

# The Use of Plasmapheresis in Myeloma Associated Kidney Disease

*François Madore, MD, MSc*

Professor of Medicine, Université de Montréal,  
Hôpital du Sacré-Cœur de Montréal,  
Montréal, Québec, Canada

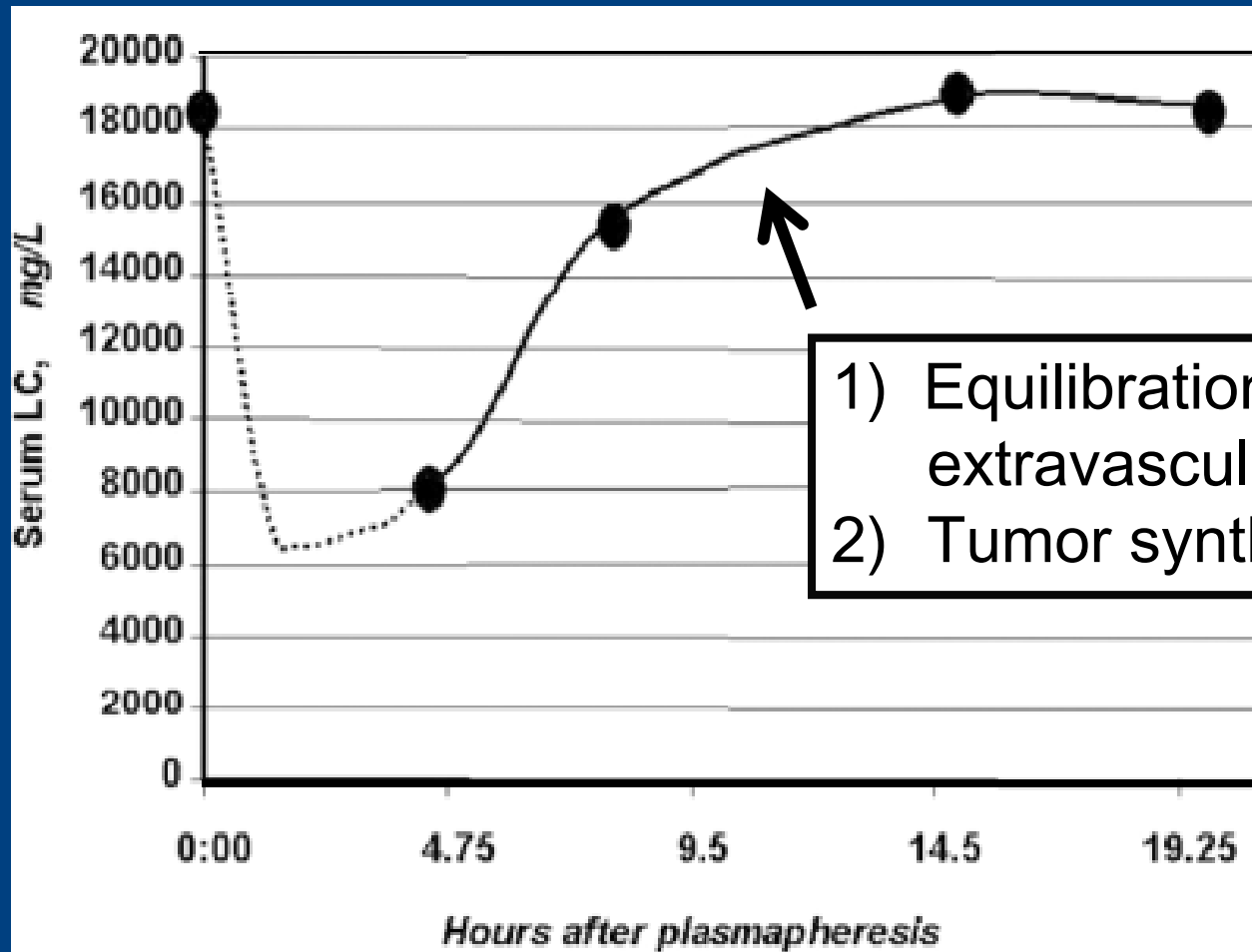
# Overview

- x Rationale for plasmapheresis in myeloma
- x Technical review
- x Randomized controlled trials
- x Recent non-randomized studies
- x On-going trials
- x Treatment recommendations

# Rationale

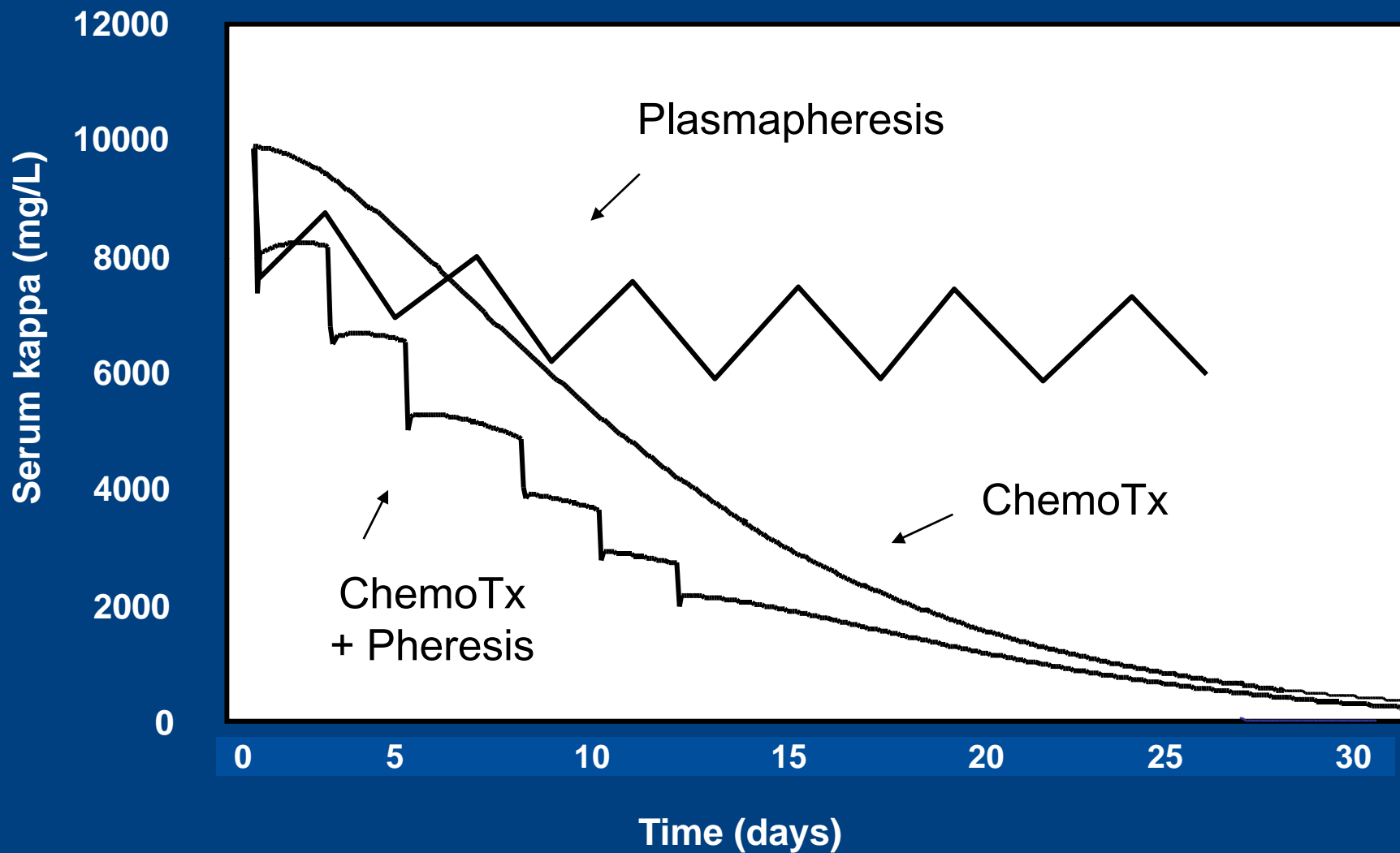
- x Reduced exposure to nephrotoxic myeloma protein
- x Removal of myeloma protein with plasmapheresis
- x Suppression of protein synthesis with chemotherapy
- x Faster decrease of myeloma protein with a combination of chemotherapy plus plasmapheresis than with chemotherapy alone

# Free light chain (FLC) removal with plasmapheresis



*Adapted from: Cserti, C. et al. Transfusion. 47:511-514, 2007*

# FLC removal with plasmapheresis



Adapted from: Hutchison, CA. et al. *CJASN*. 18:886-895, 2006

# Rationale

Plasmapheresis provides:

- x Faster decrease in circulating myeloma protein
- x Reduced exposure to nephrotoxic myeloma protein

Plasmapheresis cannot:

- x Decrease tumor burden
- x Improve the cytogenetic factors

# Technical overview (1)

## Basic components:

- x Withdrawal of venous blood
- x Separation of plasma from cellular components
- x Reinfusion of cellular elements plus either autologous plasma (plasma exchange) or an alternate replacement solution (plasmapheresis)

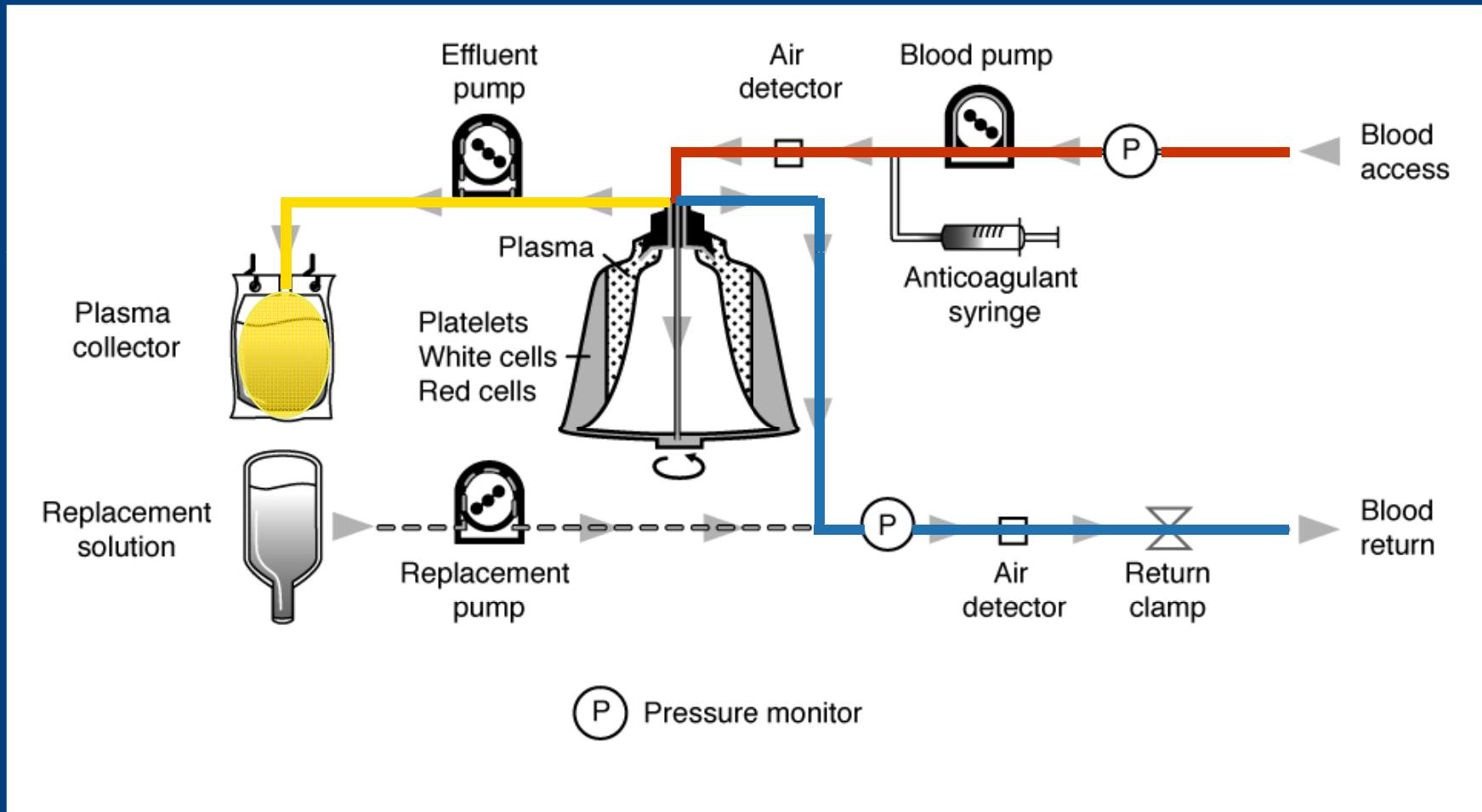
## Technical overview (2)

Separation of plasma from cellular components by:

- x centrifugation (intermittent or continuous)
- x membrane filtration (continuous)



# Plasmapheresis: Centrifugation

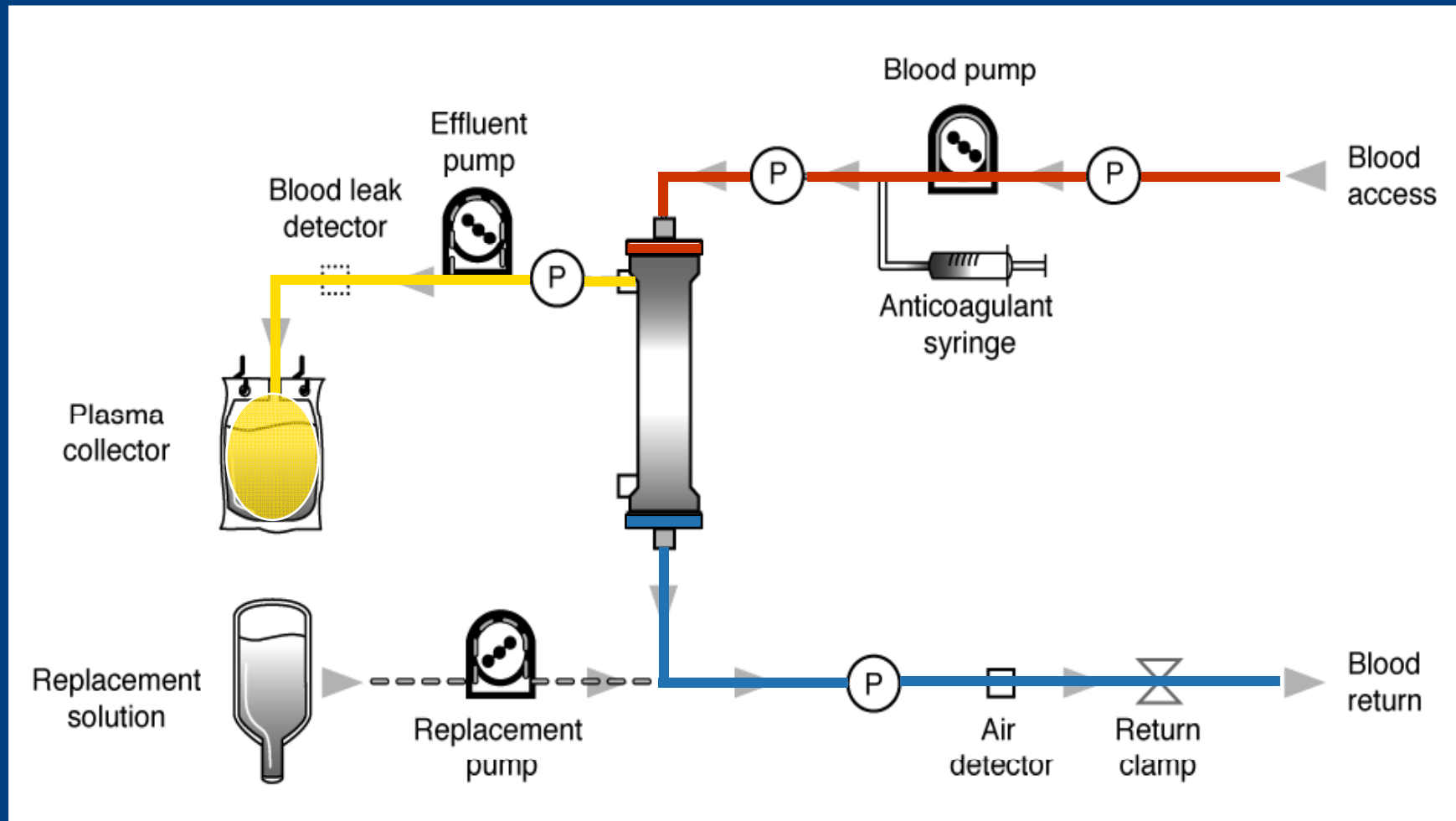


*Adapted from: Madore, F. Crit. Care Clin. 18:375-392, 2002*

# Plasmapheresis: Centrifugation



# Plasmapheresis: Filtration



*Adapted from: Madore, F. Crit. Care Clin. 18:375-392, 2002*

# Plasmapheresis: Filtration



# Technical overview

## Centrifugation versus filtration:

- x Similar efficacy
- x Differences with regard to:
  - costs of equipment
  - mobility of equipment
  - type of venous access

# Technical overview

## Standard treatment:

- x Duration of 2 to 4 hours
- x Removal of 2.5 to 4 liters of plasma
- x Reinfusion volume : volume  
with albumin / saline / fresh frozen plasma

# Overview

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- x **Randomized controlled trials**
- x **Recent non-randomized studies**
- x **On-going trials**
- x **Treatment recommendations**

# Randomized controlled trials

## 3 trials:

- x Zucchelli et al. – 1988  
*(Kidney Int. 33:1175-1180, 1988)*
- x Johnson et al. – 1990  
*(Arch. Intern. Med. 150:863-869, 1990)*
- x Clark et al. – 2005  
*(Ann. Intern. Med. 2005, 143:777-784)*



# Zucchelli et al. (1)

*(Kidney Int. 1988)*

- x Population: n = 29
- x Multiple myeloma:  
Diagnosis 2 to 14 months prior to study with 80% treated previously with cytotoxic drugs
- x All patients were treated with forced diuresis and chemotherapy (Melphalan / Prednisone)

Zucchelli et al. (2)  
**Interventions**

- x Group 1 (n=15):  
Plasmapheresis <sup>1</sup> + HD (as needed)
- x Group 2 (n=14):  
Peritoneal dialysis (pre-emptive)

<sup>1</sup> *Daily for 5 days, 3-4 liters, replacement with FFP / saline*

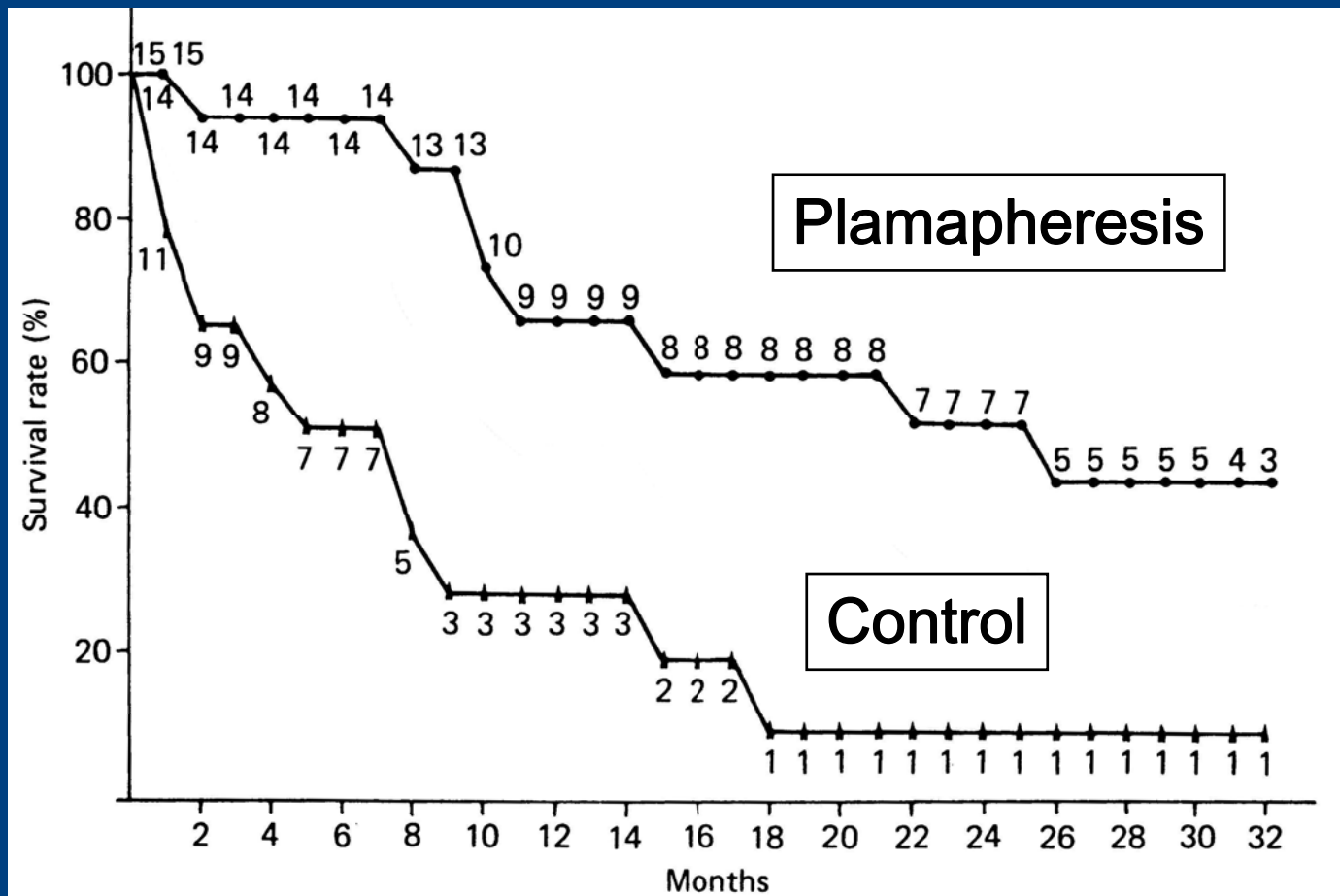
Zucchelli et al. (3)  
**Results: Renal Function**

	Control	Pheresis	P
Number of patients	14	15	
Patients requiring dialysis at onset (%)	11 (78%)	13 (86%)	NS
Patients interrupting dialysis (%)	2 (18%)	11 (84%)	<0.01
Serum creatinine at the end of the 2 <sup>nd</sup> month, mean $\pm$ SD	7.7 $\pm$ 1.9	2.6 $\pm$ 2.1	<0.001

*Adapted from: Zucchelli P. et al. Kidney Int. 33:1175-1180, 1988*

# Zucchelli et al. (4)

## Results: Patient Survival



*Zucchelli P. et al. Kidney Int. 33:1175-1180, 1988*

Zucchelli et al. (5)

# Summary

Plasmapheresis provides significant benefit in:

- x Renal outcome
- x Patient Survival

Limitations:

- x Mixture of newly diagnosed and existing patients with myeloma
- x Survival effect related to dialysis treatment?
- x Very small sample size

# Johnson et al. (1)

*(Arch. Intern. Med. 1990)*

- x Population: n = 21
- x Multiple myeloma:  
Diagnosis 0 to 14 months prior to study with  
exclusion of patients with resistance to Melphalan /  
Prednisone
- x All patients were treated with forced diuresis and  
chemotherapy (Melphalan / Prednisone)

Johnson et al. (2)  
**Interventions**

- x Group 1 (n = 11):  
Plasmapheresis <sup>1</sup> + HD (as needed)
- x Group 2 (n = 10):  
HD (as needed)

<sup>1</sup> *Thrice weekly, 3-12 sessions, 3-4 liters, replacement with albumin / saline*

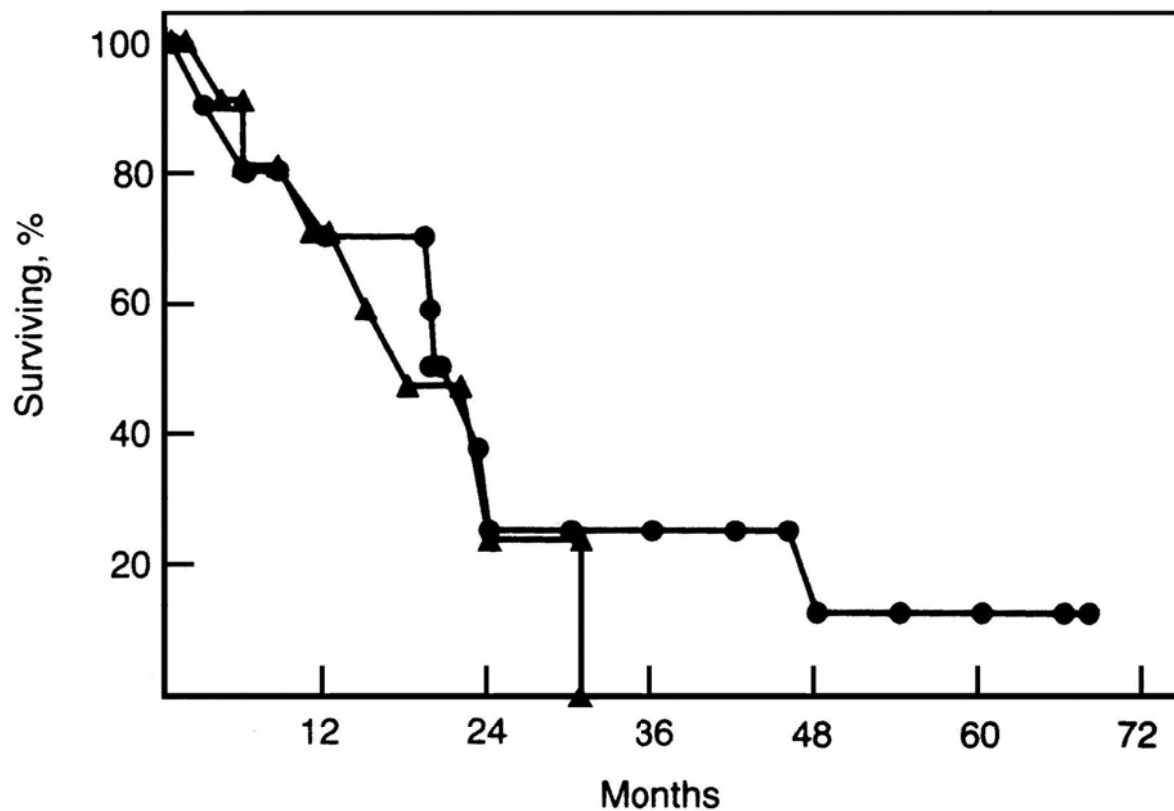
Johnson et al. (3)  
**Results: Renal Function**

	Control	Pheresis	P
Number of patients	10	11	
Patients requiring dialysis at onset (%)	5 (50%)	7 (63%)	NS
Patients interrupting dialysis (%)	0 (0%)	3 (43%)	NS
Final serum creatinine, mean $\pm$ SD	2.3 $\pm$ 1.1	2.9 $\pm$ 1.4	NS

*Adapted from: Johnson WJ et al. Arch. Intern. Med. 150:863-869, 1990*



# Johnson et al. (4) Results: Patient Survival



*Johnson WJ et al. Arch. Intern. Med. 150:863-869, 1990*

Johnson et al. (5)

## Summary

Plasmapheresis does not provide any significant improvement in:

- x Renal outcome
- x Patient Survival

Limitations:

- x Very small sample size (n=21)
- x More severe cases in the plasmapheresis group

# Clark et al. (1)

*(Ann. Intern. Med. 2005)*

- x Population: n = 97
- x Multiple myeloma:  
New cases with exclusion of patients with prior treatment for myeloma
- x All patients were treated with chemotherapy:  
Melphalan / Prednisone or VAD (Vincristine / Adriamycin / Dexamethasone)

## Clark et al. (2)

# Interventions

- x Group 1 (n = 58):  
Plasmapheresis <sup>1</sup> + HD (as needed)
- x Group 2 (n = 39):  
HD (as needed)

<sup>1</sup> *Within 10 days, 5-7 sessions, 3-4 liters, replacement with albumin / saline*

## Clark et al. (3)

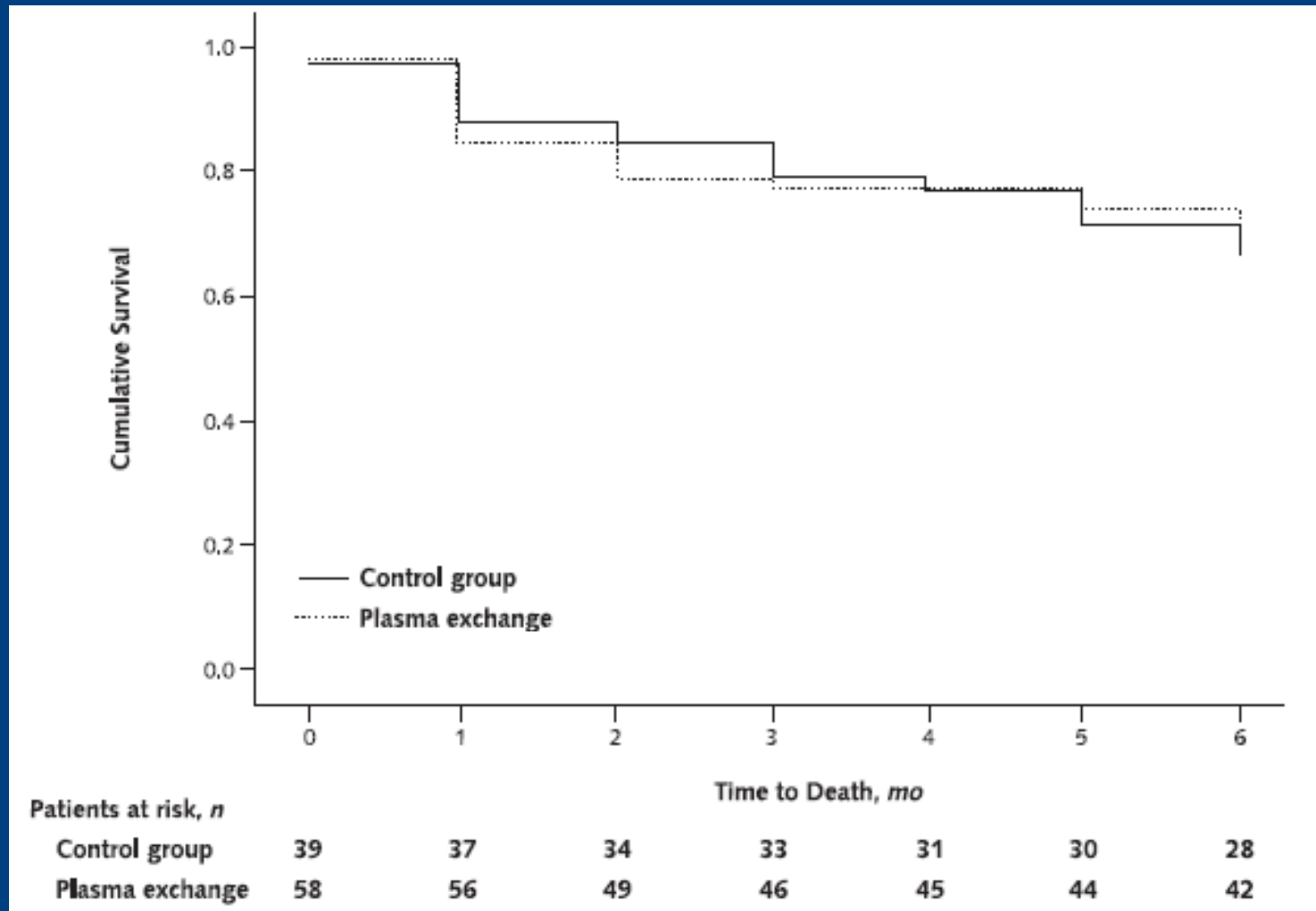
# Results: Renal Function

	Control	Pheresis	P
Number of patients	39	58	
Patients requiring dialysis (%)	14 (36%)	15 (26%)	NS
Patients interrupting dialysis (%)	7 (50%)	10 (66%)	NS
Final MDRD GFR (mean $\pm$ SD)	44.5 $\pm$ 28.2	46.8 $\pm$ 24.1	NS

*Adapted from Clark WF et al. Ann. Intern. Med. 2005, 143:777-784*

# Clark et al. (4)

## Results: Patient Survival



*Adapted from Clark WF et al. Ann. Intern. Med. 2005, 143:777-784*

Clark et al. (5)  
**Summary**

Plasmapheresis does not provide any significant improvement in:

- x Renal outcome
- x Patient Survival

Limitations:

- x No biopsy results
- x No light chain levels measurement
- x High recovery from dialysis dependence
- x Limited power

## Conclusions from RCTs

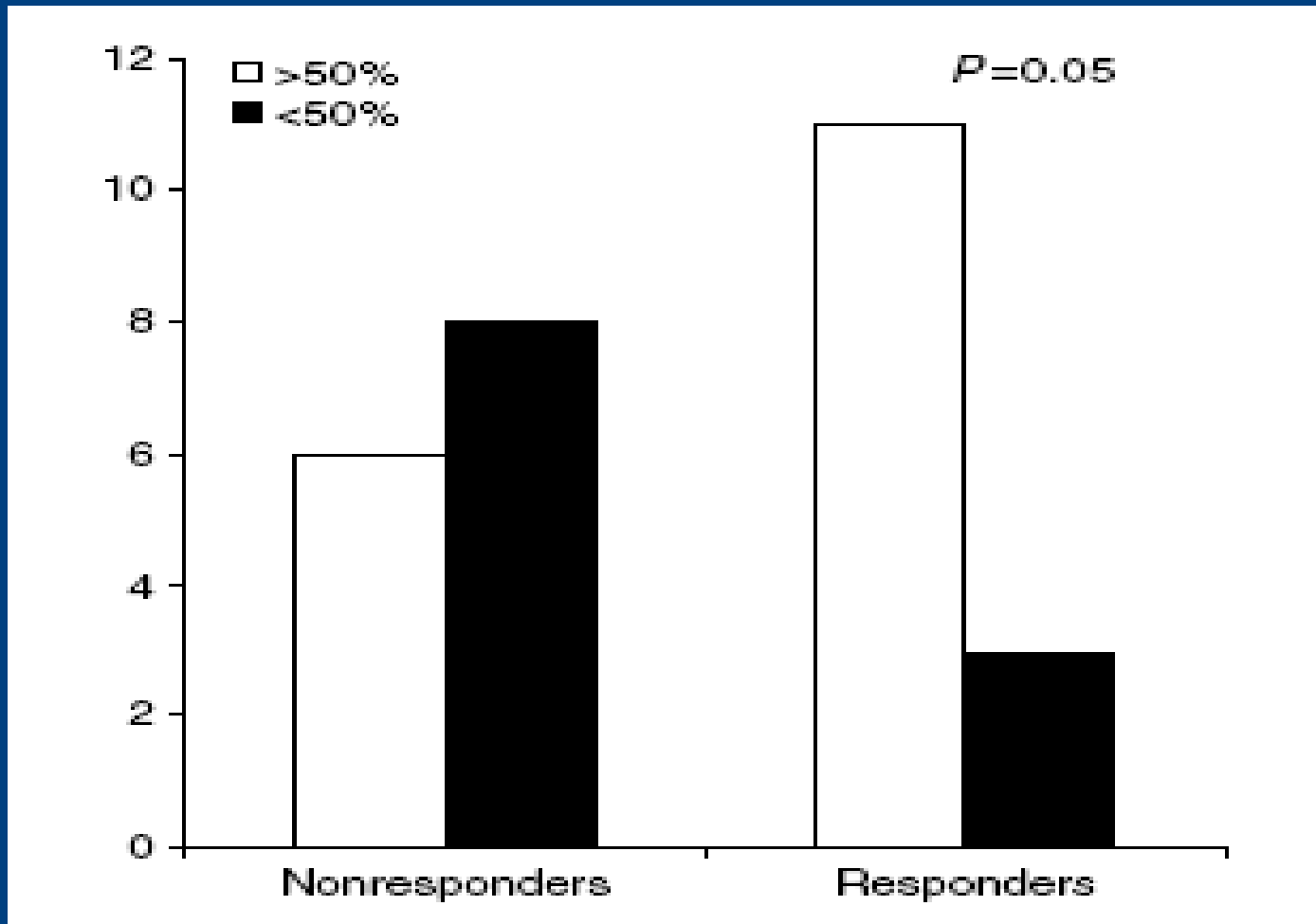
- x 2 small trials with opposite results  
(Zucchelli et al. - Johnson et al. )
- x One larger negative trial (Clark et al.)
- x On-going controversy...



## Recent observational studies

- x Leung et al. (*Kidney Int*, 2008)
- x Retrospective analysis of 40 cases
- x 75% renal recovery rate in patients with free light chain reduction > 50%

# Renal recovery associated with early reductions in serum FLCs



*Leung et al, Kidney Int, 73: 1282-1288, 2008*

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- x **Treatment recommendations**

# On-going trials (1)

MERIT (MyEloma Renal Impairment Trial)

Leukemia Research Fund and Cancer Research UK

- x Target N = 280 patients over 5 years (start date 2004)
- x Dexamethasone followed by VAD (4 cycles)  
+/- plasmapheresis (7 in 14 days)
- x Primary endpoint: proportion of patients alive and dialysis independent at 100 days

## On-going trials (2)

**EuLITE** (European trial of free Light chain removal by exTended hemodialysis in cast nephropathy)

UK Clinical Research Network

- x Intervention: extended hemodialysis with high cut-off (HCO) membrane
- x Aim: establish evidence base for FLC removal with HCO hemodialysis in patients with cast nephropathy

# HCO hemodialysis: an alternative strategy for removal of FLC

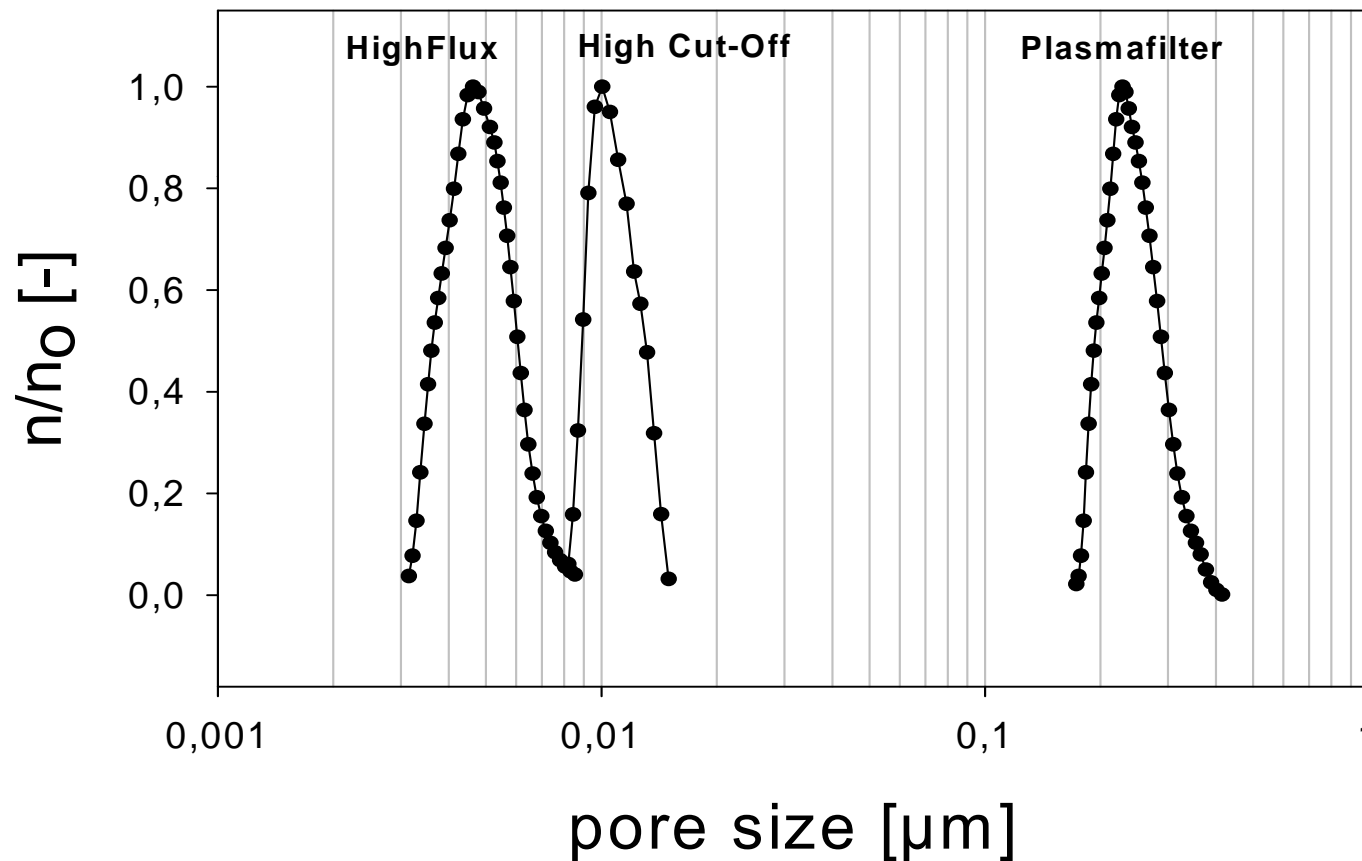
- x Hemodialysis with high cut-off (HCO) membranes
- x HCO membranes with moderately increased pore sizes compared to conventional dialysis membranes provide significant clearances of FLC
- x HCO membranes may provide a more favorable balance between FLC removal and loss of albumin and coagulation factors than plasmapheresis

# HCO hemodialysis: an alternative strategy for removal of FLC



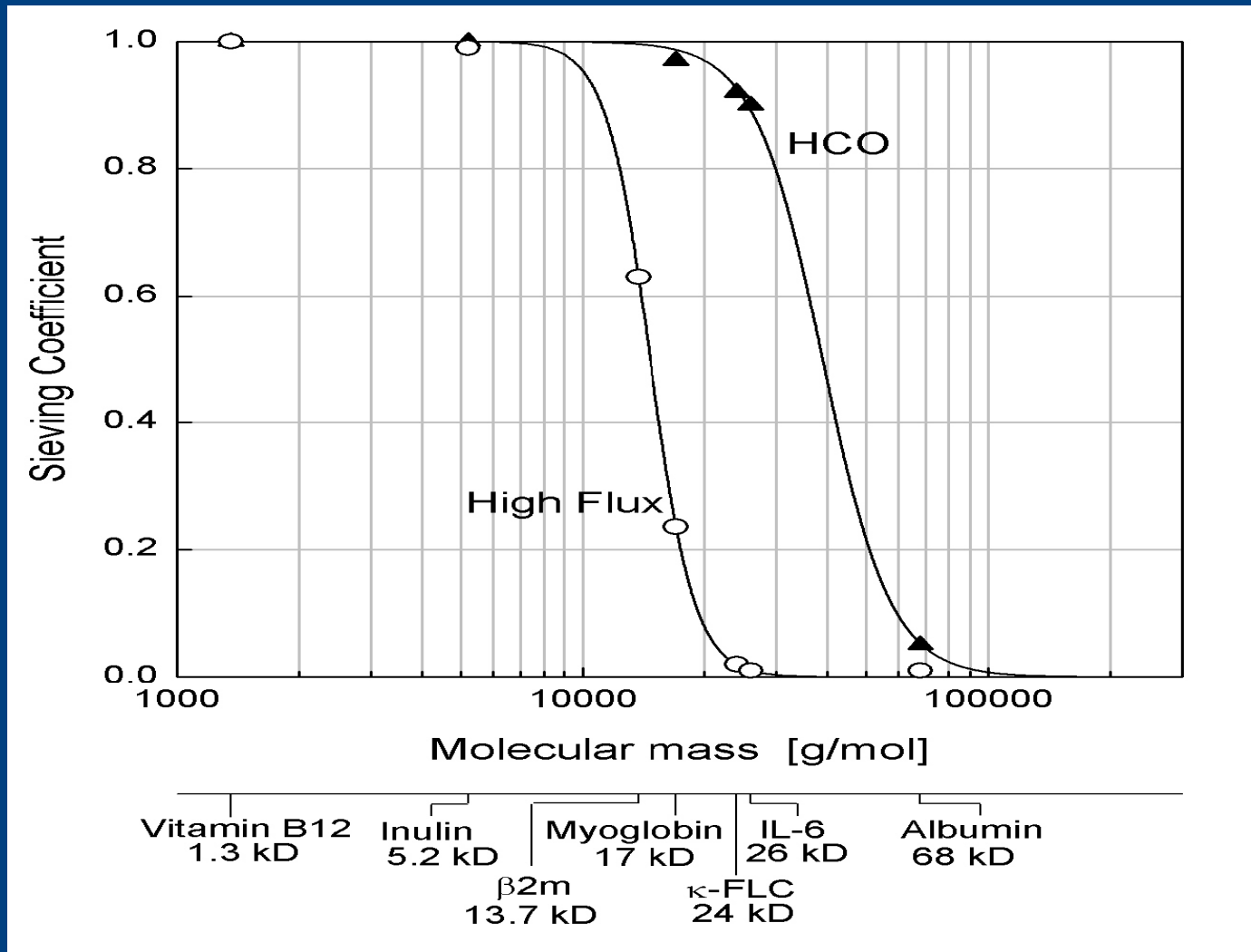
HCO membrane (Gambro HCO 1100 )

# Pore sizes of HCO membranes

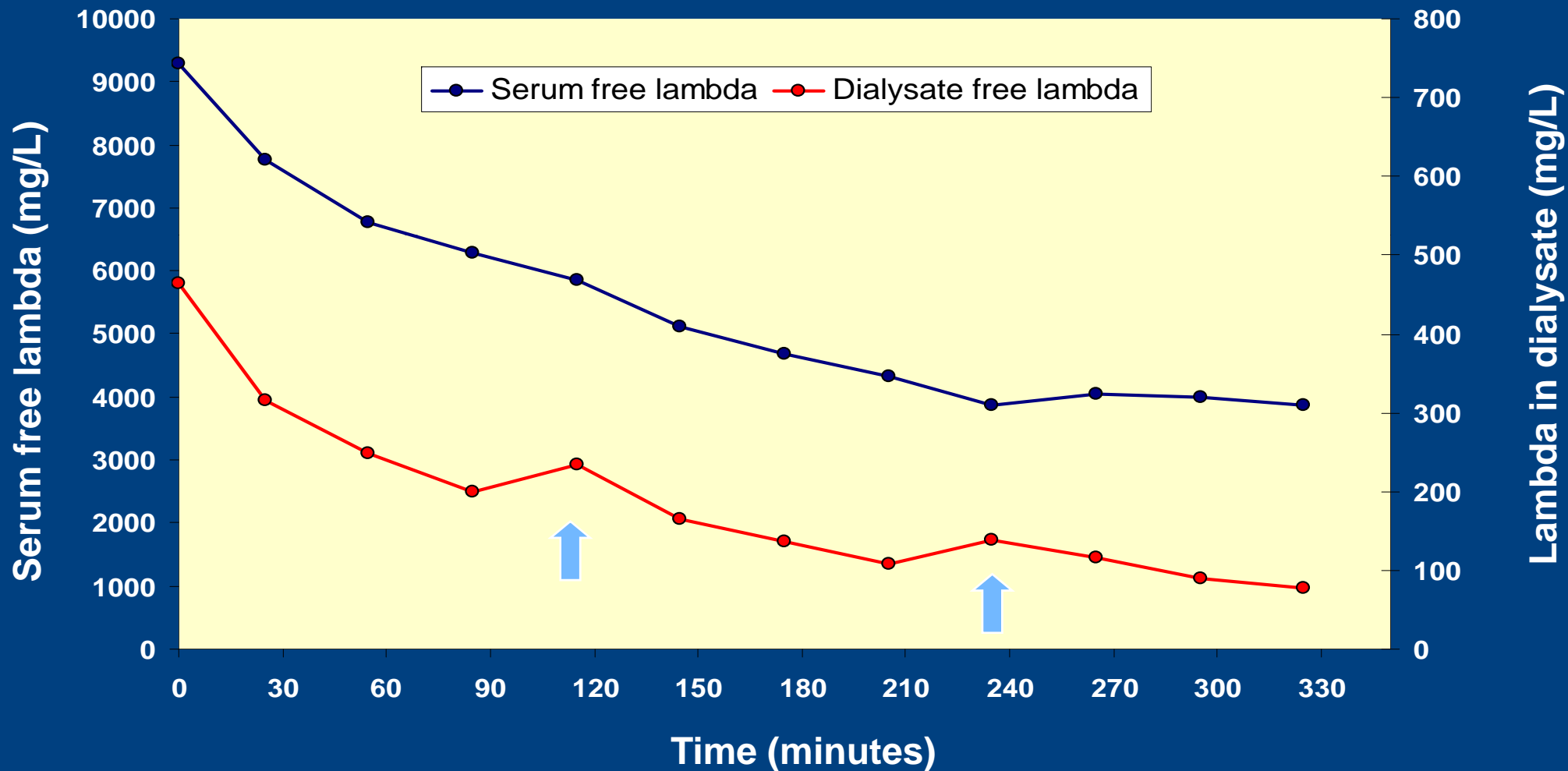




# HCO membranes: permeability

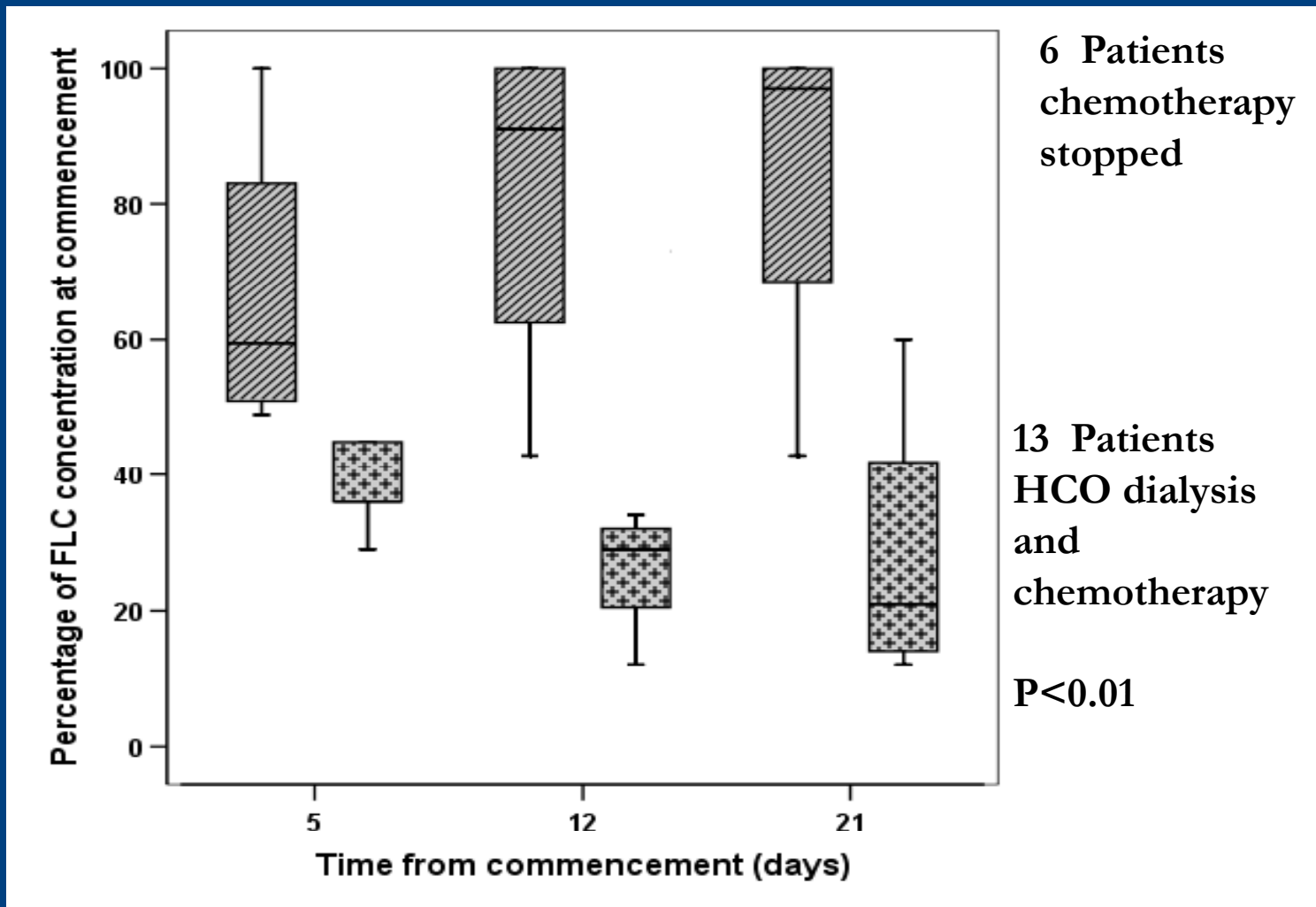


# FLC clearance during HCO hemodialysis



*Hutchison, CA et al. CJASN 18:886-895, 2007*

# HCO hemodialysis: preliminary results



*Hutchison, CA et al. CJASN 4:745-754, 2009*

# On-going trials

**EuLITE** (**E**uropean trial of free **L**ight chain removal by **exTE**nded hemodialysis in cast nephropathy)

- x N = 90 patients sought
- x Bortezomib, Adriamycin, Dexamethasone
- x Standard high-flux HD versus HCO hemodialysis
- x Primary endpoint: independence of dialysis at 3 months

# Conclusions / Recommendations (1)

- x The benefits of plasmapheresis remain to be clearly demonstrated
- x Plasmapheresis can reduce exposure to nephrotoxic proteins
- x Plasmapheresis alone does not provide lasting response in the absence of effective chemotherapy

## Conclusions / Recommendations (2)

- x Some patients may benefit from a more rapid reduction in FLC levels with plasmapheresis
- x The results of future trials will hopefully provide more definitive answers
- x HCO hemodialysis: an interesting alternative to plasmapheresis?

