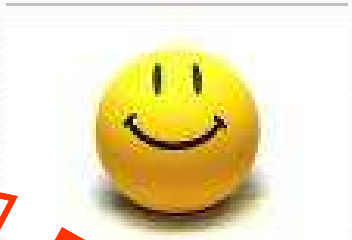
Low creatinine <100

Cardiovascular?

Risk of relapse

MPA
antiMPO+

High creatinine



Duration of CS and IS

REMAIN EUVAS trial (results June 2012?)
Walsh et al, Arthritis Care Res. 2010;62(8):1166-73

Mild relapses, 2007 and 2012…

- Mild flare, 2007
  - Treated with Azathioprine until 2009

- Mild flare, January 2012
  - Anorrhexia, malaise, chills, weight loss
  - Cough, hemoptysis

  - Started on methotrexate 15mg q week, Prednisone 40 mg OD, Septra DS 3X/week by rheum.

EARLY SYSTEMIC GPA (<150 µM)

NORAM

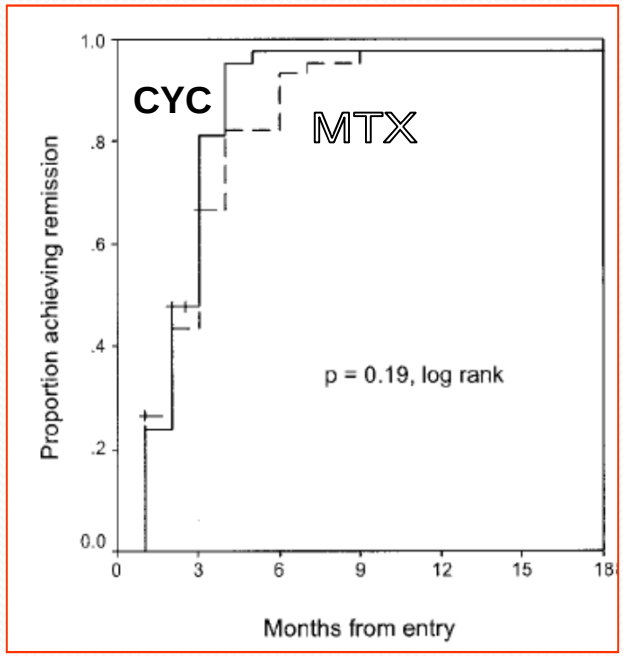
- Methotrexate vs oral Cyclophosphamide for induction
- Non-inferiority trial (d=15%) for remission at 6 months
- 95 p. with “early systemic” GPA for 12 months (6 MPA)

Remission at 6 mo
MTX 89.8%
CYC 93.5% (P=0.04)

Relapse at 18 mo
MTX 69.5%
CYC 46.5% (P=0.02)

CYC Leukopenia
MTX liver enzymes

CS at M18
8.8 g MTX vs 6.2 CYC
(P<0.01)



de Groot et al. *Arthritis Rheum* 2005;52:2461–9

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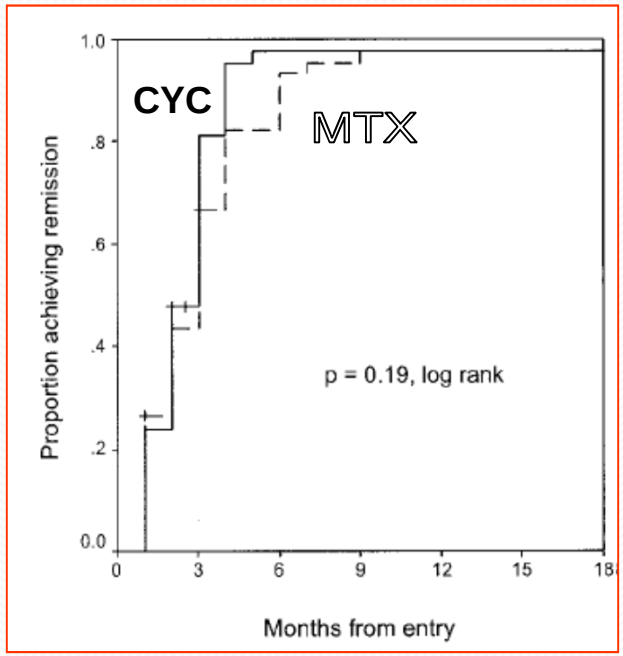
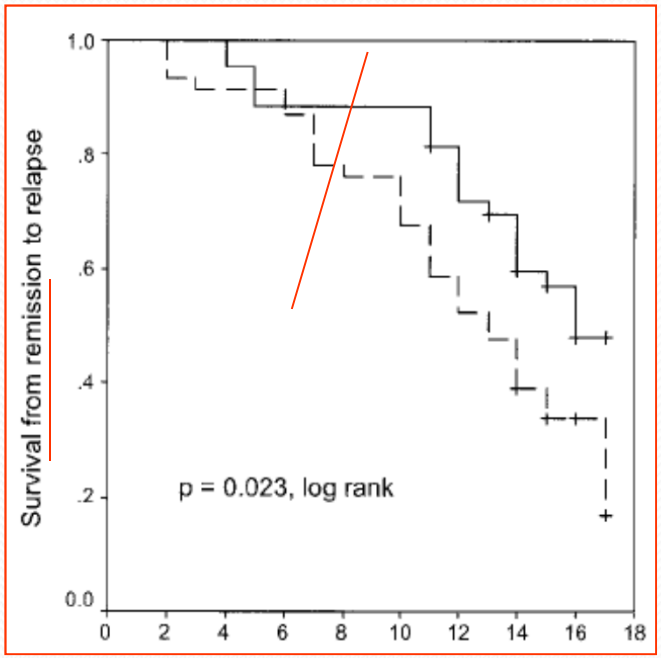
CS at M18
8.8 g MTX vs 6.2 g CYC
(P<0.01) and longer

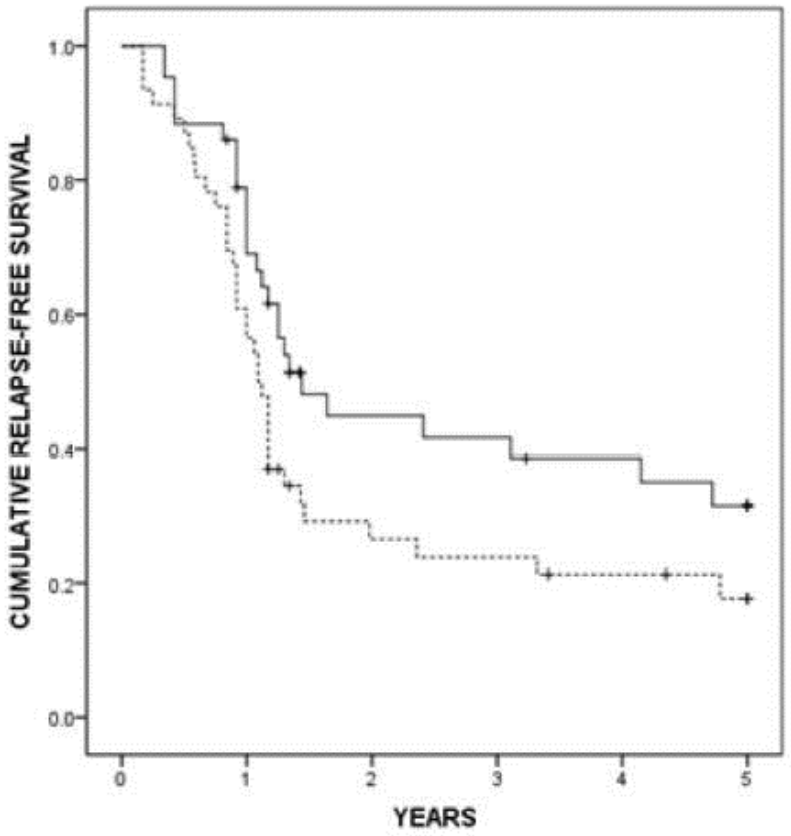




de Groot et al. *Arthritis Rheum* 2005;52:2461–9

NORAM long-term f/up

- Median f/up 6.0 (0.1-10.8) yrs
- N=72 with f/up >18 mo.
- 1 patient ESRD (MTX, NS)
- 11 died (NS)
- AES did not differ between groups
- MTX patients were exposed to CS, CYC, IS for longer periods than those CYC patients (p=0.004; p=0.037; and p=0.031, respectively)
- Cumulative relapse-free survival tended to be lower in the MTX groups (p=0.056)



CYC	43	32	14	13	11	9
MTX	46	28	10	9	7	5

Cumulative relapse-free survival from time of 1st remission:
69%, 32%, and 24%
after 1, 3, and 5 years of f/up

Faurschou et al. Arthritis Rheum; E-pub May 2012

NORAM long-term f/up

"the intensity of first-line immunosuppressive treatment is inversely related to the risk of relapsing disease in AAV"

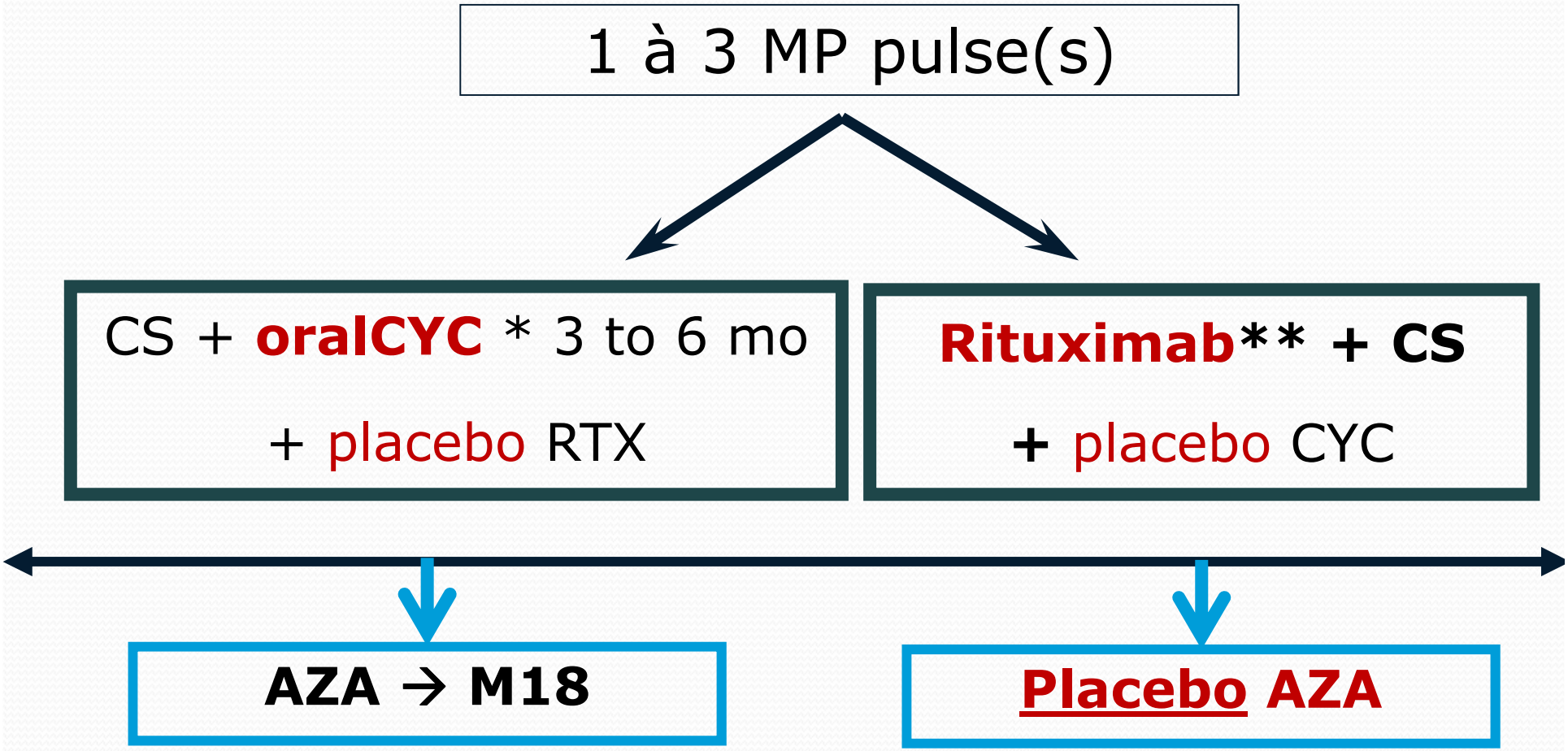
Faurschou et al. Arthritis Rheum; E-pub May 2012

… to severe relapse, 2012

- c-ANCA > 8.0, p-ANCA <0.2, Anti-GBM negative
- Creat 467, 24-hour urine protein 6.3 g/day, RBC casts
- Popliteal DVT
- Hb 89, plt 342, WBC 13.8
- CXR small nodule RUL

(<350 µM)

RAVE

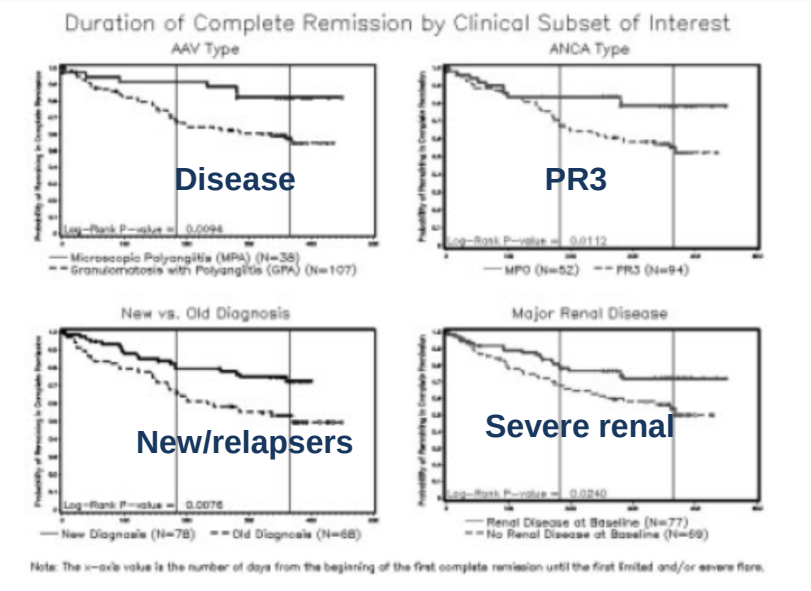


* oral CYC 2 mg/kg/d

** RTX 375 mg/m2 x 4

Extended RAVE follow-up

- 197 patients ANCA+ (49% new, 51% relapsers)
- CR (NS)
  - At M6: 64% RTX vs 53% CYC/AZA
  - At M12: 47% RTX vs 39% CYC/AZA
  - At M18: 39% RTX vs 33% CYC/AZA
- Higher risk of relapse
  - Relapsers
  - No renal disease
  - PR3+
  - GPA

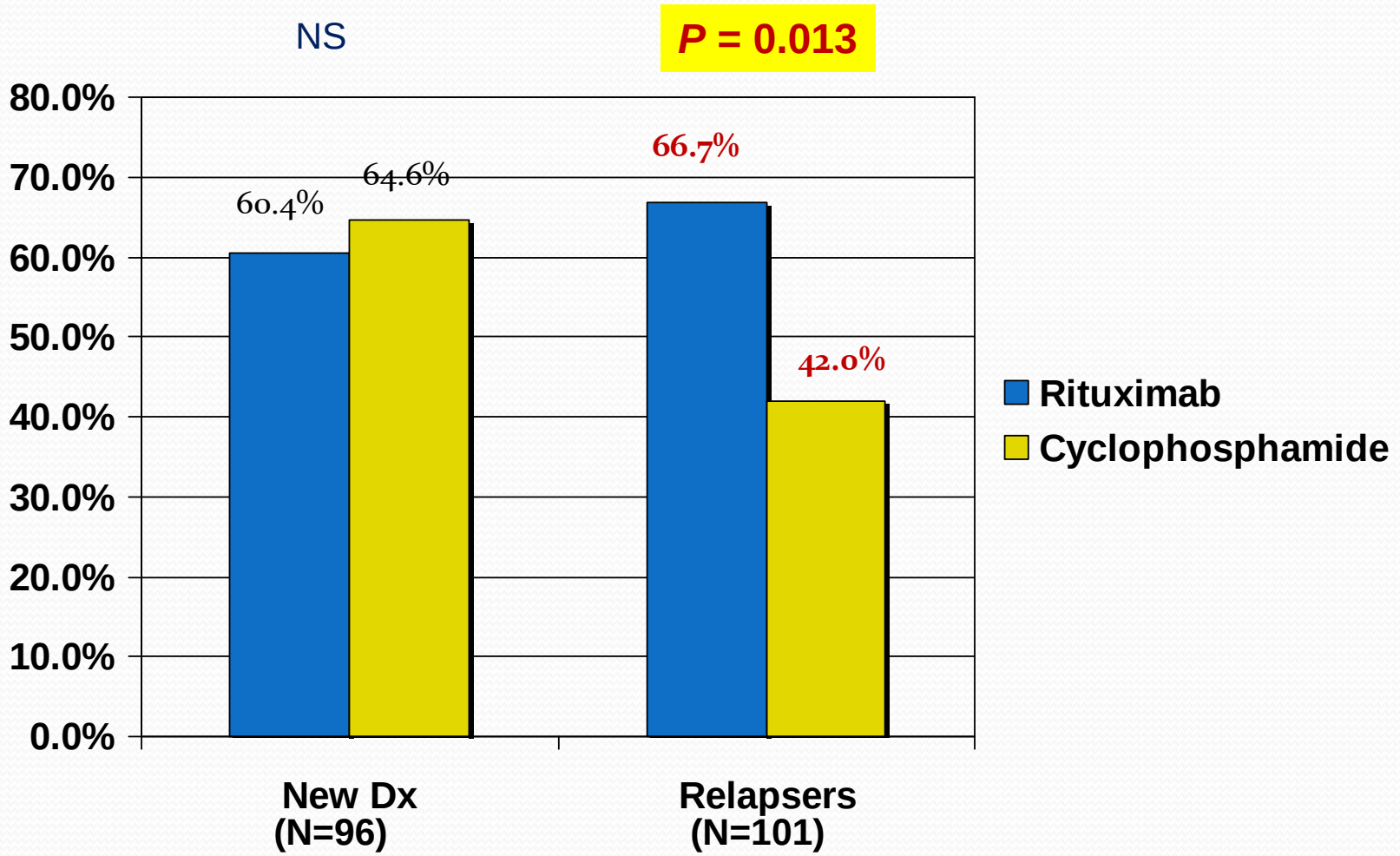


- Flares occured only after B cell reconstitution in RTX arm

Stone JH et al. #2432 OP

Better response in relapsers

(vs newly-diagnosed)



Stone JH et al, *N Engl J Med* 2010;363(3):221-32

REIMBURSEMENT CRITERIA

For the induction of remission of severely active Granulomatosis with Polyangiitis (GPA) OR microscopic polyangiitis (MPA) as combination treatment with glucocorticoids, in patients who meet all of the following criteria:

1. The patient must have severe active disease that is life- or organ-threatening. At least one supporting laboratory and/or imaging report must be provided. The organ(s) and how the organ(s) is(are) threatened must be specified.
2. There is a positive serum assays for either proteinase 3-ANCA (anti-neutrophil cytoplasmic autoantibodies) or myeloperoxidase-ANCA. A copy of the laboratory report must be provided.
3. Cyclophosphamide cannot be used for the patient for at least ONE of the following reasons:

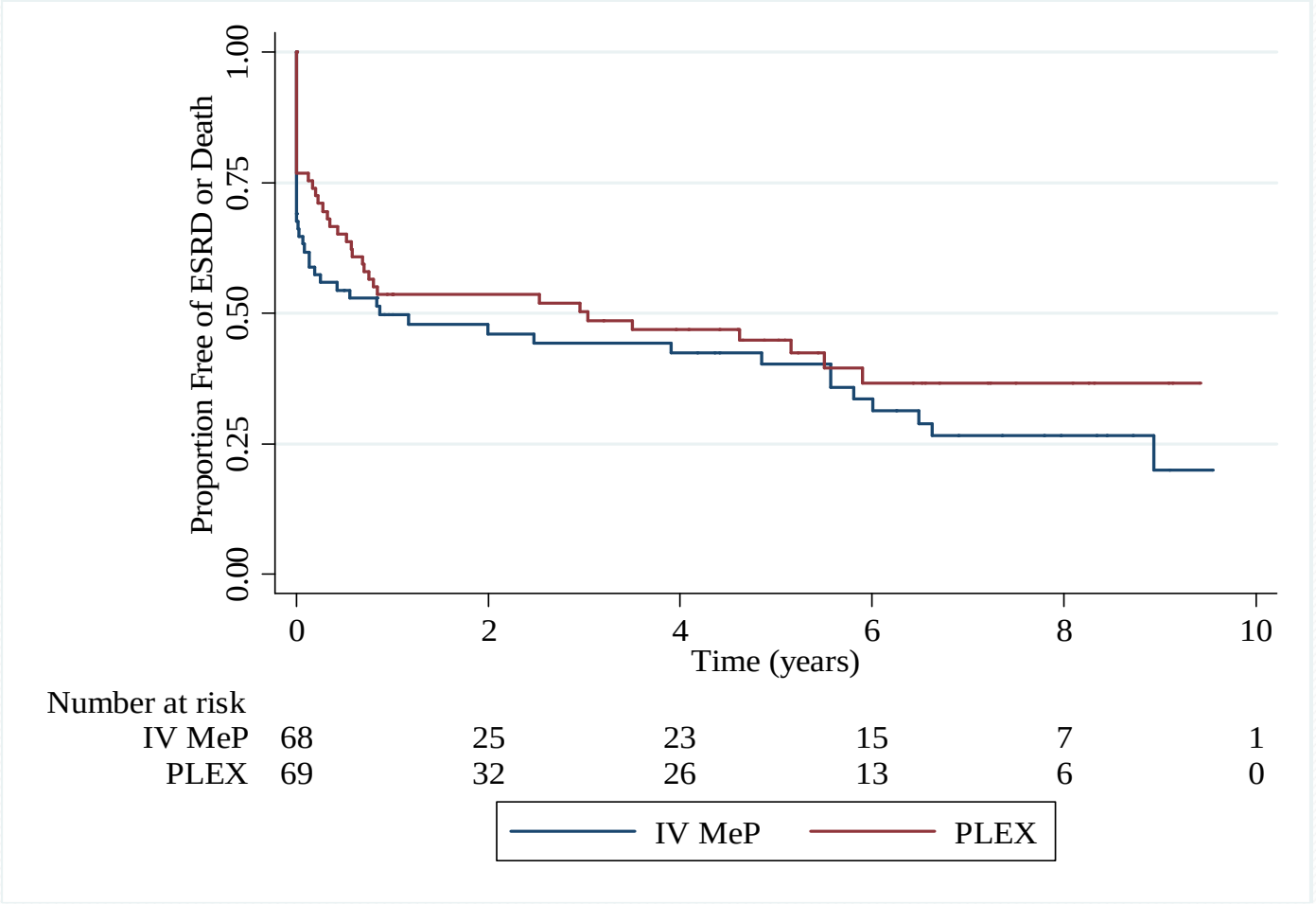
a) The patient has failed a minimum of six IV pulses of cyclophosphamide; OR
b) The patient has failed three months of oral cyclophosphamide therapy; OR
c) The patient has a severe intolerance or an allergy to cyclophosphamide; OR
d) Cyclophosphamide is contraindicated; OR
e) The patient has received a cumulative lifetime dose of at least 25 g of cyclophosphamide; OR
f) The patient wishes to preserve ovarian/testicular function for fertility.

The initial treatment would be a once weekly infusion dosed at 375 mg/m^2 x 4 weeks.

The physician must confirm that the treatment would not be a maintenance infusion as maintenance infusions will not be funded.

Renewals will be considered provided that, the patient meets the same criteria for initial approval and the request for retreatment is made no less than 6 months after the last does of the patient's last treatment cycle with Rituxan.

MEPEX Revisited



Hazard ratio for ESRD or Death: 0.91 (95% CI 0.53 to 1.23; p=0.32)

Hazard ratio for ESRD: 0.64 (95% CI 0.40 to 1.05; p=0.08)

Hazard ratio for Death: 1.08 (95% CI 0.67 to 1.73; p=0.75)

PLEX for patients with Lung Hemorrhage?

- EUVAS data 108/535 patients had alveolar hemorrhage (ventilator dependent excluded)
  - AH associated with death in ¾ trials (HR 1.6)
- 41 MEPEX patients (PLEX vs IV steroids) with hemorrhage (25 hemoptysis, 16 infiltrates only)
  - Treatment with PLEX did **not** improve outcome
    - 10/21 (47%) IV Mep vs 12/20 (60%) PLEX died in first year (p=0.56) (mostly sepsis)
    - Adjusted estimate HR=1.6 for PLEX (p=0.31)

Casian et al. Unpublished. 2011.

PEXIVAS

a RCT of plasma exchange and glucocorticoid dosing in ANCA associated vasculitis

3 Co-PIs: Mike Walsh (Canada), David Jayne (UK) and Peter Merkel (USA)

NHS National Institute for Health Research

FDA

NIAMS National Institute of Arthritis and Musculoskeletal and Skin Diseases

Australian Government National Health and Medical Research Council NHMRC

CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

CaridianBCT

Fresenius Medical Care

GAMBRO

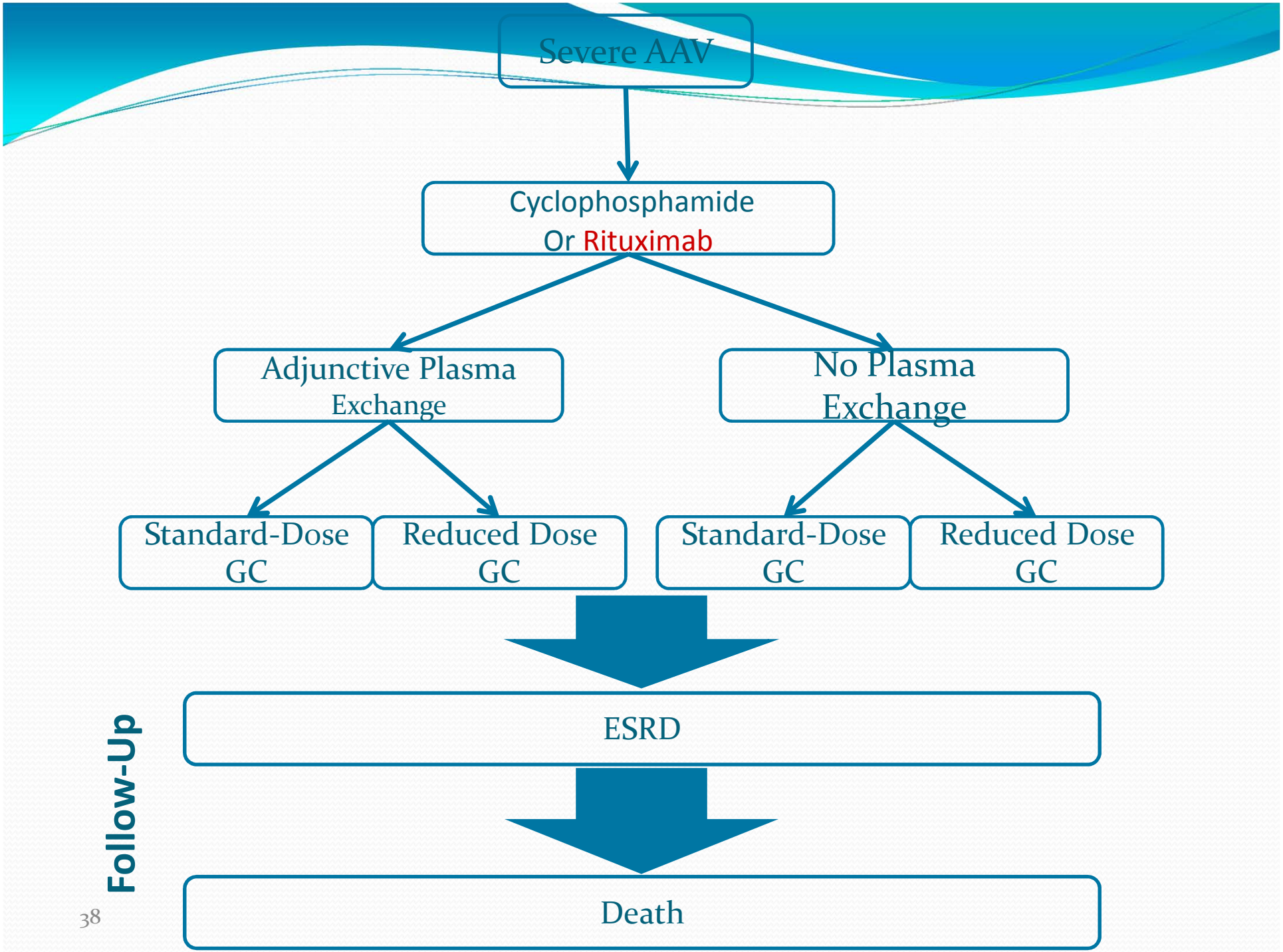
PEXIVAS

Inclusion

- New or Previously diagnosed GPA or MPA
- ANCA + (by ELISA)
- Current “severe” manifestation
  - GN with eGFR <50 ml/min
  - Lung Haemorrhage
- Informed Consent or Deferred Consent

Exclusion

- <18 years old (<15 in peds centres)
- Concomitant anti-GBM or other non-AAV vasculitis
- Pregnant
- Received significant therapy for this presentation already
  - >1 IV dose or 2 weeks CYC
  - >1 dose RTX within 1 month
  - >21 days pred >30 mg/day
- Likely has ESRD already
- Physician feels PLEX mandated*


Severe AAV
Cyclophosphamide
Or Rituximab
Adjunctive Plasma Exchange
No Plasma Exchange
Standard-Dose GC
Reduced Dose GC
Standard-Dose GC
Reduced Dose GC
ESRD
Death
Follow-Up

2nd annual CanVasc meeting

Montréal, QC

November 22nd, 2012

Registration and information on

http://www.canvasc.ca

April 14 - 17 2013

16th International Vasculitis & ANCA Workshop

"Institut des Cordeliers"
Paris - France

Scientific committee :

Pr. Loïc Guillevin
(president)

Organisation :

Maud Placines-Charier
Nex & Com Medical Events
159 rue de Silly
92100 Boulogne Billancourt
Tel : +33 1 46 43 33 23
Fax : +33 1 46 43 33 24
Email : m.placines@nex-com.com

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