

# online-HDF

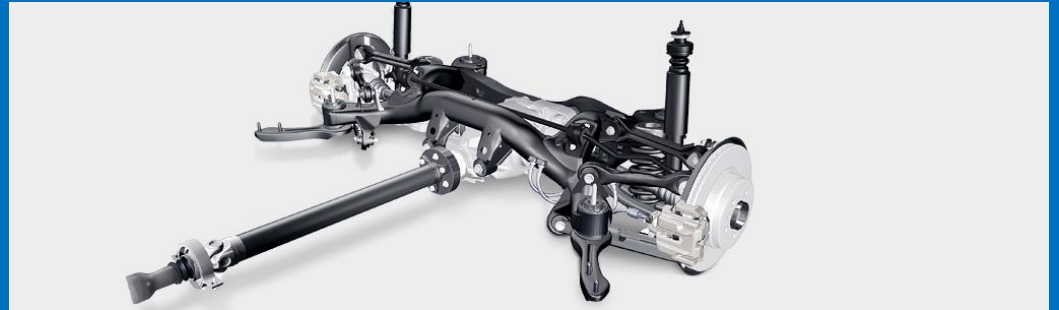
the superior quality of treatment

Thomas Ryzlewicz



axle of the cart of Ben Hur

... comparable to High-Flux HD



multi-link rear suspension of BMW

... comparable to online-HDF



**"Stanley Shaldon . . . a man with the unusual ability to be proven right in the long run in almost everything he says"**

**editorial NEPHRON 1981 27:1**

# High-Flux HD?

**HEMO study**  
5000 pat.

**MPO study**  
5000 pat.

Low-Flux : High-Flux



***NO better survival for High-Flux(!)***

# online-Therapy

- 1982 S. Shaldon: Interleukin-1-Hypothesis
- 1983 S. Shaldon: on-line-Hämofiltration as (Prototyp): two-step procedure, 20 Ultra-Filters(!)
- 6/1993 first on-line-Monitor of today in Germany (in reality: in-line)

# 3 advantages of online-HDF

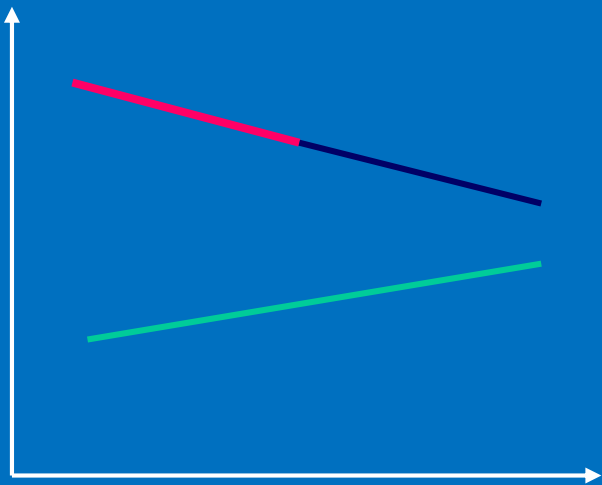
1. sterile Dialysis Fluid

2. additional secondary big Clearance

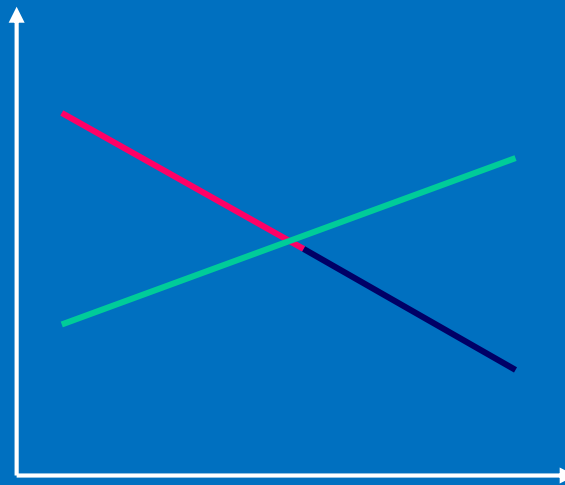
3. additional elimination of big molecules ( $\beta_2$ M, up to 40 kD)



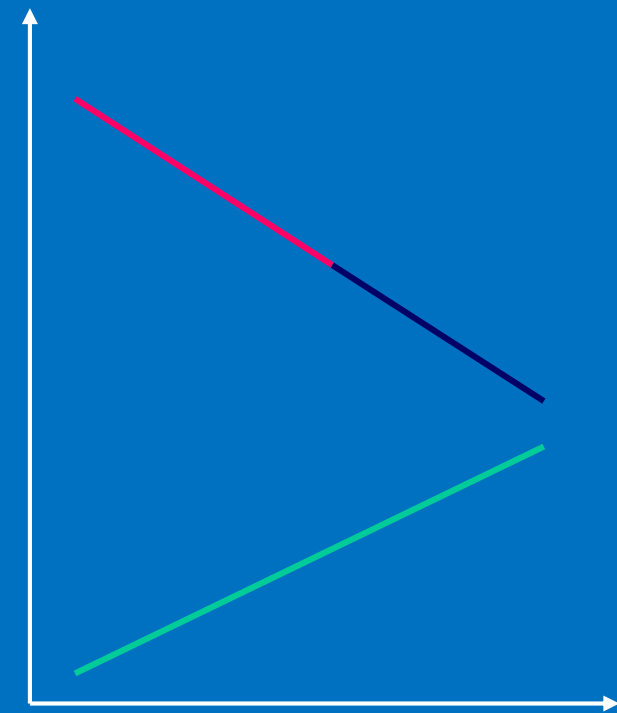
pressures in the Dialyzer



Low-flux-HD



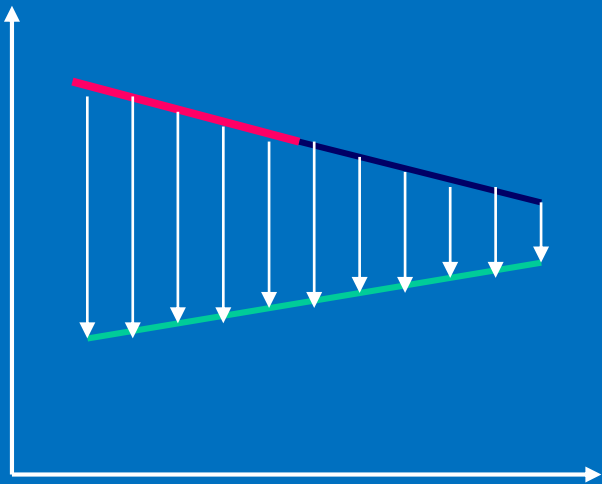
High-flux-HD



online-HDF



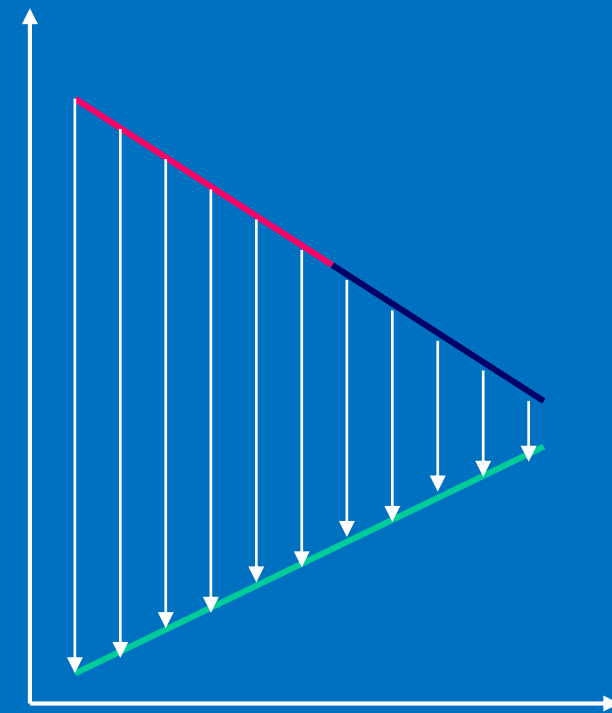
## pressures in the Dialyzer



Low-flux-HD

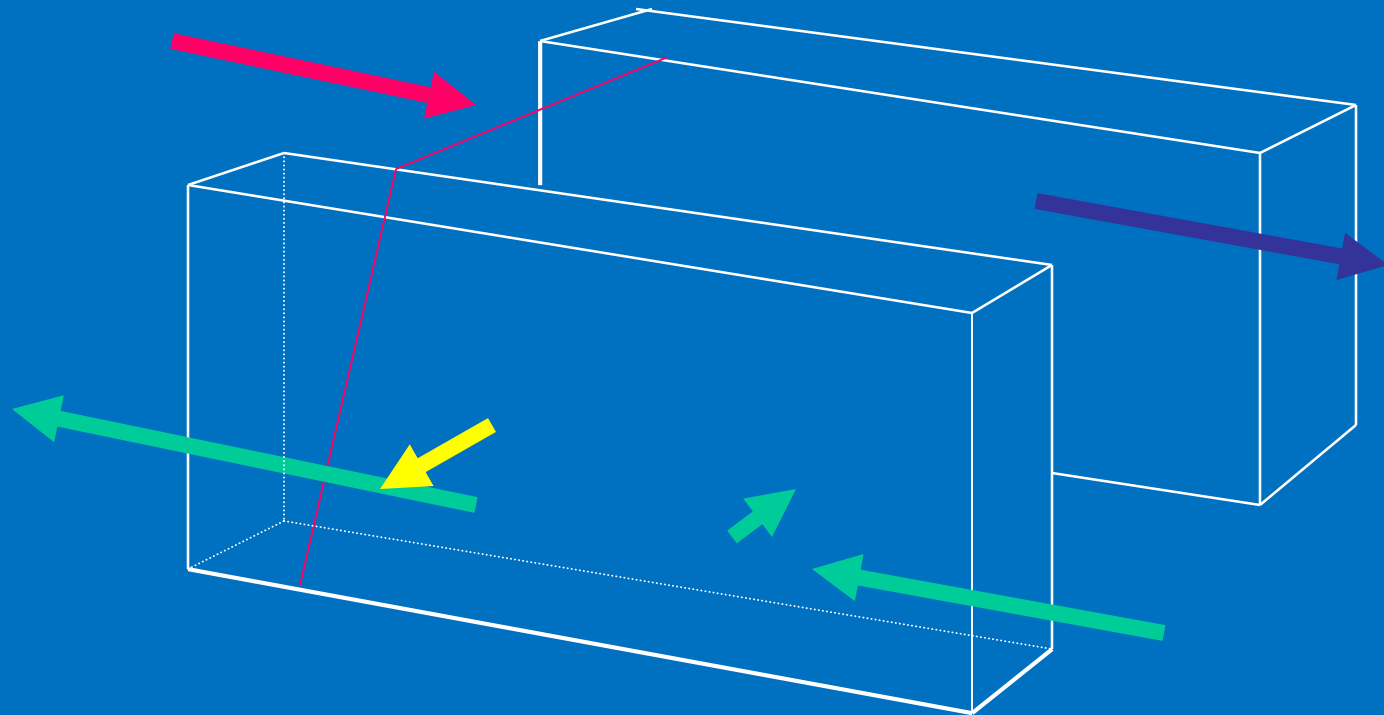


High-flux-HD

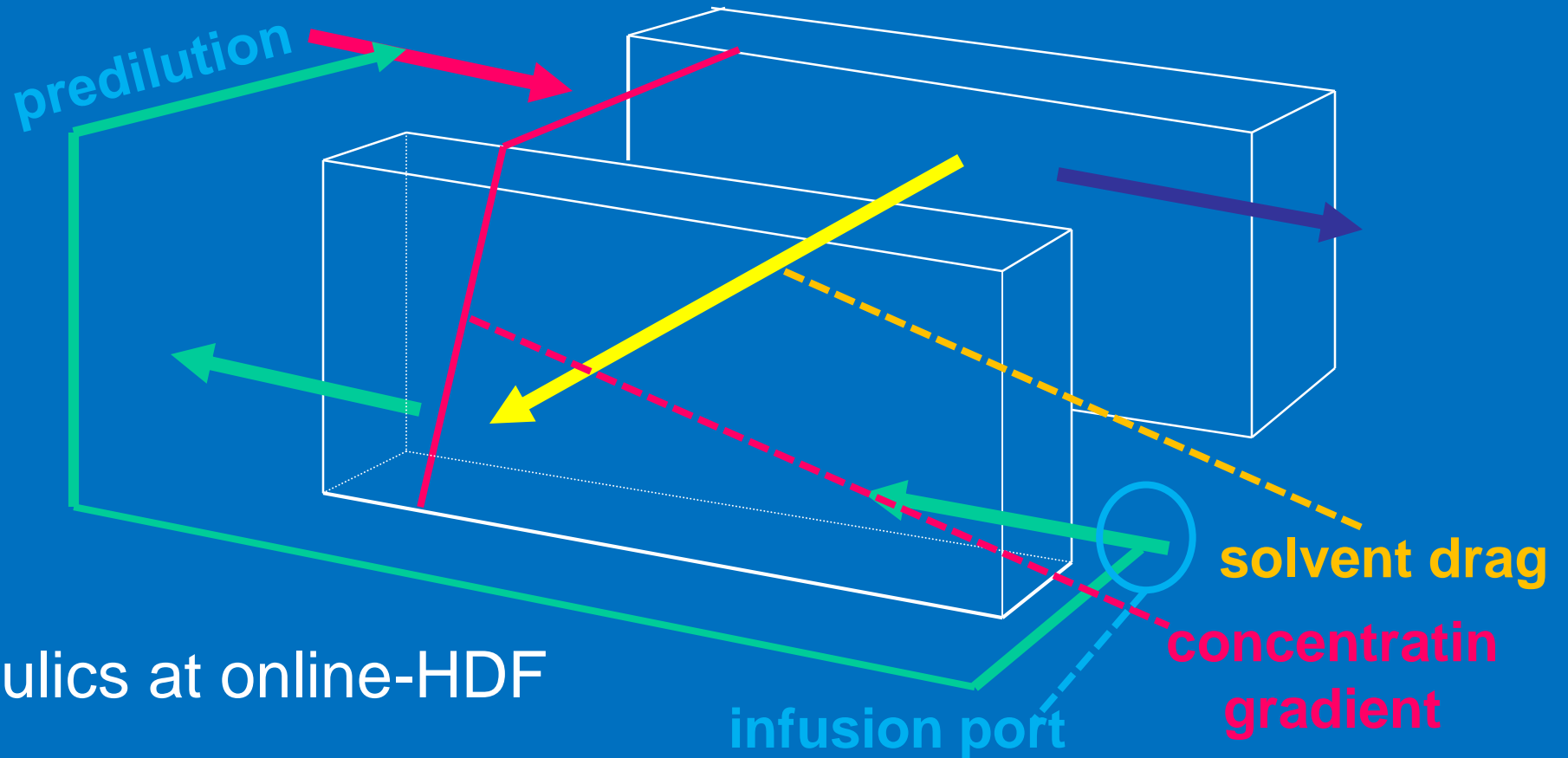


online-HDF





hydraulics at Highflux-HD



hydraulics at online-HDF

online-Therapy is the production of  
Infusion Fluid!

CFU's in the Dialysis Fluid:

how much is *little*?

# online-Therapy is the production of Infusion Fluid!

European

Pharmacopoeia 2005  
did not know online-  
production of Infusion  
Fluid(!)

Infusion Fluid must be  
sterile

ISO-Norm 11663-2014  
quality of Dialysis Fluid  
and related Therapies  
(sterile and free of  
pyrogen (=>EU<0,03/ml))

SAL > 6 (sterility assurance level)  
corresponds

$10^{-8}$  CFU reduc./ml

3 Filtre (ultra)  $10^{-11}$ /ml

# online-Therapy is the production of Infusion Fluid!

according to I. Ledebor

ISO-Norm 11663-2014



Softener &  
Reverse-  
Osmosis

Conzentrats

Ultrafiltration

Ultrafiltration

bakteriolog. Qualität

CFU/ml

$< 10^{-2}$

$< 10^2$

$< 10^{-3}$

SAL\* > 6

EU/ml

< 0,25

< 0,50

< 0,03

< 0,03

Use in the  
Dialysis

Basics for every  
Dialysis Fluid

Lowflux  
synthetic

Highflux-HD &  
Low.-Vol.-HDF

online-HDF/HF  
Infusion Fluid

SAL\* = sterility assurance level

# online-Therapy is the production of Infusion Fluid!

the Ultra concept:

one step Ultrafiltration      CFU reduction of  $10^{-5}$       SAL 3

two step Ultrafiltration      CFU reduction of  $10^{-8}$       SAL 6

three step Ultrafiltration      CFU reduction of  $10^{-11}$       SAL 9

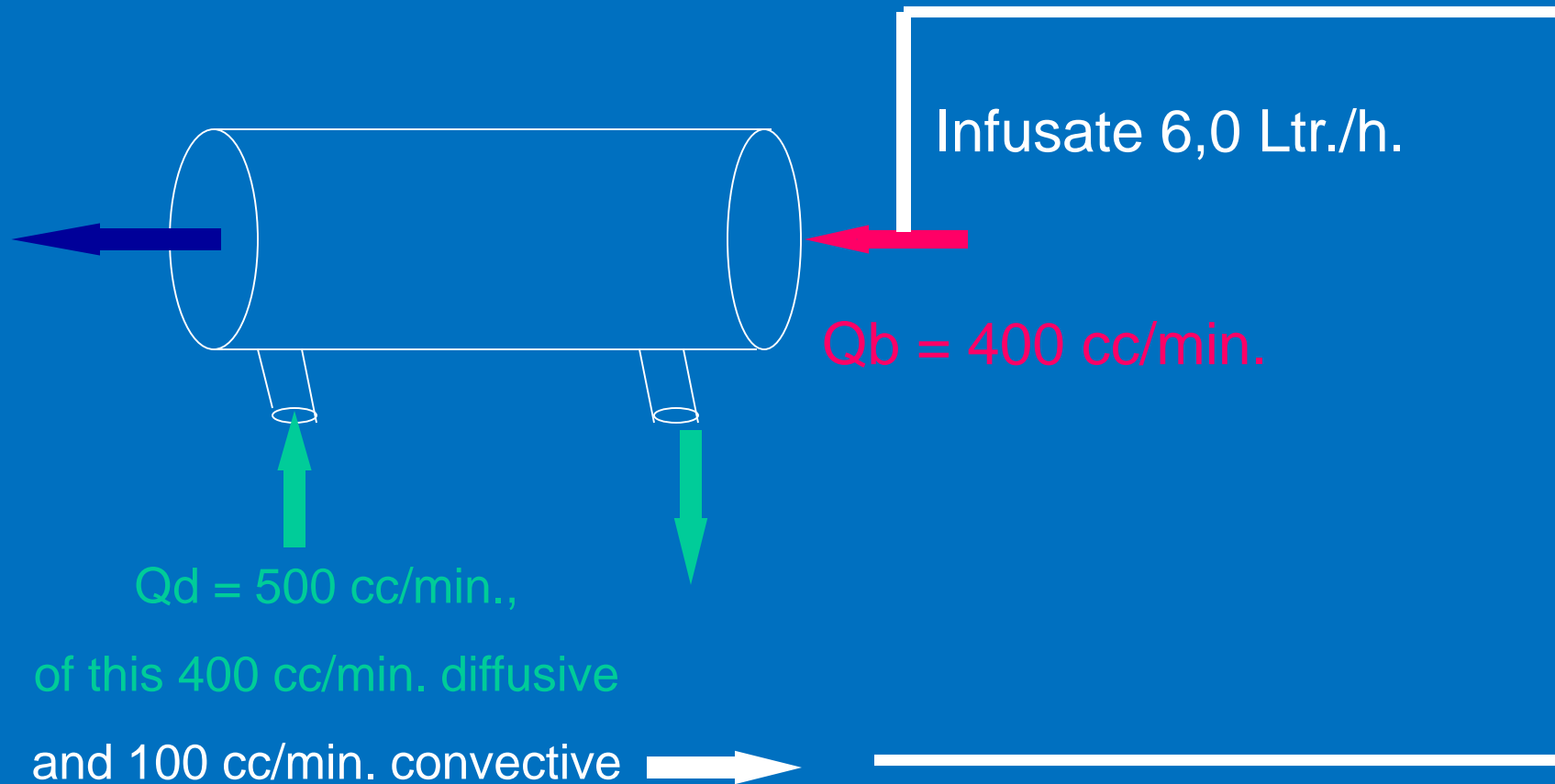
(with U-2000-Filter)

# online-Therapy is the production of Infusion Fluid!

## therefore:

1. Disinfektion with Peracetic Acid (Dialox)
2. Monitor should not used for online-Therapy, if there was no qualified Disinfection
3. Test for chemical residue must be done
4. Bacteriology from the Infusion-Port before the exchange of the Ultrafilters (U 8000 S) every 8 weeks

# how does a HDF-Regime look like?





# HDF-Regime in numbers

- largest Highflux
- high Blood Flow (preferably 15 G cannulas)
- operation in Volume mode / Predilution
- Filtration 6,0 Ltr./h., this means 27 Ltr. in 4:30 h

# HDF: Predilution or Postdilution?



# HDF: Predilution oder Postdilution?



- disadvantage:  
reduction of the  
concentration gradient



- disadvantage:  
lengthening of the way  
of Diffusion by the  
packed RBC's
- disadvantage:  
development of a clear  
secondary membrane

# online-Hemofiltration

(I. Ledebø 1993)

## Predilution

$Q_b = 400$  cc/min.  
tubule 15 G

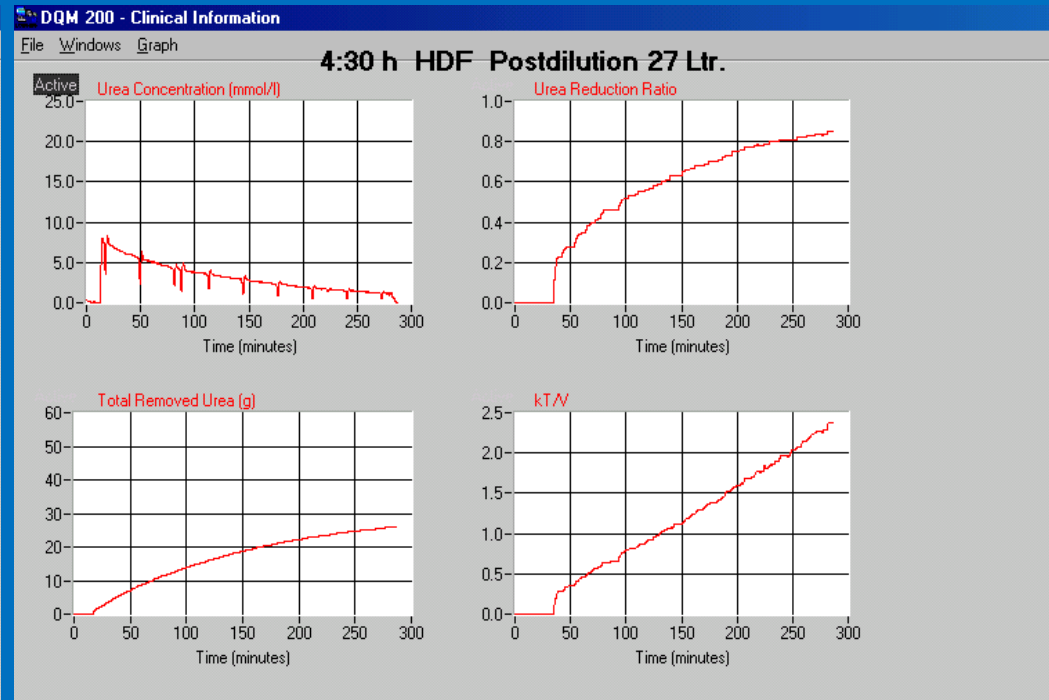
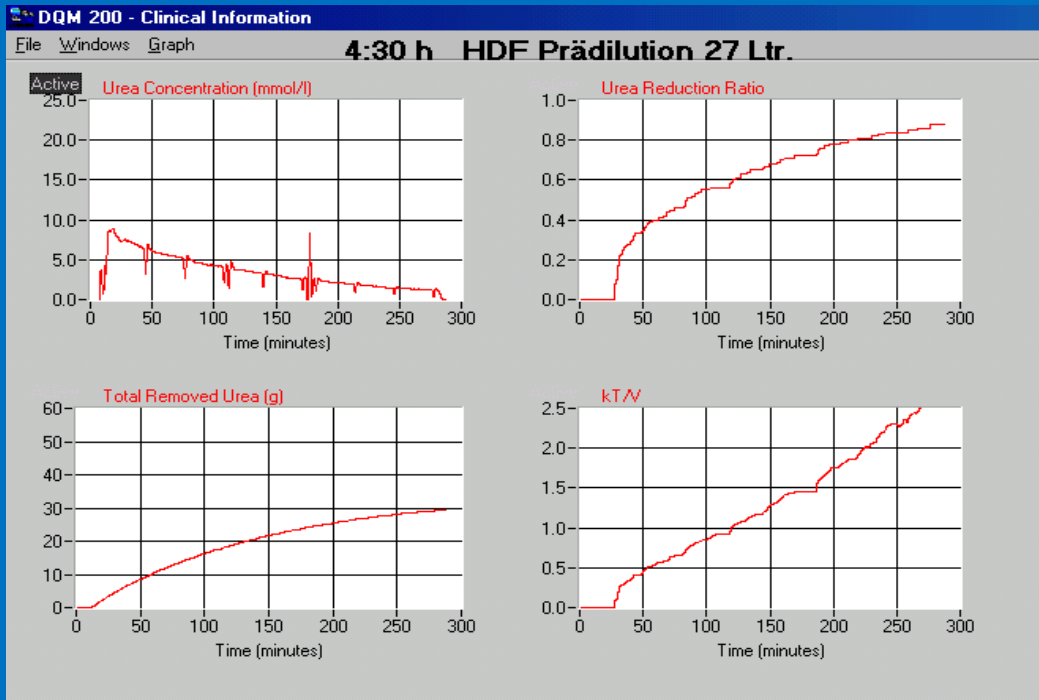
HF 1967 Lee Henderson  
as Predilution

## Postdilution

$Q_b = 700$  cc/min.  
tubule 14 G

shifted to Postdilution  
because of costs  
**but in online-therapy costs  
are not the problem!**

# Predilution or Postdilution?



4:30 h Predilution 27 Ltr.

4:30 h Postdilution 27 Ltr.

9 years treatment time, body weight both ~ 55 kg  
reached 40 years RRT after 31 years RRT

## online-HDF Studies

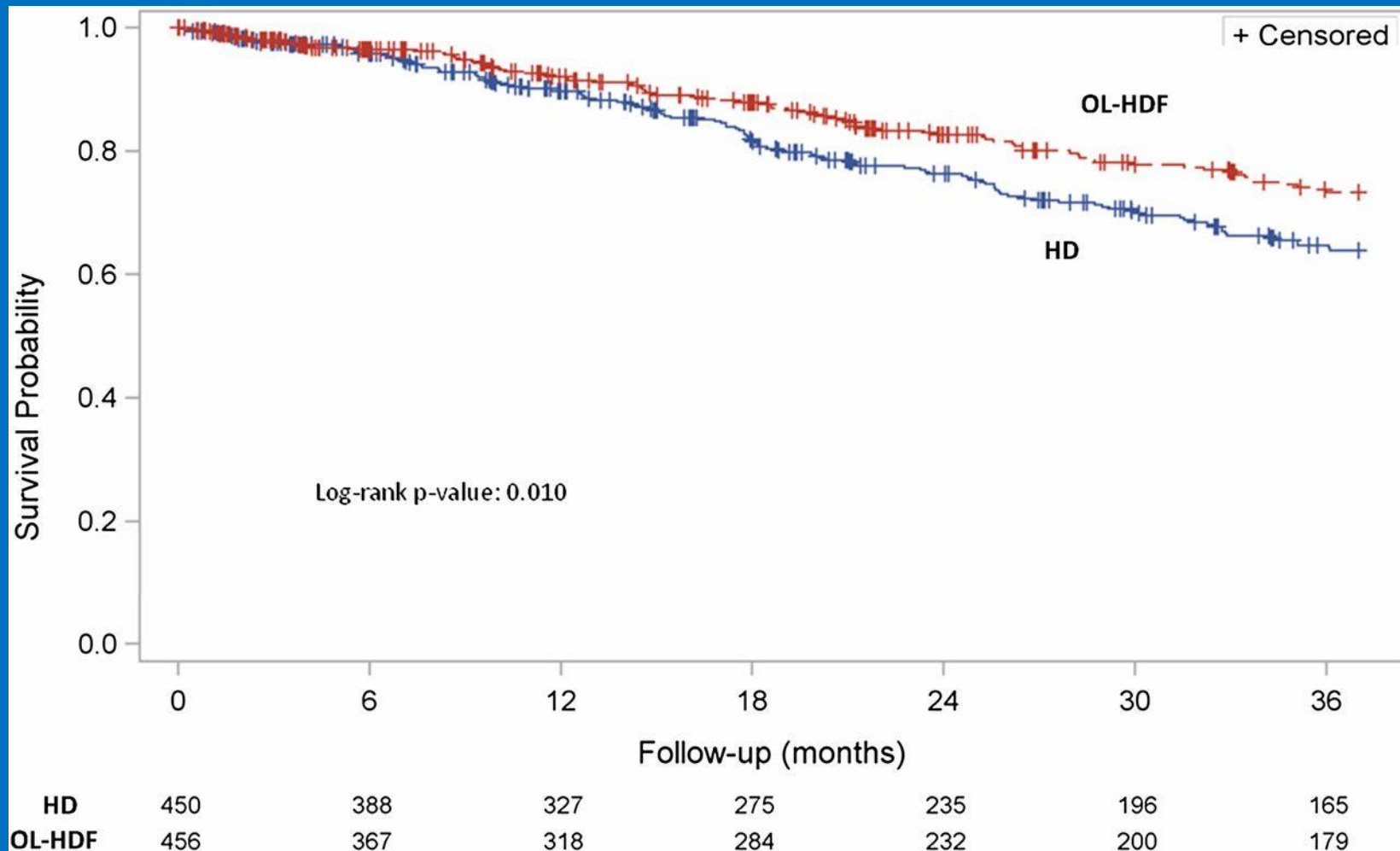
B. Canaud 2004 retrospective  
indication for longer survival

CONTRAST 2012 prospective  
no longer survival

F. Maduell 2012 prospective  
proven longer survival

E. Ok 2013 prospective  
no longer survival

Kaplan–Meier curves for 36-month survival in the intention-to-treat population (P=0.01 by the log-rank test).



Francisco Maduell et al. JASN doi:10.1681/ASN.2012080875



## how many liters of exchange?

Turkish

Ok 17 l

Postdilution

**Volume Mode**

**no better survival**

CONTRAST

Blankestijn 19,8 l

Postdilution

Autoprocessing

**no better survival**

ESHOL

Maduell 20,8 – 21,8 l

Postdilution

Autoprocessing

proven longer survival



# Problems of these 3 studies

## all the three:

**treatment time  
too short**

**blood flow  
too low**

Advantages of Predilution  
not used (> higher  
convective exchange with  
lower requirement of  
blood flow(!))

## additional Ok study:

**Postdilution  
without  
Autoprocessing**

# Difficulties & Problems of online-Therapy

## **Postdilution**

the wrong decision of the Industry, escape: **Autoprocessing**

## **2-step Ultrafiltration**

done *later on*, ISO Norm 11663(!), CFU controlling!

## **Disinfection**

the Disinfection: the concept should not be weakened by the mode of Disinfection!

# Improvement for online-HDF?

## Qualified Therapy:

2 m<sup>2</sup> High-Flux

Postdilution 6 ltr/h

(= 100 cc/min.)

**Autoprocessing**

(easy to handle with High-Tech-Monitor)

## Improved Therapy:

2 m<sup>2</sup> High-Flux

**Predilution 7,5 or**

**9,0 ltr/h (= 125 or**

**150 cc/min.)**

**Volume Mode**

**(Standard Monitor,  
*not-well-understood*)**

# Prime : Option

## High-Flux HD:

short treatment time  
no interests for Kt/V  
no interests for  
clean fluid  
re-use

## online-HDF:

intention for longer  
patient's survival  
realized efficacy  
also with longer  
treatment time  
clean fluid realized  
no re-use

# Points of discussion for the FDA?

*door-opening by Blankestijn?*

## 2-step Ultrafiltration

realizing ISO norm 11663-2014  
with bacteriologic sampling  
and an effective Disinfection(!)

documentation of processed  
Infusion and Kt/V

additional payment only, when  
quality parameters are fulfilled

**So the US Ministry of Health is kindly asked . . .**

**to make the FDA Dep. Med. Products working**

**or to renew the FDA-BOARD!**