THE HEMODIALYSIS PRESCRIPTION: TREATMENT ADEQUACY

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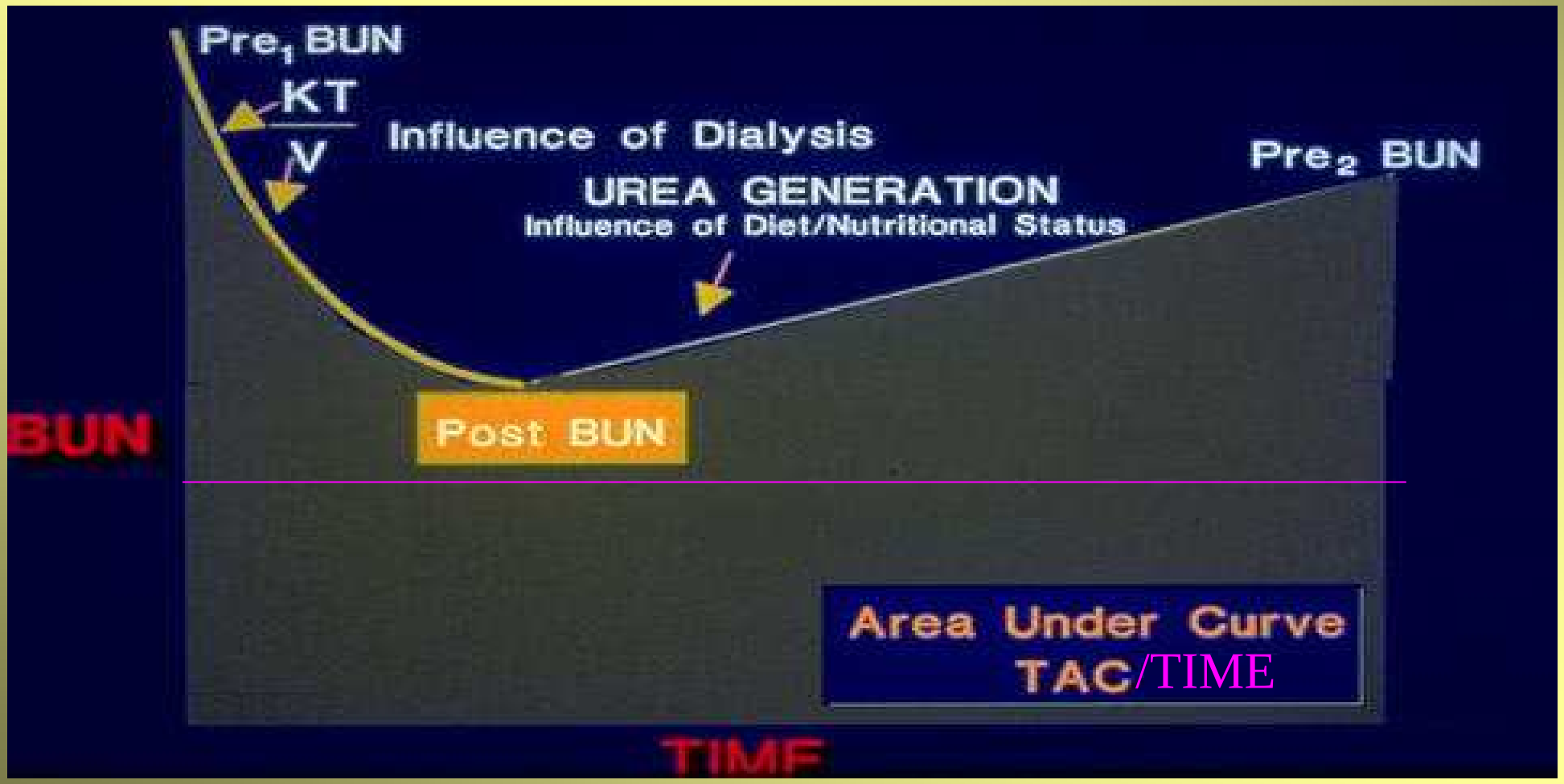
THE DIALYSIS CYCLE



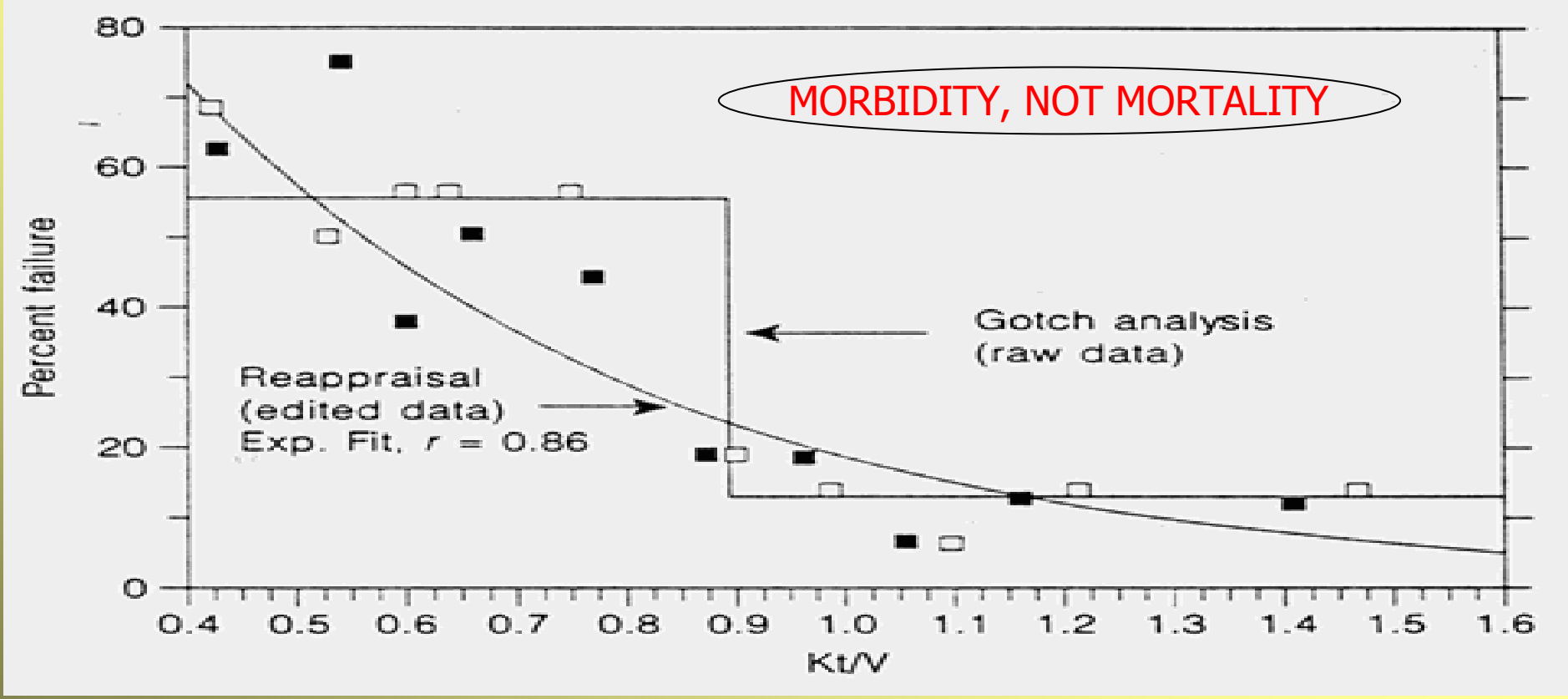
DESIGN OF THE NATIONAL COOPERATIVE DIALYSIS STUDY

TABLE 7 CONTROL ACHIEVED ACCORDING TO STUDY GROUP

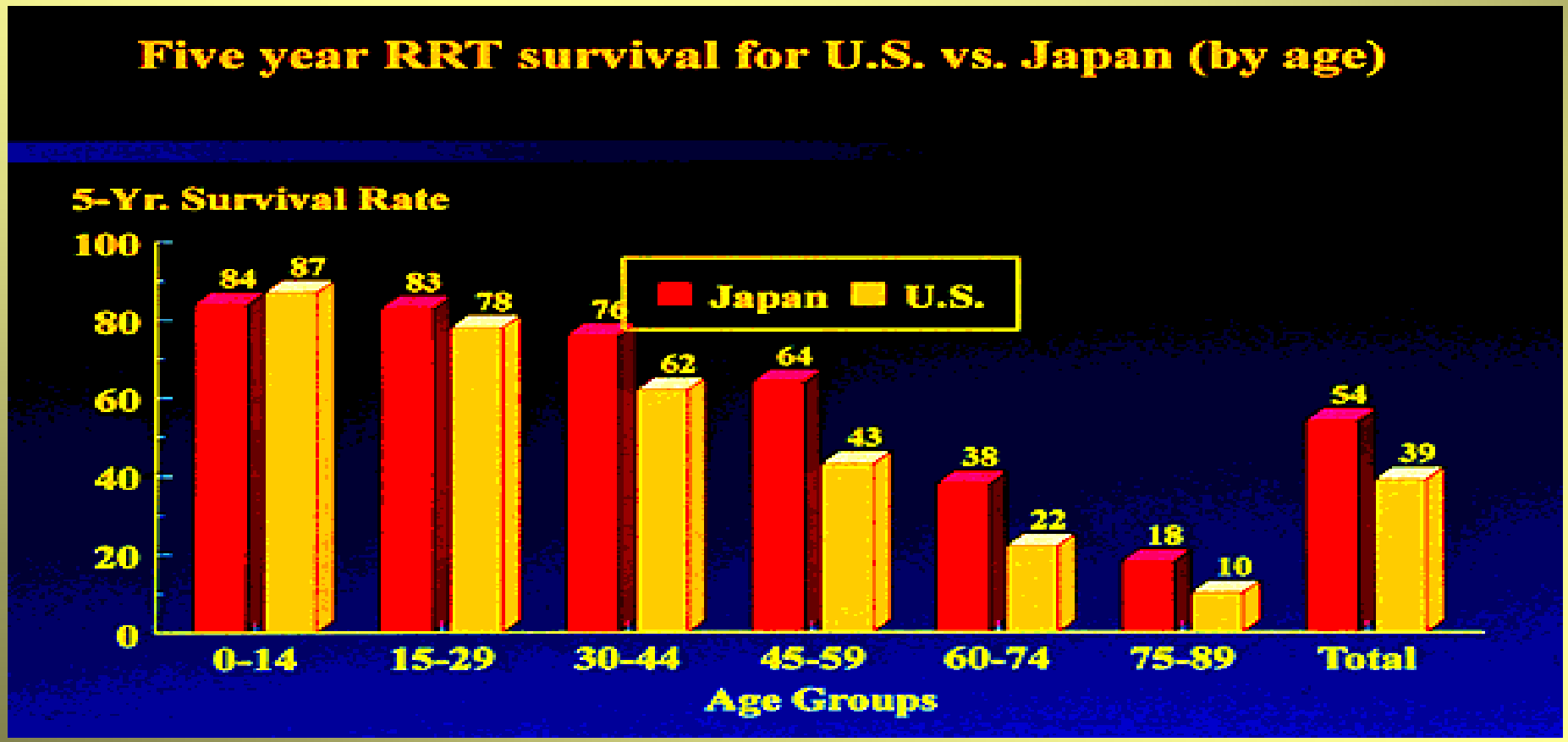
Group and Factor Analyzed	Duration of Dialysis (Hr:Min)	Midweek Predialysis BUN (mg/dl) Mean ± S.E.M.	Time-Averaged BUN (mg/dl) Mean ± S.E.M.
I	4:29 ± 0:03	71.2 ± 1.4	51.3 ± 1.1
II	4:31 ± 0:03	104.9 ± 1.7	87.7 ± 1.4
III	3:19 ± 0:03	73.1 ± 1.4	54.1 ± 1.1
IV	3:14 ± 0:03	109.1 ± 1.5	89.6 ± 1.2
TIME*	$P < 0.0001$	$P < 0.05$	$P < 0.05$
BUN*	$P > 0.1$	$P < 0.0001$	$P < 0.0001$
Interaction*	$P > 0.1$	$P > 0.1$	$P > 0.1$

* The probabilities indicate the significance of differences between means for the variable with respect to the experimental factor. *(Reproduced with permission from Lowrie EG, Laird NM, Parker TF, Sargent JA, The effect of the hemodialysis prescription on patient morbidity, N Engl J Med 1981; 305:1176–1181.)*

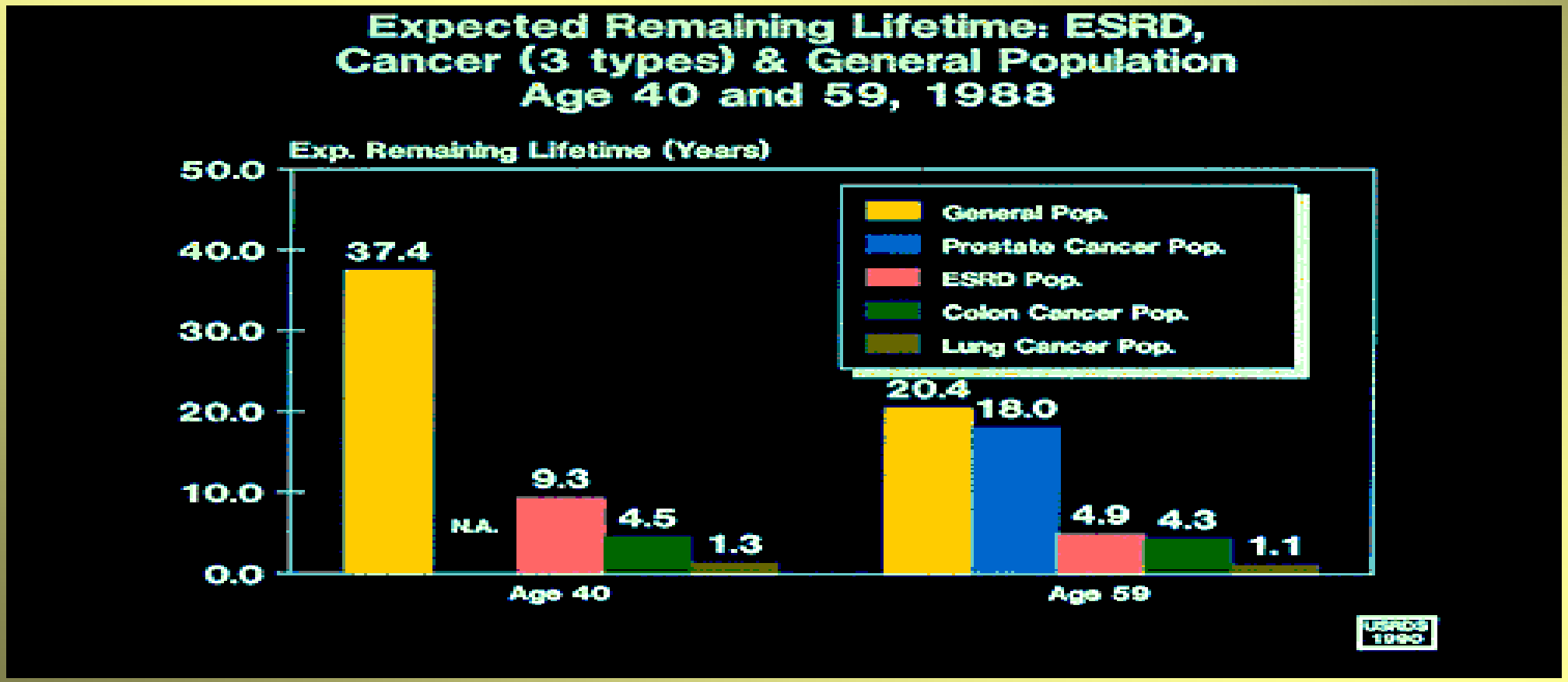
REVISED NCDS RESULTS EXPRESSED AS Kt/V



COMPARATIVE MORTALITY RATES



IMPLICATION OF US DIALYSIS MORTALITY RATE



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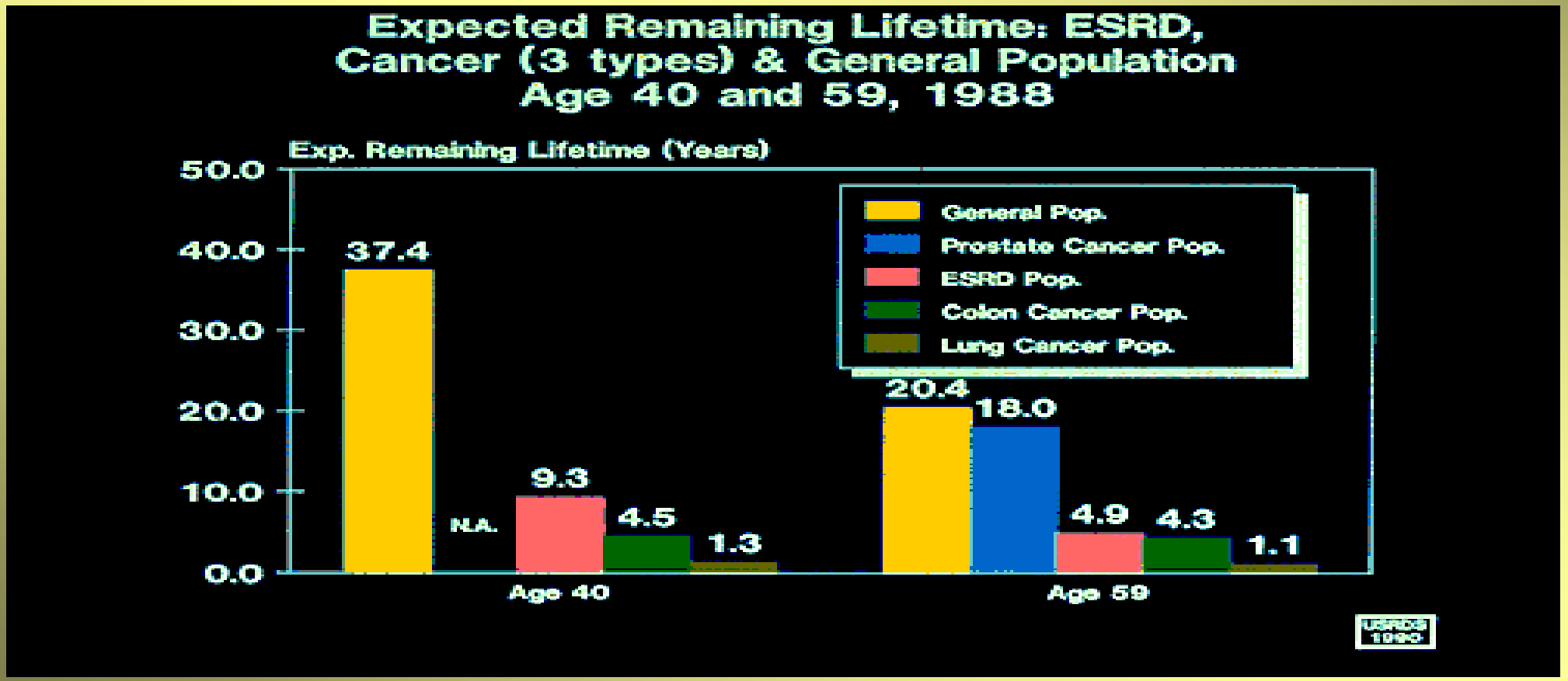


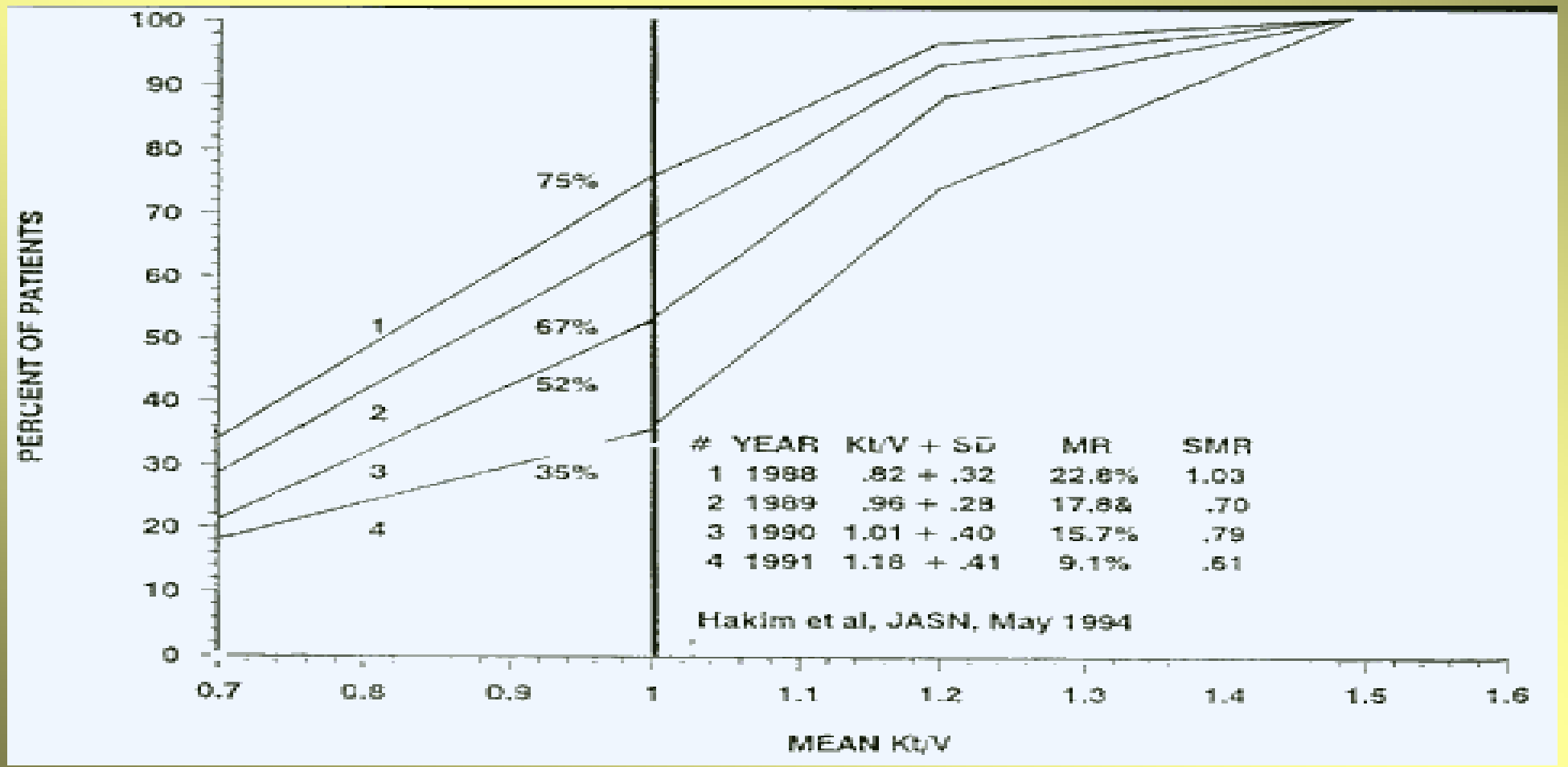
TASSIN EXPERIENCE

Table 6. Survival in a Dialysis Unit With Kt/V of 1.67

Initial Age (yr)	No. of Patients	Survival			
		5-Year	10-Year	15-Year	20-Year
<35	112	93%	88%	80%	71%
35-44	84	92%	81%	63%	39%
45-54	111	88%	76%	53%	—
55-64	98	83%	60%	21%	—
>64	40	69%	64%	—	—
All patients	445	87%	75%	55%	43%

Data from Laurent et al.[71]

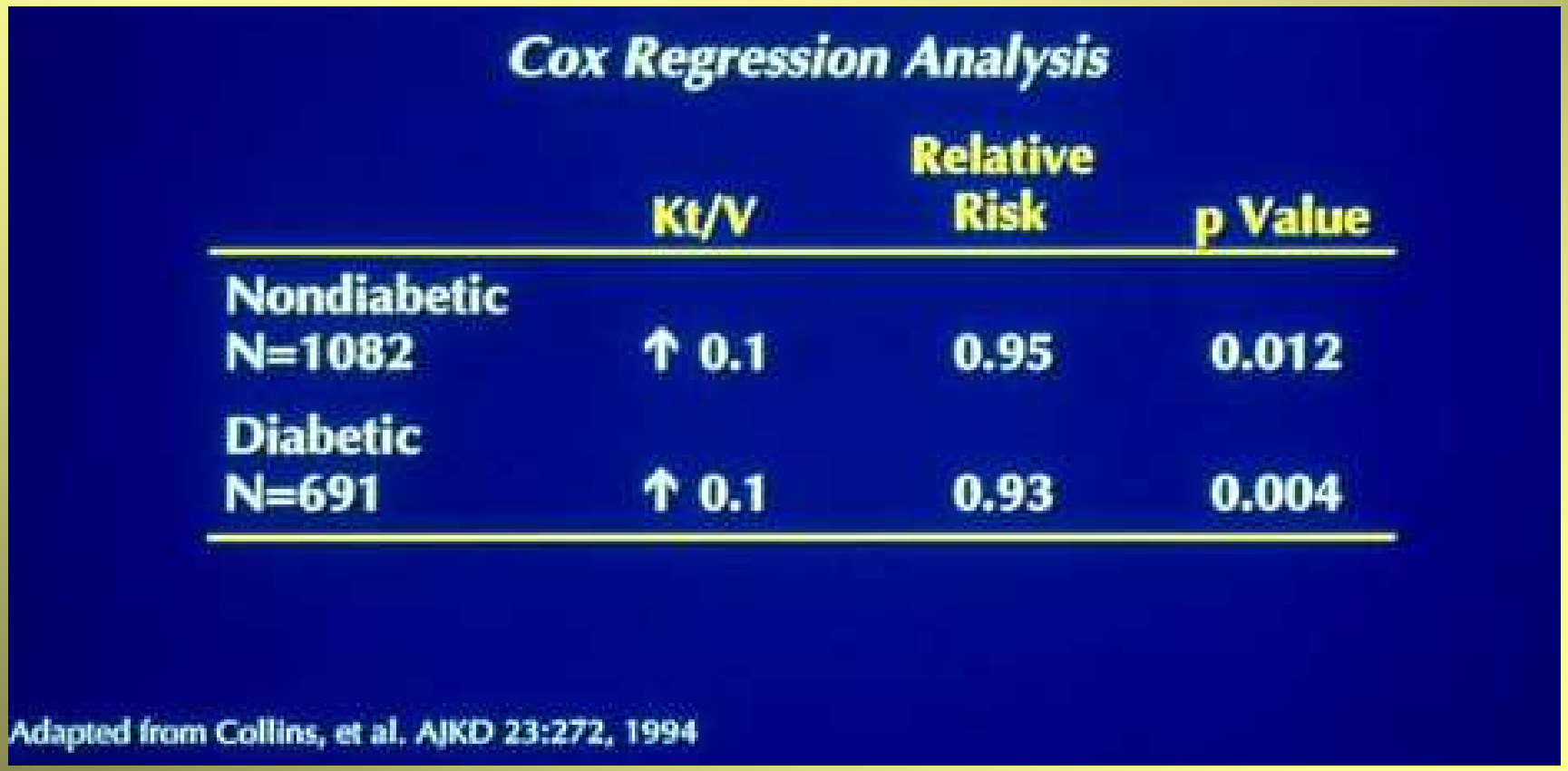
Kt/V AND MORTALITY



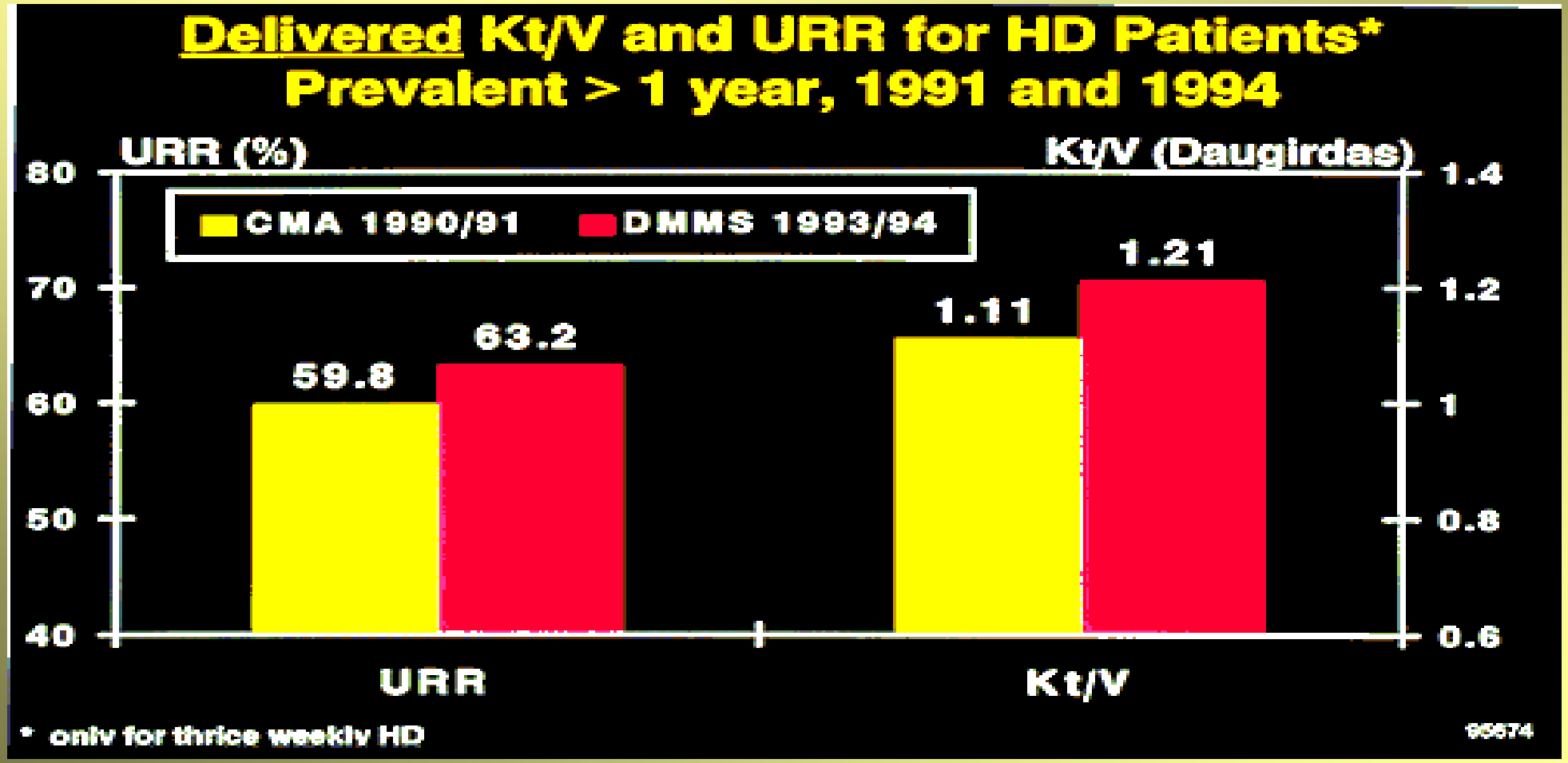
Kt/V & RISK OF MORTALITY

KT/V	RR	
	no DM	DM
	n = 1082	691
1.0 <1.2	1.00	1.00
1.2 < 1.4	0.64	0.70
≥ 1.4	0.67	0.60

Kt/V & MORTALITY: MINNESOTA EXPERIENCE



CHANGING TRENDS IN THERAPY



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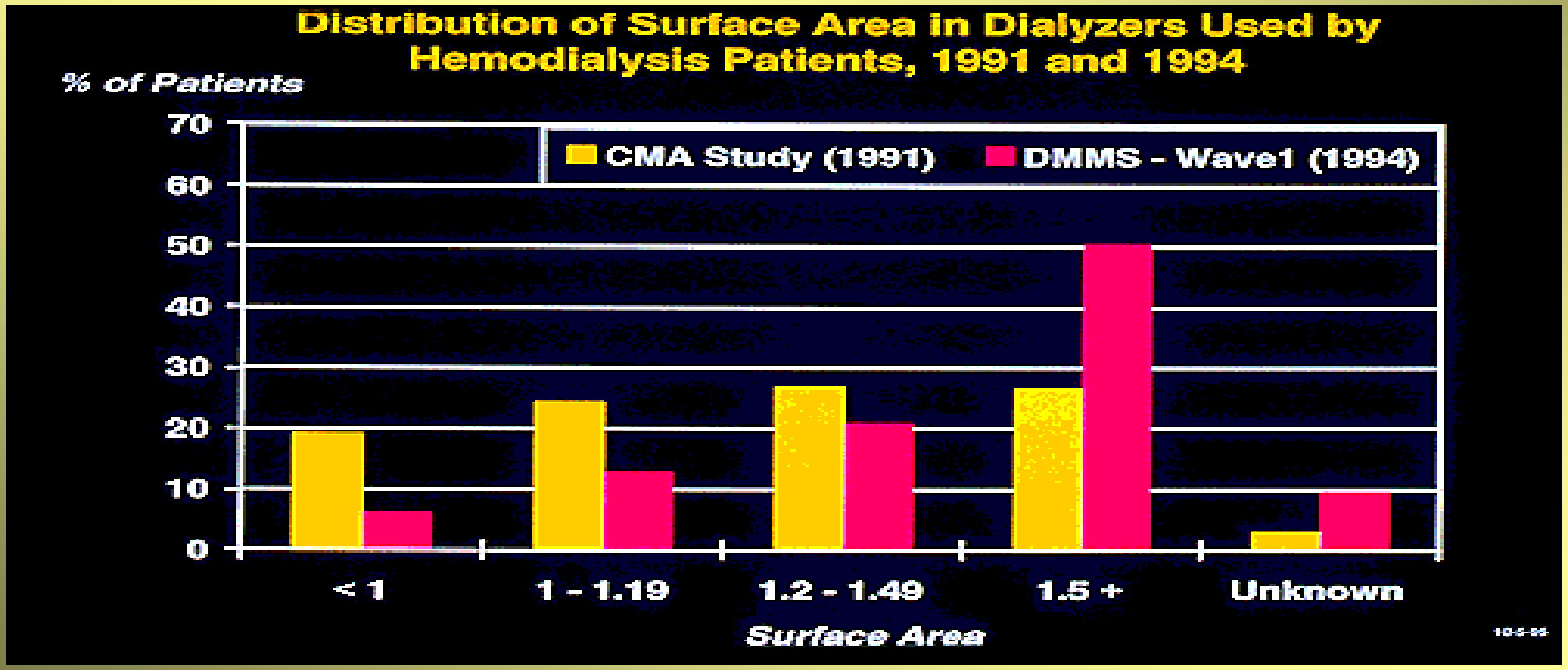

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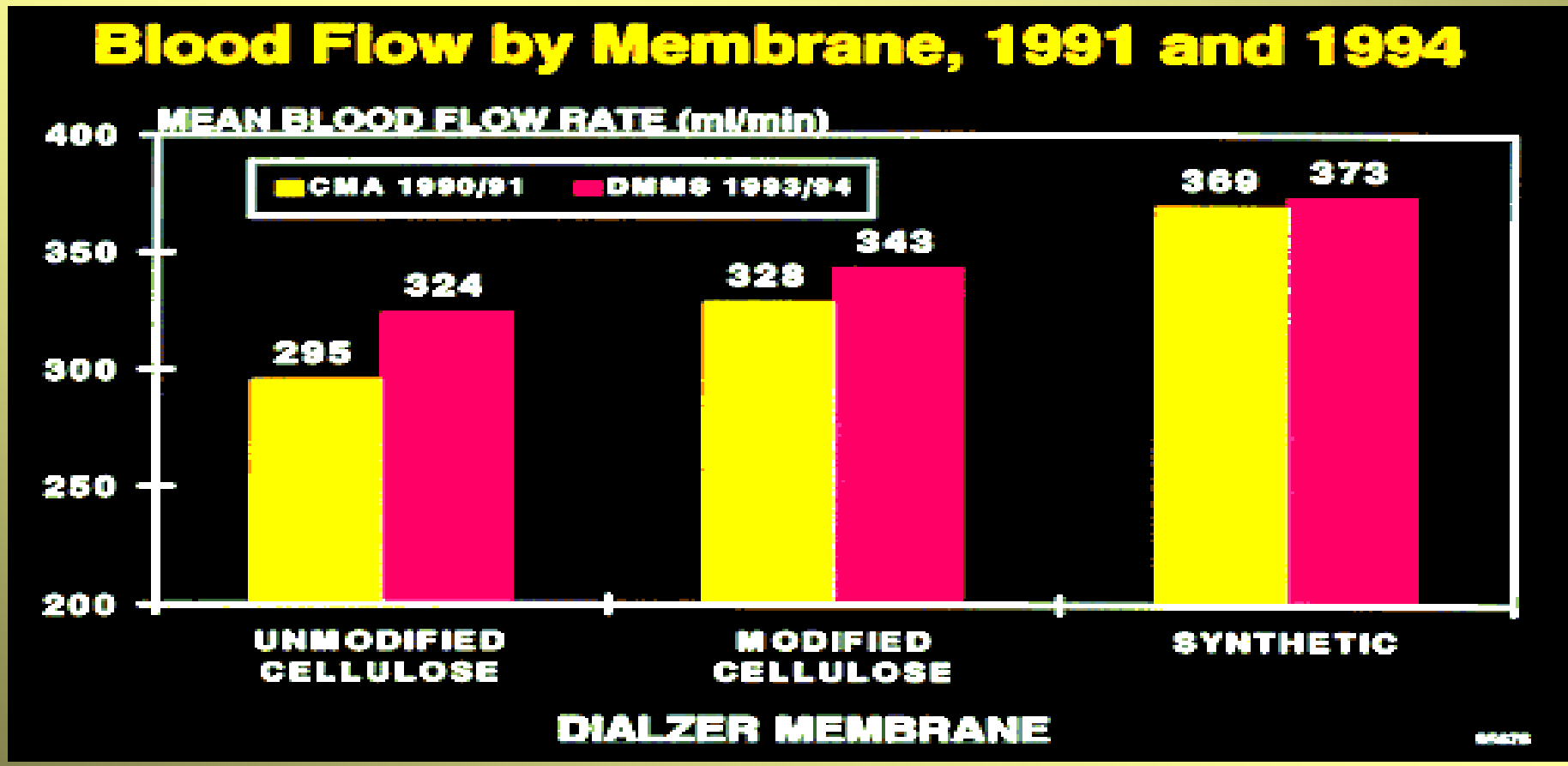

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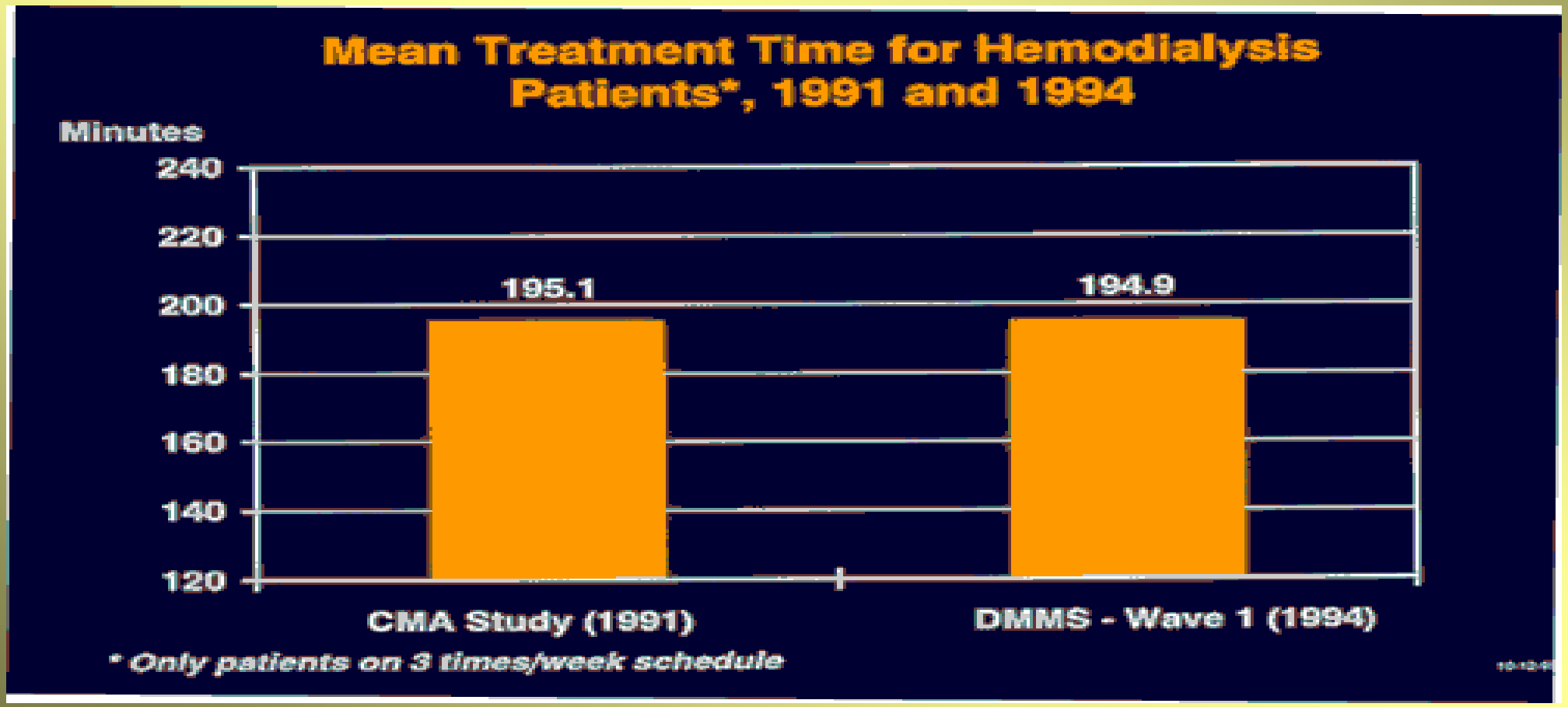
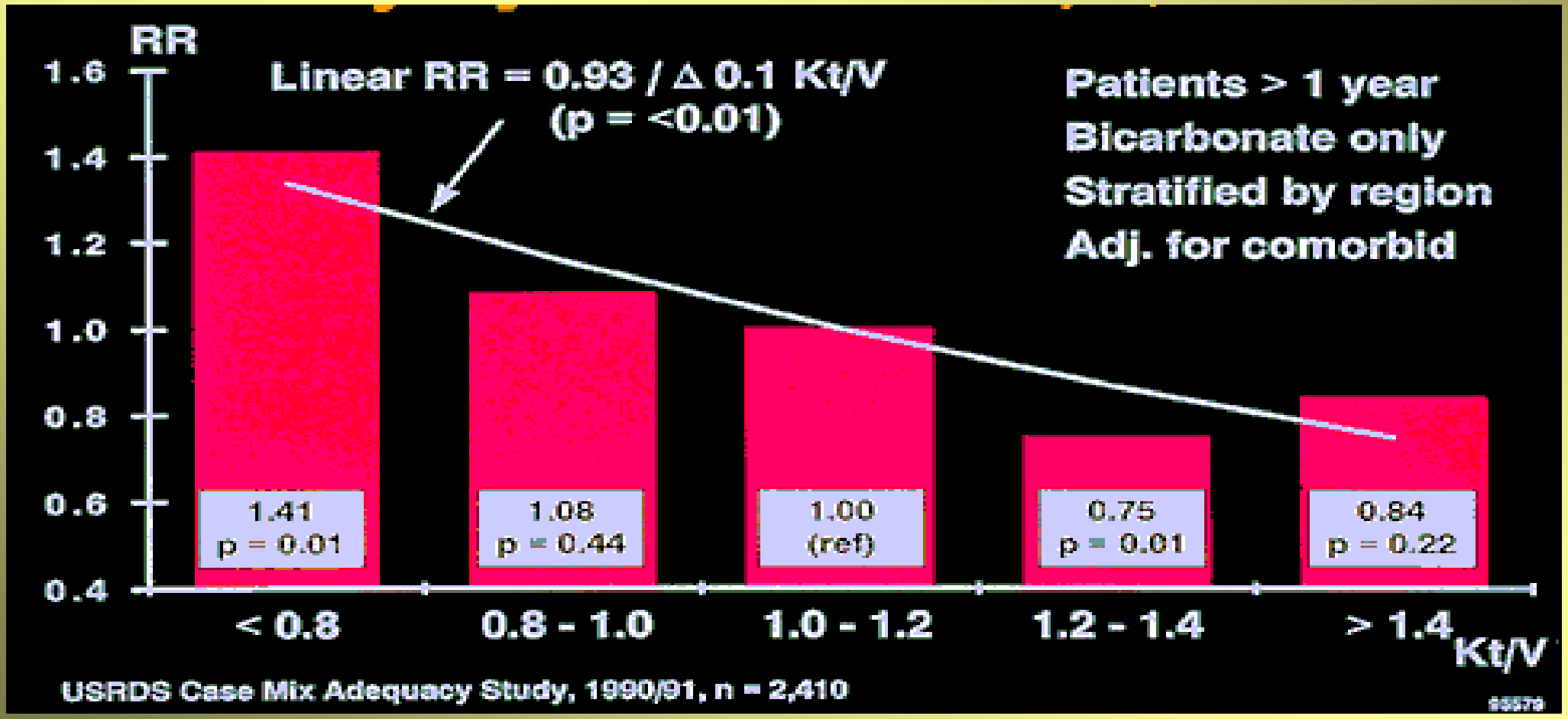


Mortality by Delivered Kt/V, 1990-93



MEMBRANE FLUX: A POTENTIAL CONFOUNDING VARIABLE

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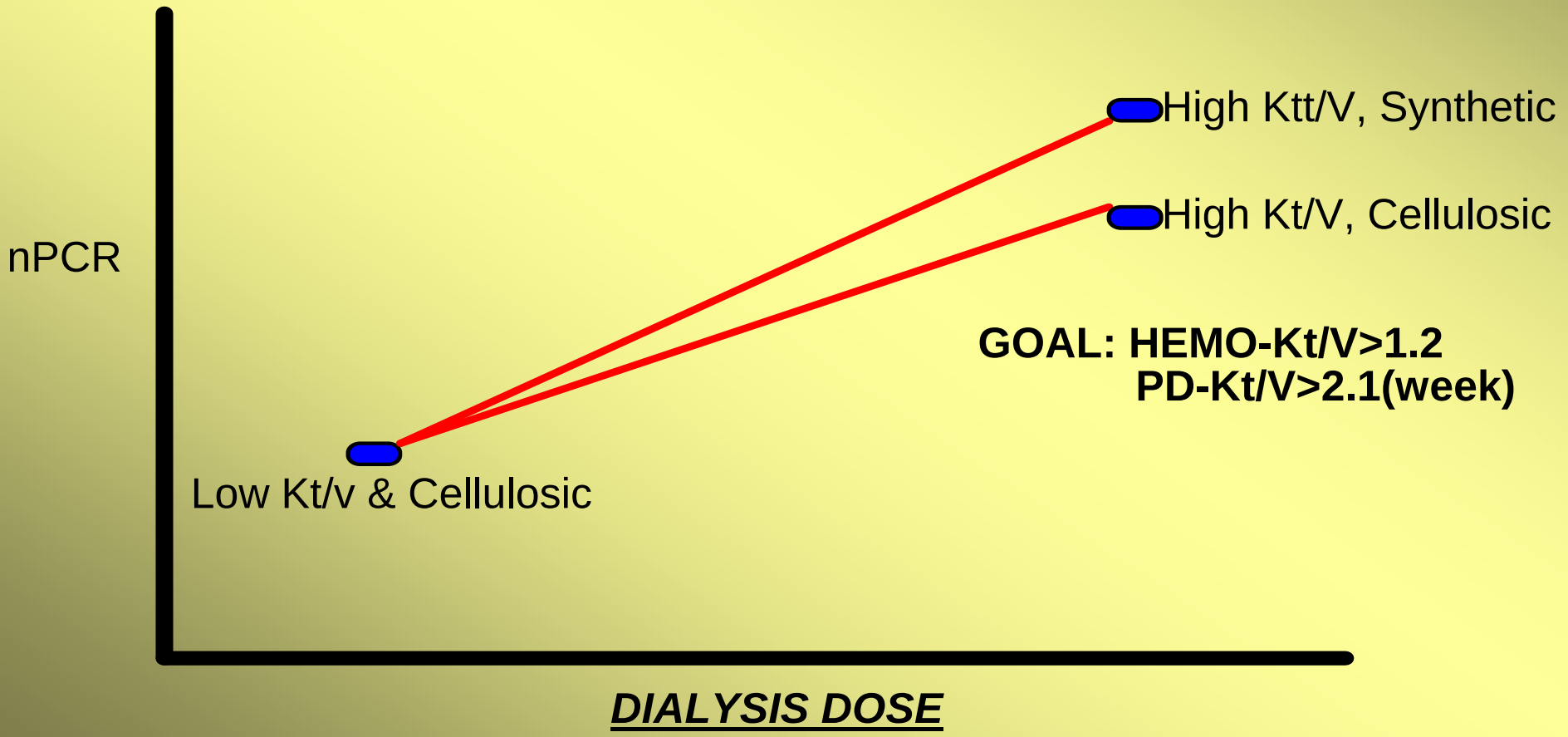
- HOWEVER, BECAUSE OF LOW T_D, THE FULL EFFECT OF HFM IS NOT EVIDENT. REMOVAL OF HIGH MW SUBSTANCES ARE ALSO TIME DEPENDENT.

INFLUENCE OF DOSE AND DIALYZER CHOICE ON NUTRITION



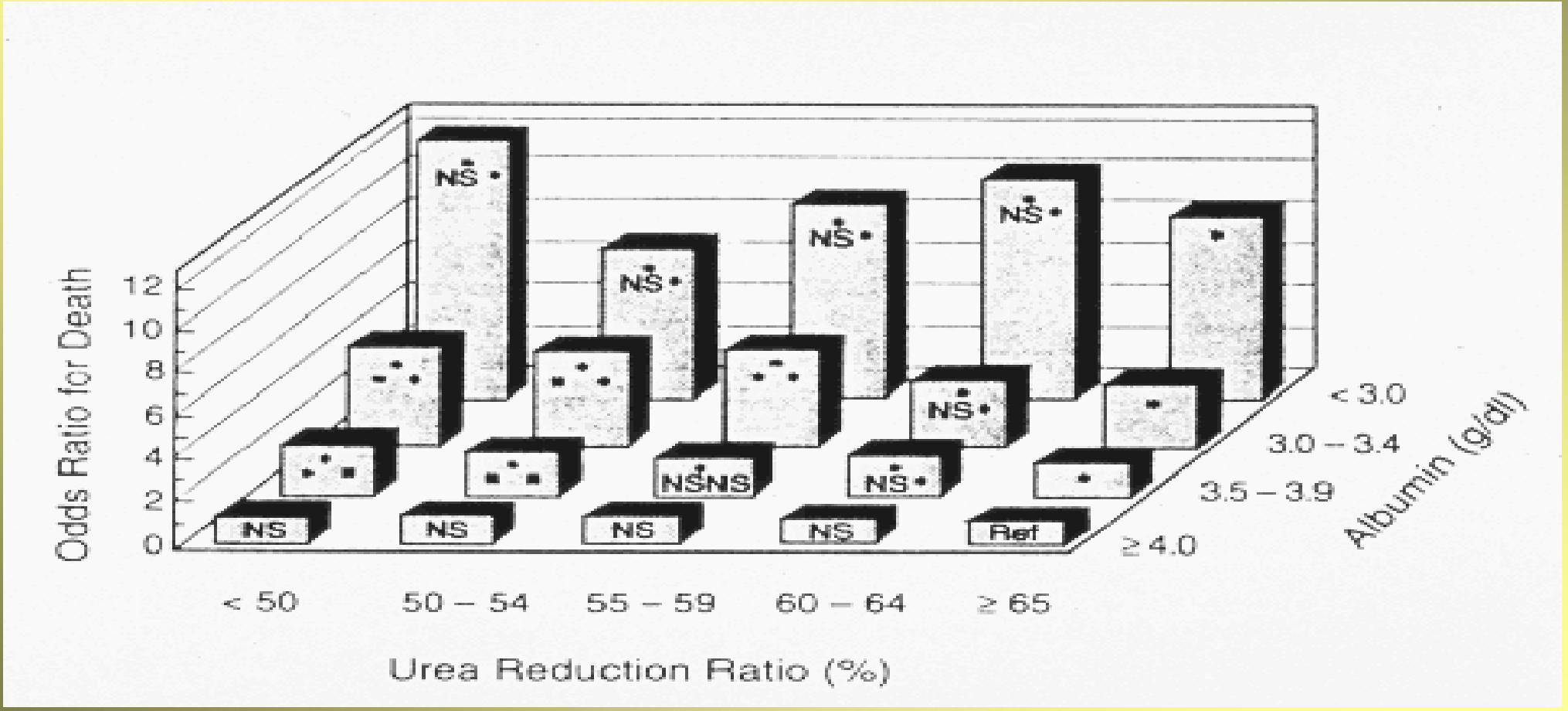
ADEQUACY AND NUTRITIONAL STATUS

NUTRITIONAL PARAMETERS AND YEARLY AVERAGE KT/V
VUMC Dialysis Patients

N	Yearly Average Kt/V	Albumin	Transferrin	PCR
16	< 0.86	3.5 ± 0.3	220 ± 34	0.83 ± 0.19
16	> 1.21	3.9* ± 0.2	257* ± 64	1.00* ± 0.19

* P < 0.05

ADEQUACY AND ALBUMIN LEVEL



HEMODIALYSIS TIME: THE UNRESOLVED PARAMETER

- K_D IS A MERE TECHNICAL ISSUE
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- SHORT TIME MAKES HEMODIALYSIS UNFORGIVING:

Prescribed Kt/V	Calculated Kt/V	Delivered Kt/V
1.56 ± 0.28	1.50 ± 0.28	1.37 ± 0.23

- EXCEPT FOR TASSIN, NO MODERN STUDIES HAS EXAMINED LONG (>5 HOURS) TIME AND OUTCOME

THE NCDS POPULATION

Table 5. NCDS Inclusion/Exclusion

Age, 18-70 years (mean, 49.0 ± 12.7)
(US 1988 mean, 57 years)
(US 1988 median, 60 years)
Average time on dialysis, 4.2 ± 2.3 years
No diabetes
(1988 US acceptance rate, 30%)
No malignancy
No significant cardiovascular disease
No hospitalization for past 6 months
T_e range, 2.5-5.5 hours during study
(mean before participation, 4.3 hours)
Cooperative
Compliant

FACTORS RELATED TO DIALYSIS ADEQUACY

- **HEMODIALYSIS RELATED FACTORS**
  - **DOSE**
    - **LOW MW SOLUTES**
    - **HIGH MW SOLUTES**
    - **DIALYSIS TIME**
- **MEMBRANE**
  - **FLUX**
  - **BIOCOMPATIBILTY**
  - **REUSE**
- **PATIENT RELATED FACTORS**
  - **NUTRITION**
  - **ACIDOSIS**
  - **CA x P**
  - **BLOOD PRESSURE**
  - **LIPIDS**
  - **CARDIOVASCULAR MORBIDITY**
  - **INFLAMMATION**

ALTERNATIVES FOR THE HEMO STUDY

HEMO STUDY

Choice	Controversy
• Dialysis Dose	• We know the answer
• Dialysis Time	• Does not reflect U.S. practice
• Biocompatibility	• Confounded by reuse techniques
• Flux	• Definition
• Nutrition	• Prohibitive cost

Remember: Limited Funds Dictates 2 x 2 Design

THE HEMODIALYSIS (HEMO) STUDY

AN NIH-NIDDK SPONSORED RANDOMIZED, MULTI-CENTER CLINICAL TRIAL

THE CHOICE: OBJECTIVES OF THE HEMO STUDY

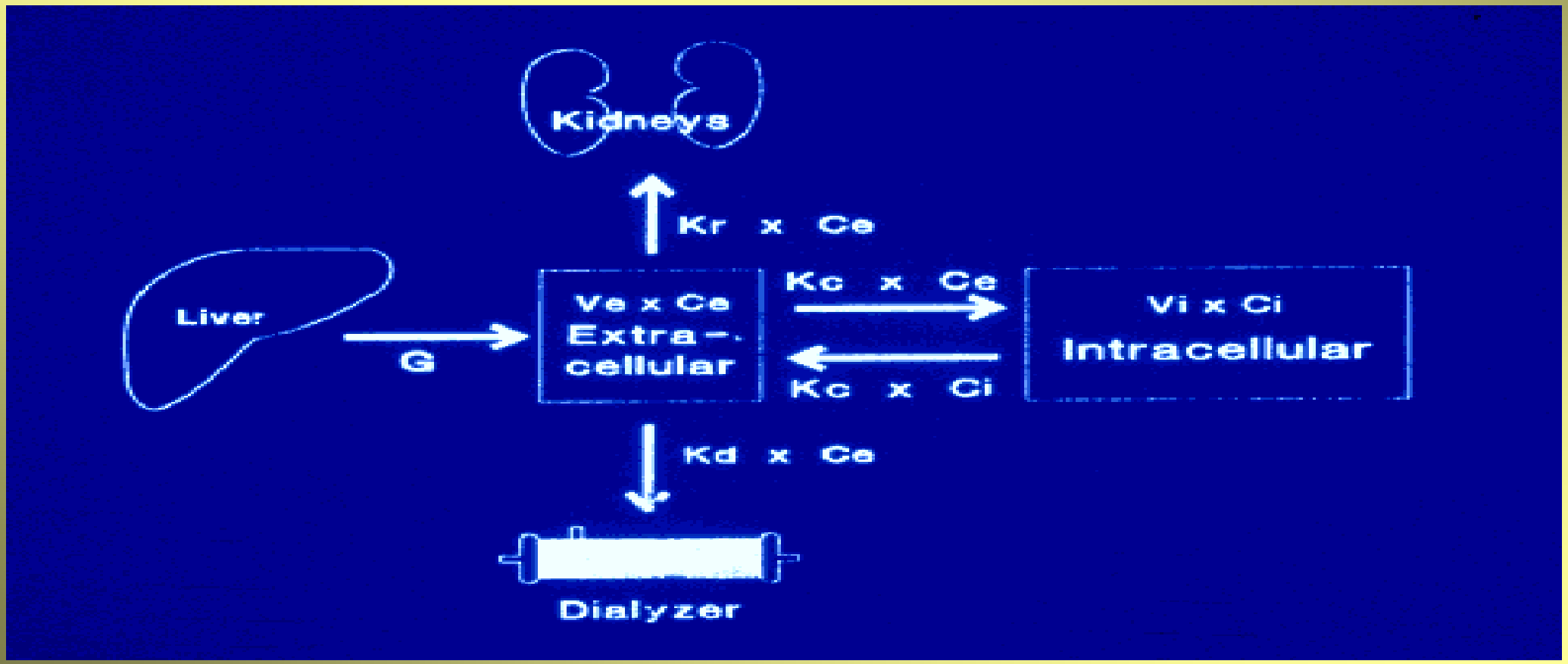
In patients undergoing 3x/week maintenance hemodialysis, to determine whether

- **higher dose, or**
- **high-flux membrane**

affect

- **mortality (primary outcome), or**
- **morbidity (secondary outcome)**

DOUBLE POOL KINETICS



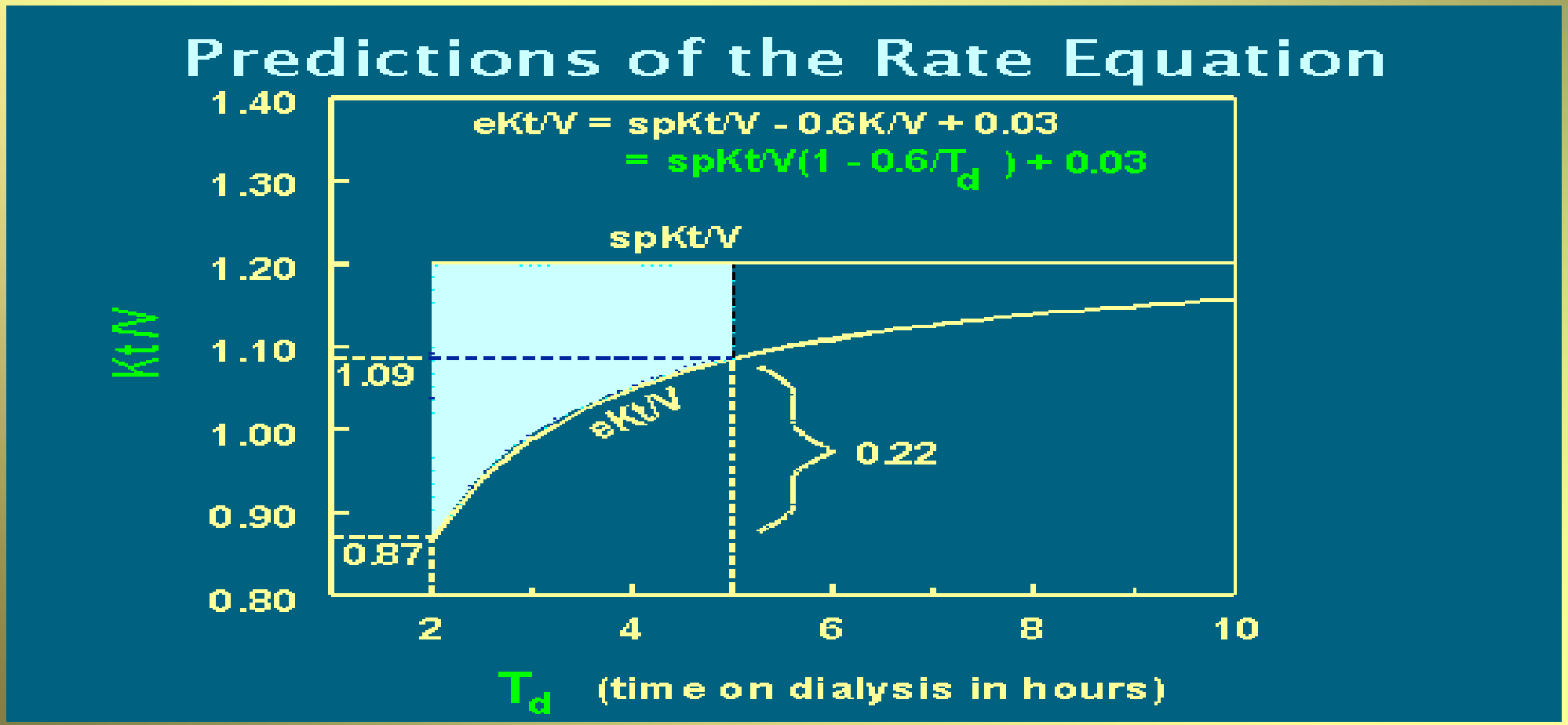
THE RATE EQUATION

Rate equation

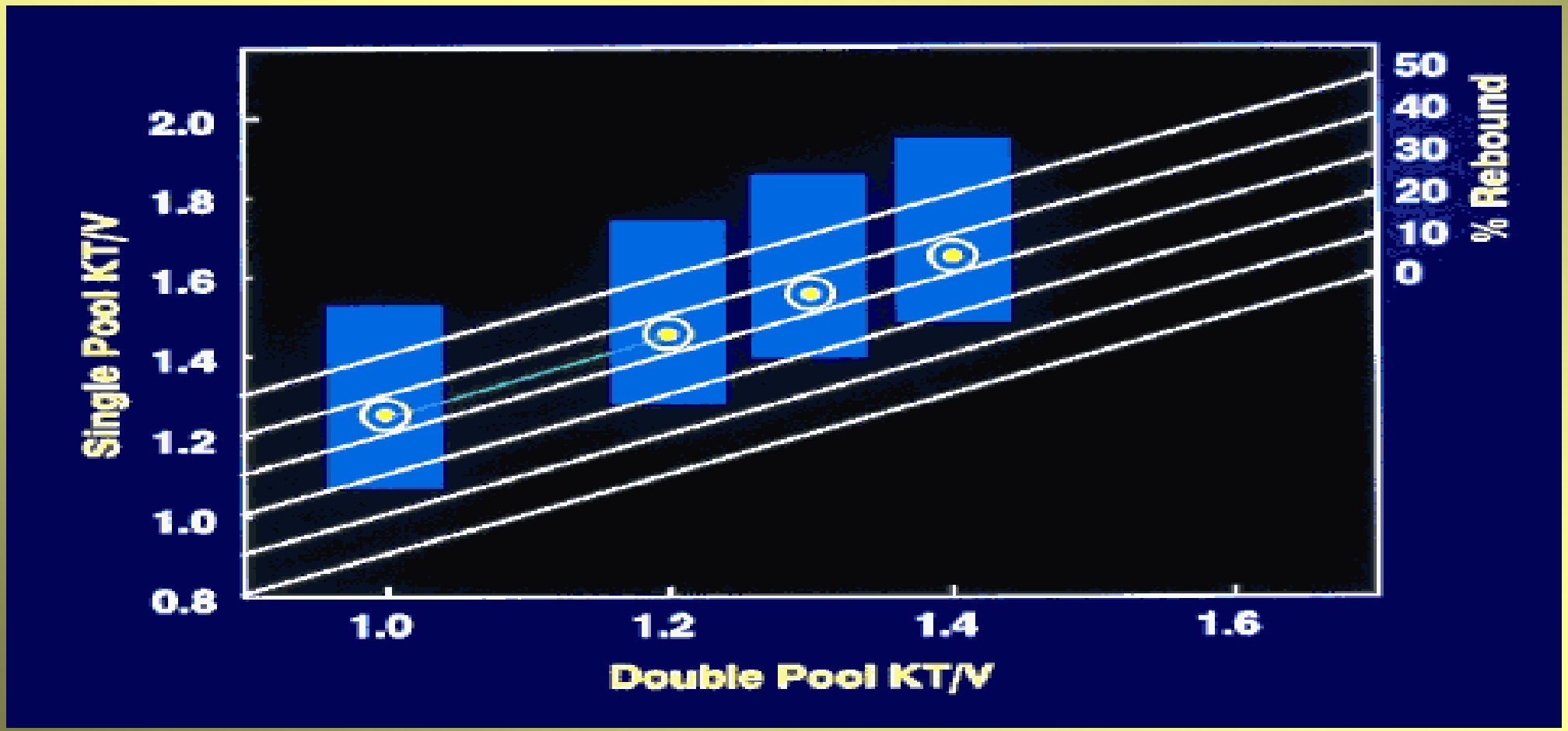
$$eKt/V = spKt/V - 0.6(K/V) + 0.03$$

(K/V in hours^{-1})

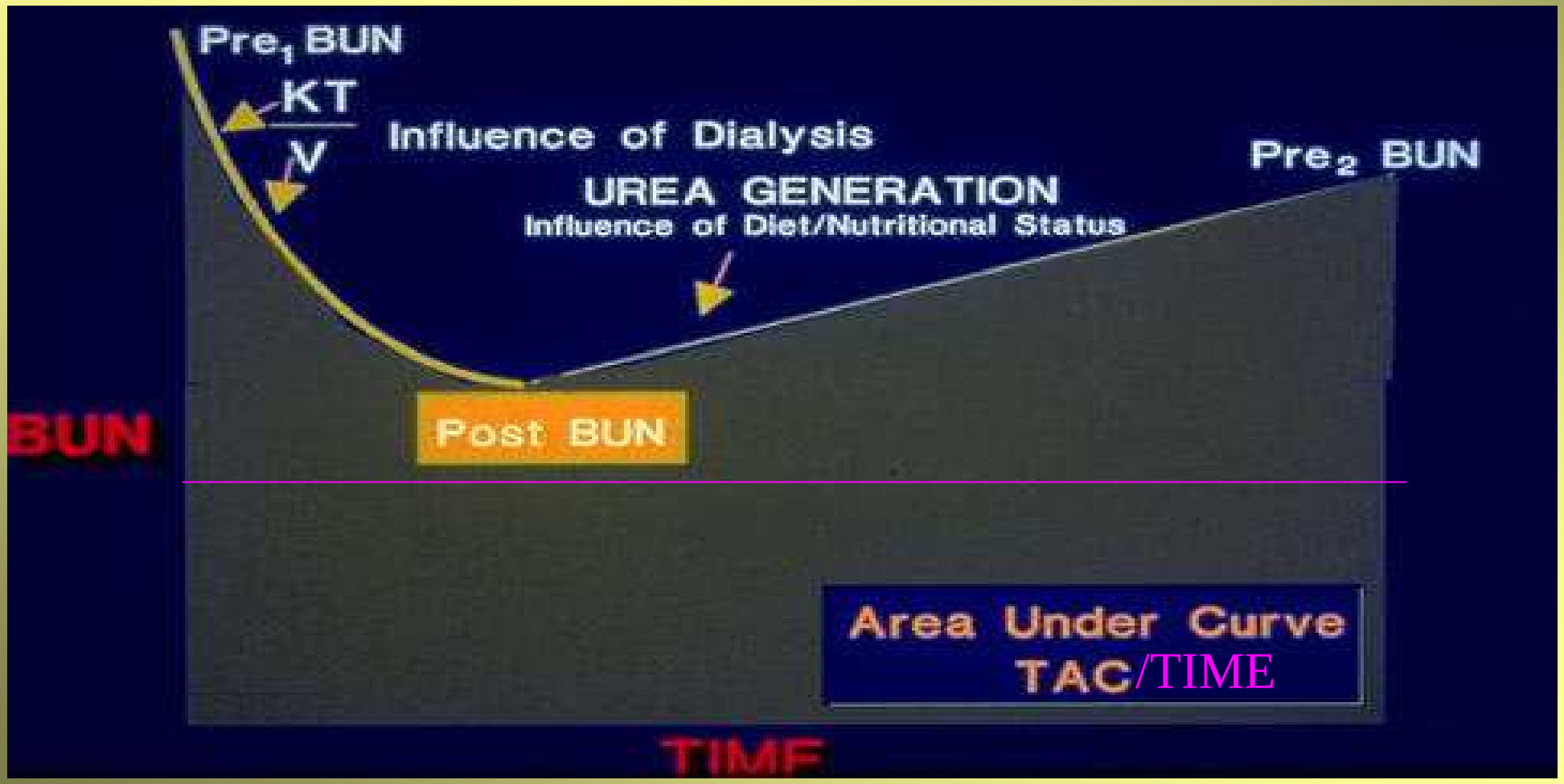
RATE EQUATION AS A FUNCTION OF TIME



RELATIONSHIP OF Kt/V_{SP} TO Kt/V_{DP} AND AS A FUNCTION OF REBOUND



THE DIALYSIS CYCLE



Dose

Standard dose

eKt/V = 1.05

spKt/V ≈ 1.25

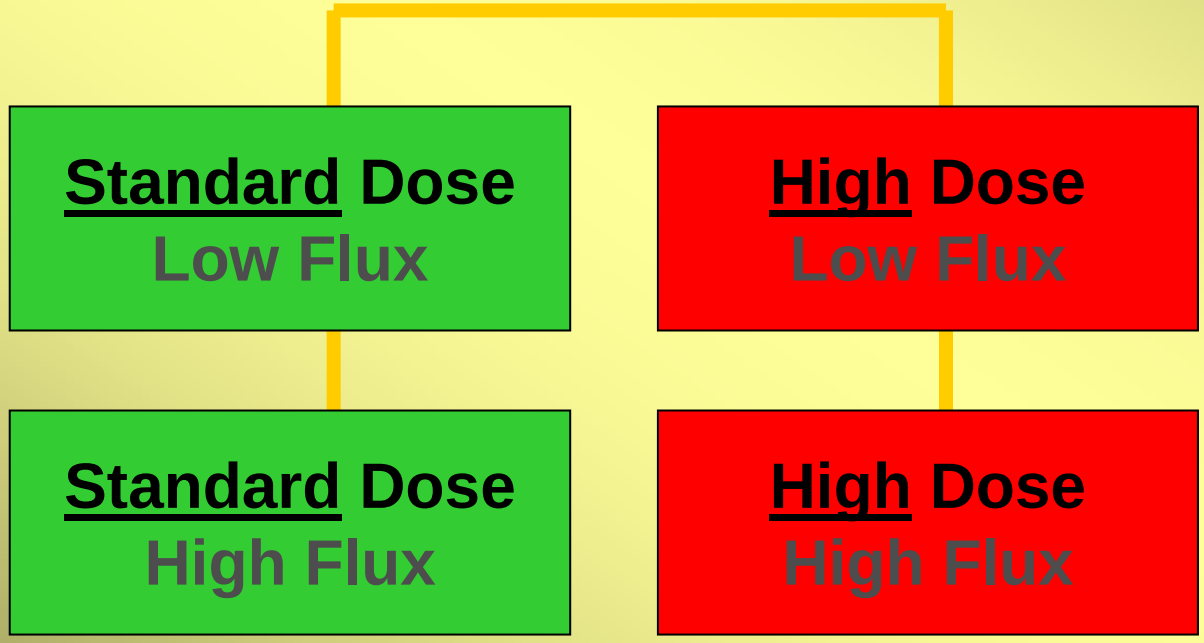
URR ≈ 65%

High dose

eKt/V = 1.45

spKt/V ≈ 1.65

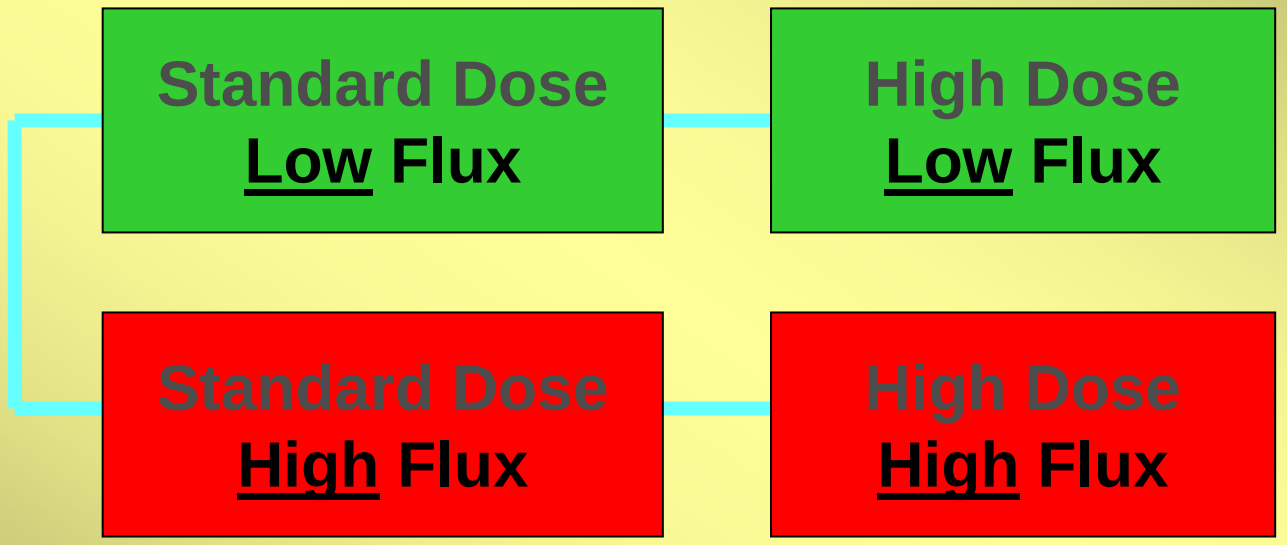
URR ≈ 75%



Flux

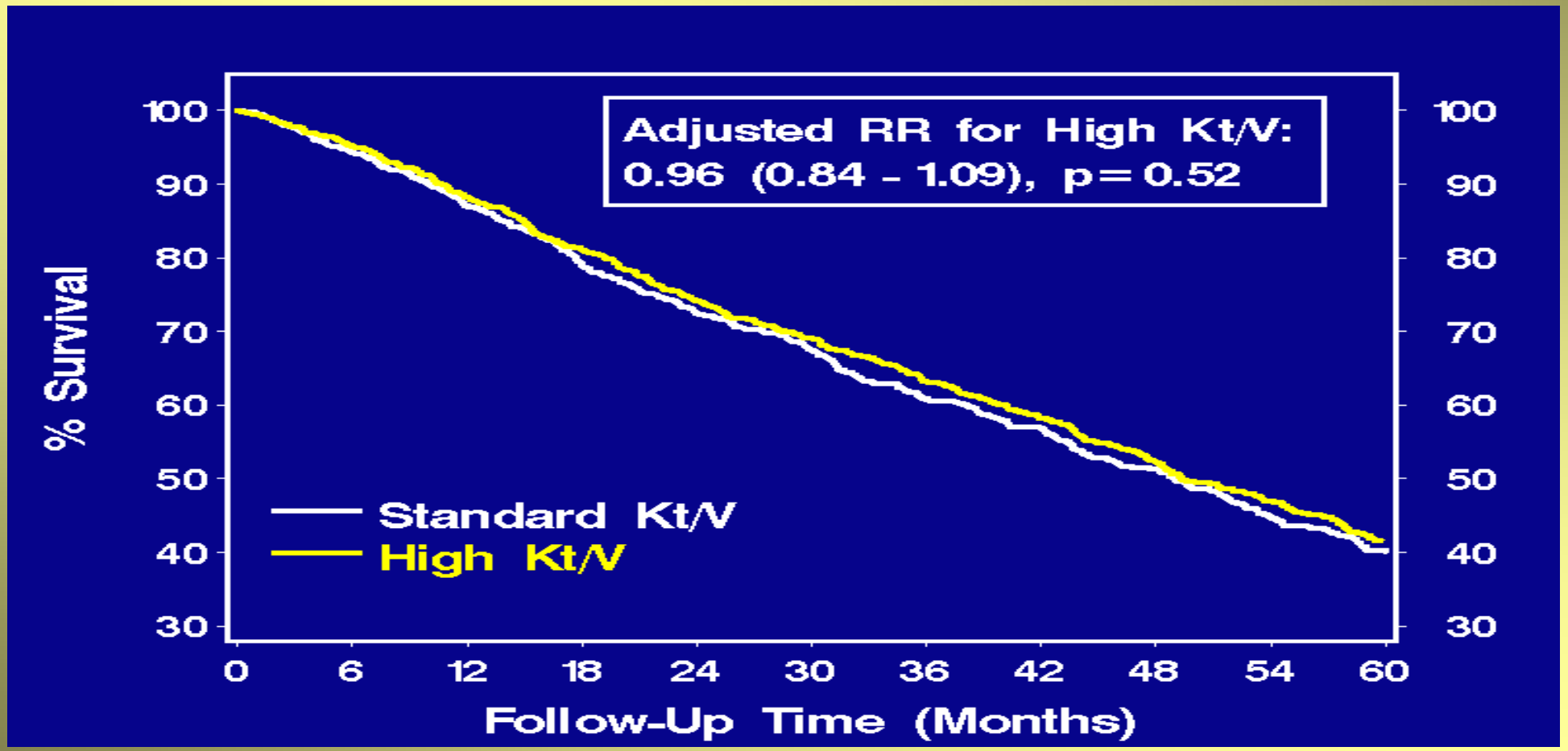
Low-flux dialyzers: β_2**M clearance** **< 10 ml/min**

Flux comparison

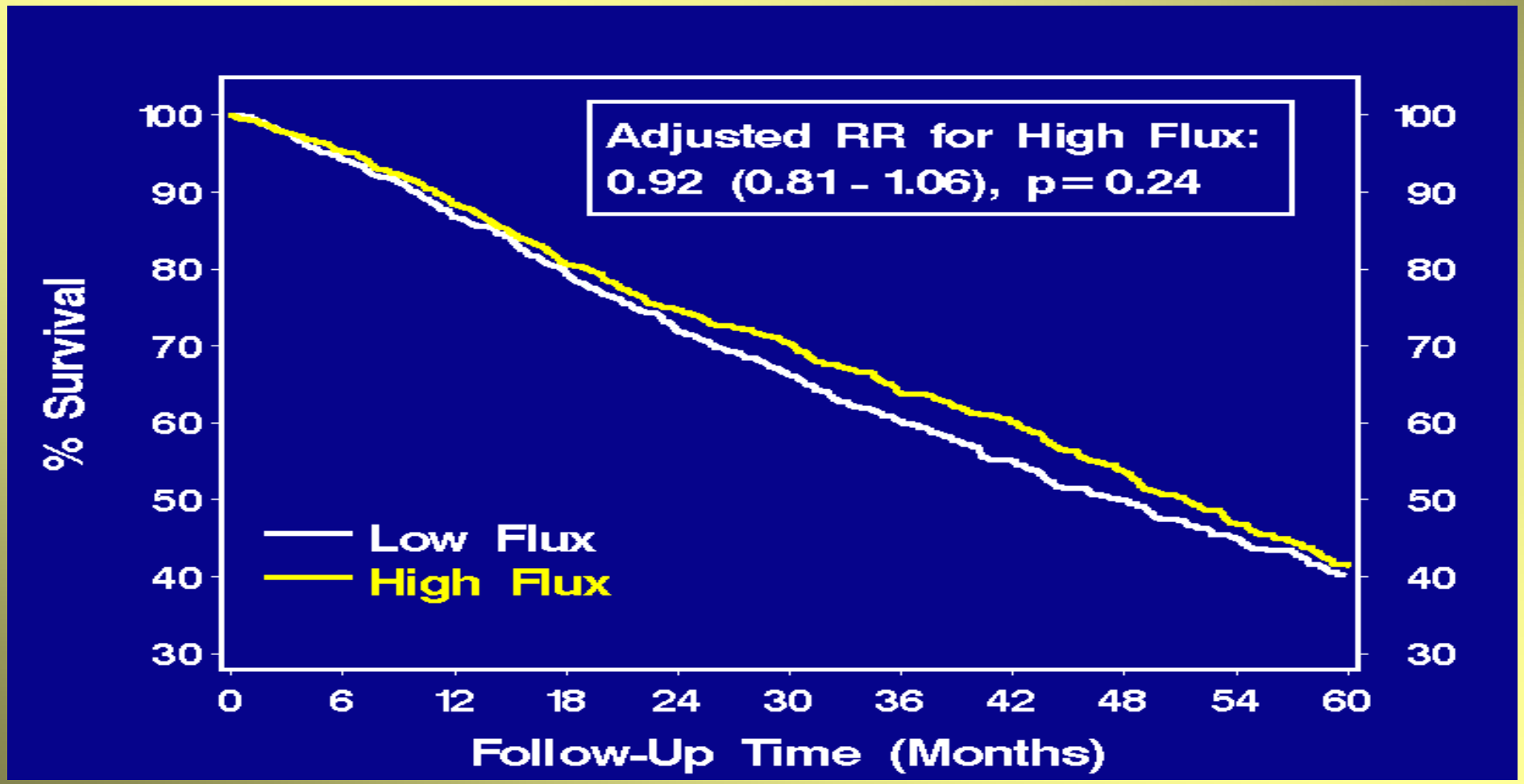


High-flux dialyzers: β_2**M clearance** **> 20 ml/min**

Time to Death by Kt/V Group



Time to Death by Flux Group



Interactions of Treatments with Baseline Characteristics

Did treatment effects differ between subgroups for seven pre-specified baseline factors?

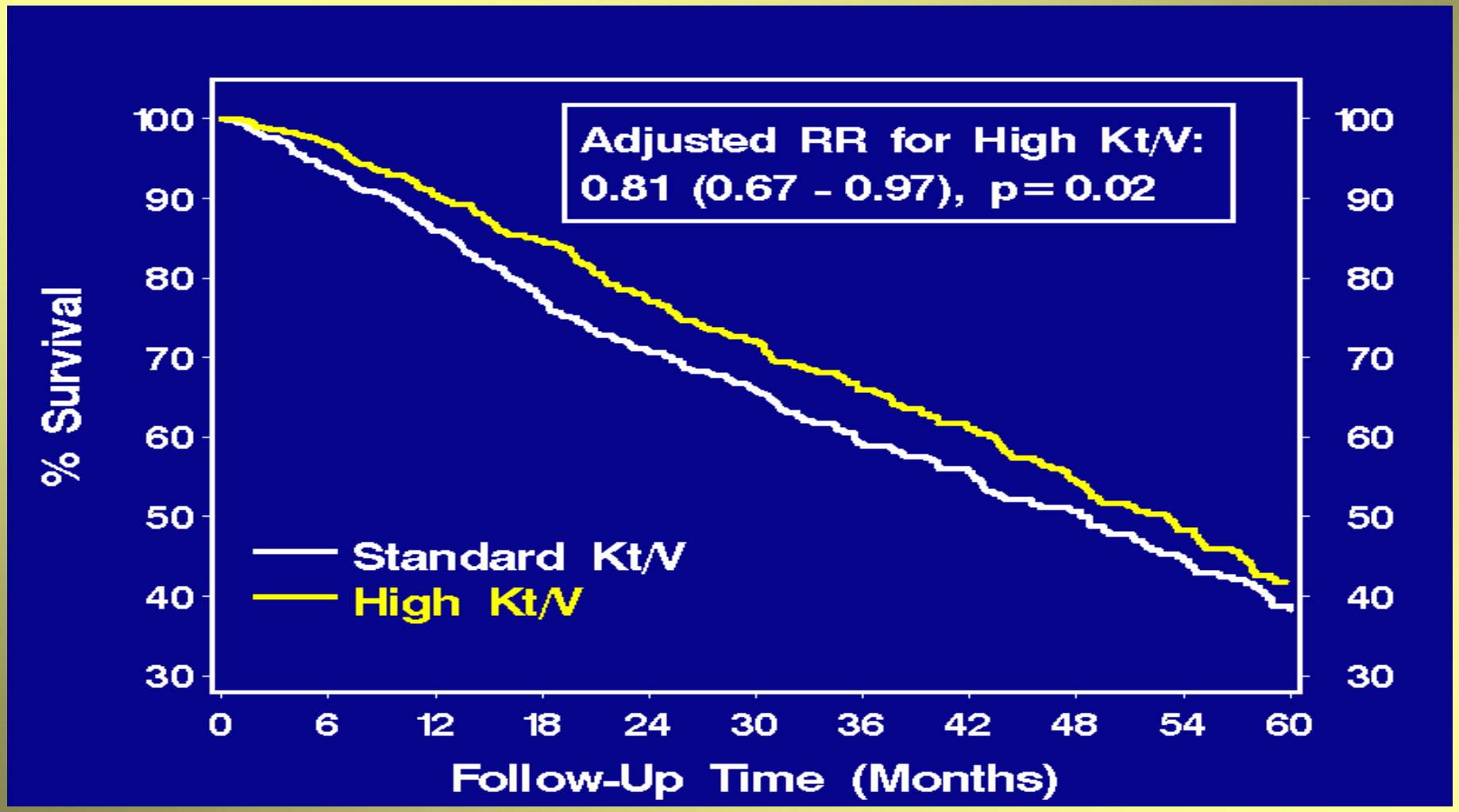
Age
Gender
Race
Diabetes
Years of dialysis
Comorbidity
Albumin

Predictors of Mortality by Cox Regression

Predictor Variable	Relative Risk	95% Confidence	p-value
High dose	**0.96**	**(0.84, 1.09)**	**0.52**
High flux	**0.92**	**(0.81, 1.06)**	**0.24**
Age (per 10 yrs increase)	**1.44**	**(1.35, 1.54)**	**<0.001**
Gender (female)	**0.86**	**(0.74, 0.99)**	**0.03**
Race (African American)	**0.76**	**(0.65, 0.89)**	**0.001**
Diabetes	**1.24**	**(1.06, 1.45)**	**<0.001**
Years of dialysis	**1.04**	**(1.02, 1.06)**	**<0.001**
Baseline serum albumin (per 0.5 g/dL increment)	**0.51**	**(0.43, 0.62)**	**<0.001**

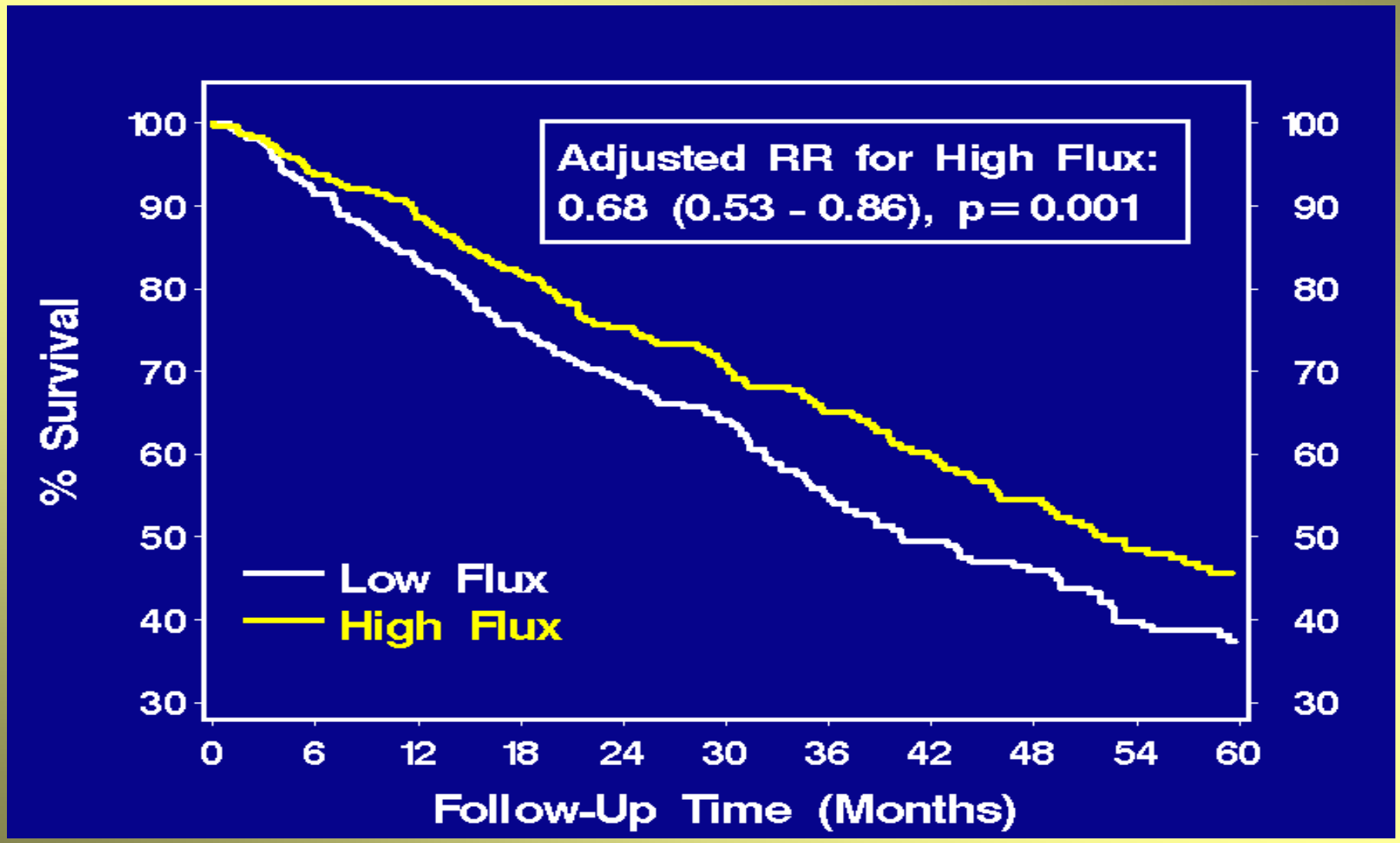
Model also includes 2 other sig. variables: ICED, albumin x time
Analysis stratified by clinical center

Time to Death by Kt/V Group
Females (484 Deaths)



Time to Death by Flux Group

Duration of Dialysis > 3.7 Years (298 Deaths)



HEMO STUDY SUMMARY

1) **THE HIGHER DOSE OF HEMODIALYSIS THRICE WEEKLY DID NOT:**

   IMPROVE SURVIVAL,

   REDUCE HOSPITALIZATIONS, OR

   MAINTAIN SERUM ALBUMIN

2) **USE OF A HIGH FLUX MEMBRANE DID NOT:**

   IMPROVE SURVIVAL,

   REDUCE HOSPITALIZATIONS, OR

   MAINTAIN SERUM ALBUMIN

HEMO STUDY SUMMARY

3) HOWEVER, EFFECTS MAY VARY AMONG CERTAIN SUBSETS OF PATIENTS:

A) IN WOMEN, THE HIGHER DOSE OF DIALYSIS MAY BE ASSOCIATED WITH INCREASED SURVIVAL

B) IN PATIENTS WITH > 3.7 YEARS ON DIALYSIS, USE OF A HIGH FLUX MEMBRANE MAY BE ASSOCIATED WITH INCREASED SURVIVAL

C) THE RESULTS ON THESE SUBSETS SHOULD BE INTERPRETED CAUTIOUSLY AND BE FURTHER INVESTIGATED

ARE WE CONFOUNDING DETERMINATION OF ADEQUACY BY THE USE OF Kt/V?

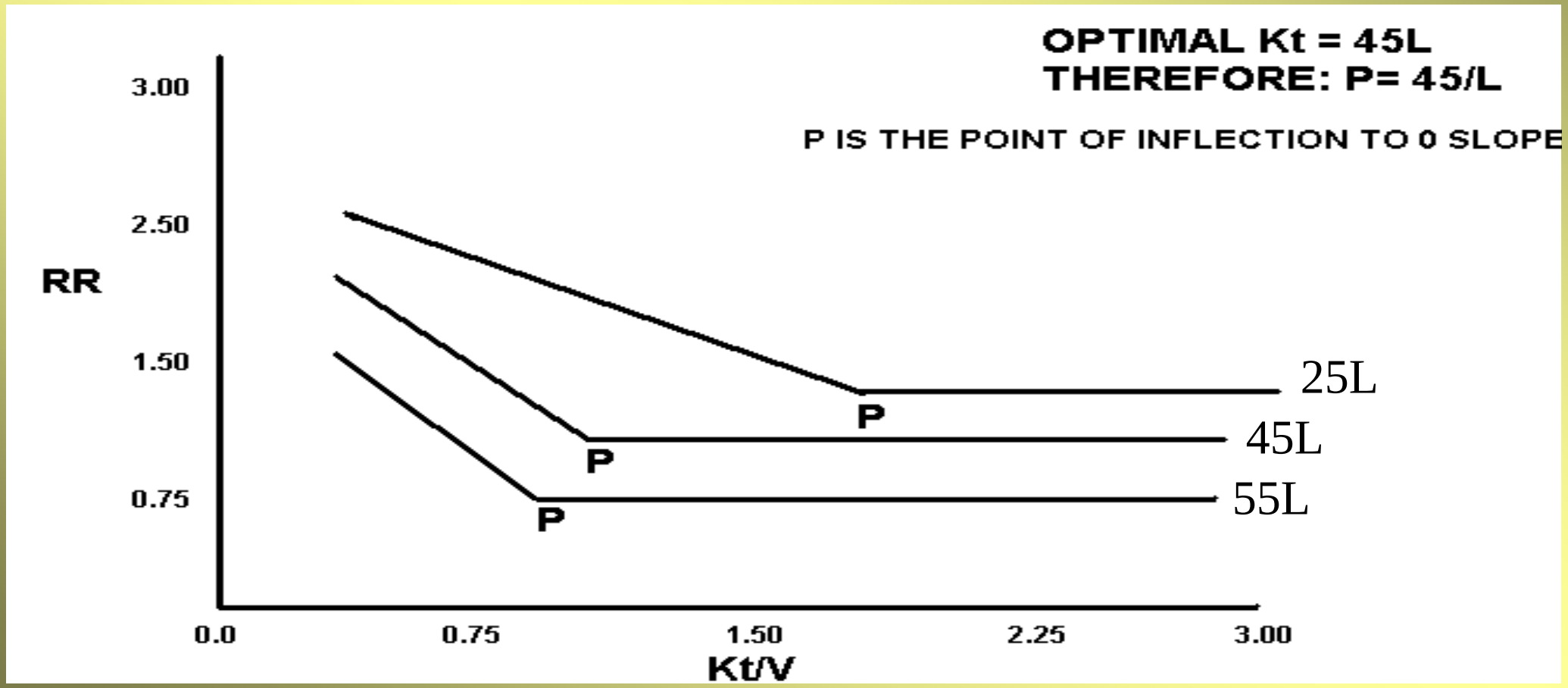
Kt/V

Kt= AMOUNT OF DIALYSIS, A GOOD THING

V= VOLUME~WEIGHT~MUSCLE MASS, A GOOD THING

A GOOD THING/A GOOD THING

UREA VOLUME AND SURVIVAL



RELATIVE RISK OF DEATH

MINEFIELDS AVOIDED BY THE HEMO STUDY

- **DESPITE ITS LENGTH, WE AVOIDED BEING ECLIPSED BY CHANGES IN COMMUNITY PRACTICE PATTERNS**
  - **T_D, Q_B, Q_D SIMILAR TO USRDS**
  - **MEMBRANES SIMILAR**
  - **STANDARD LEVEL Kt/V DELIVERED WAS BETTER OR EQUAL TO COMMUNITY PRACTICE THROUGHOUT THE STUDY. THE COMMUNITY RECOMMENDATIONS EXCEEDED HEMO STANDARD Kt/V FOR ONLY A SHORT TIME**
- **DOSE AND FLUX GOALS ACHIEVED**
- **MORTALITY NOT OVERESTIMATED**
- **ADEQUATELY POWERED**
- **WHAT WAS PILOTED *IS* WHAT WAS STUDIED**

WHY THE HEMO STUDY WAS NEEDED

- **RAPIDLY GROWING ESRD POPULATION**
  - **10 %/YEAR GROWTH RATE, COSTING $BILLIONS**
  - **WORSENING COMORBIDITY**
  - **MAJORITY TREATED BY HEMODIALYSIS**
- **US ANNUAL GROSS MORTALITY OF 21-23%**
- **OBSERVATIONAL AND CORRELATIONAL STUDIES DEMONSTRATING IMPROVED SURVIVAL FOLLOWING TREATMENT CHANGES**
  - **HIGHER DOSE AS MEASURED BY Kt/V OR URR**
  - **BIOCOMPATIBLE MEMBRANES**
  - **REMOVAL OF HIGH MW SUBSTANCES (FLUX)**

IMPLICATIONS OF THE HEMO STUDY

What situations require clinical guidelines to be updated?

- Changes in evidence on the existing benefits and harms of interventions
- Changes in outcomes considered important
- Changes in available interventions
- Changes in evidence that current practice is optimal
- Changes in values placed on outcomes
- Changes in resources available for health care

BMJ 2001;323:155-157

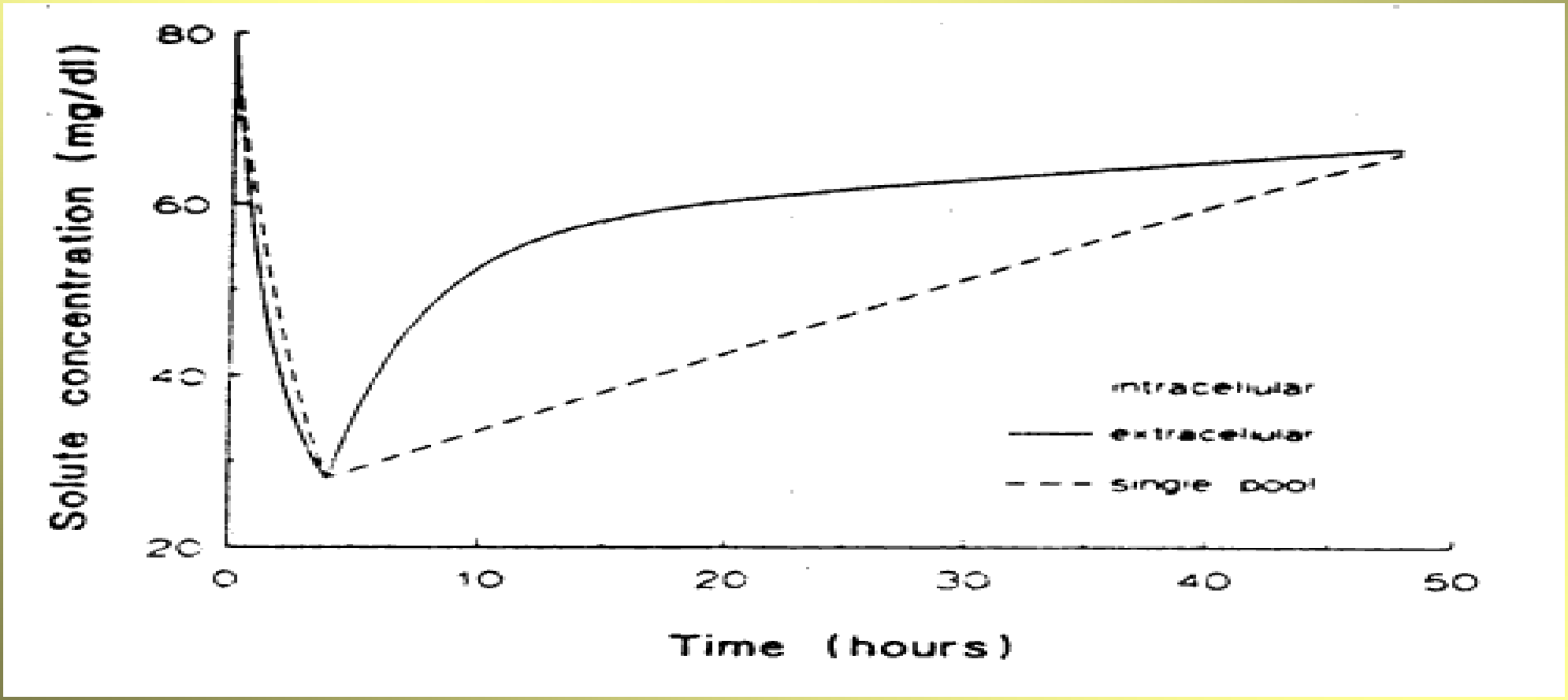
ADAPTED FROM MUJAIS; ADEMEX STUDY

PLACES TO GO NEXT

- Changing a number?
- Changing an approach:
  - Cardiovascular Risk Reduction
  - Control of Co-morbid Conditions
  - Solute Removal: beyond small solutes
  - Volume Control
  - Nutrition
  - Anemia Correction
  - Bone Disease

ADAPTED FROM MUJAIS; ADEMEX STUDY

LARGE MOLECULE REBOUND



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- HOWEVER, BECAUSE OF LOW T_D, THE FULL EFFECT OF HFM IS NOT EVIDENT: **REMOVAL OF HIGH MW SUBSTANCES ARE ALSO TIME DEPENDENT-LONGER TIMES ARE NECESSARY TO SHOW BENEFITS OF HFM**

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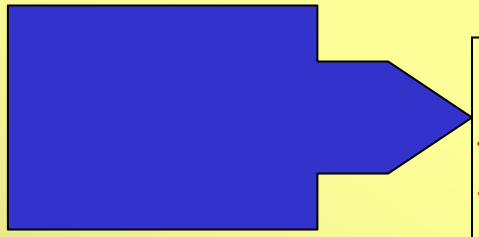
POTENTIAL PARAMETERS TO CONSIDER WITH NOCTURNAL AND DAILY HD

IS IT INCREASED TIME OR INCREASED QUANTITY?

FACTORS THAT MAY INFLUENCE MORBIDITY AND SURVIVAL ON HEMODIALYSIS

- MEMBRANES: SYNTHETIC, FLUX
- DIALYSATE: SODIUM, BICARBONATE
- PHOSPHATE, Ca x P, Ca
- EPO
- DIALYSIS KINETICS
- DIALYSIS TIME
- NUTRITION



ALTERNATE DIALYSIS SCHEDULES

ISSUES TO BE CONSIDERED

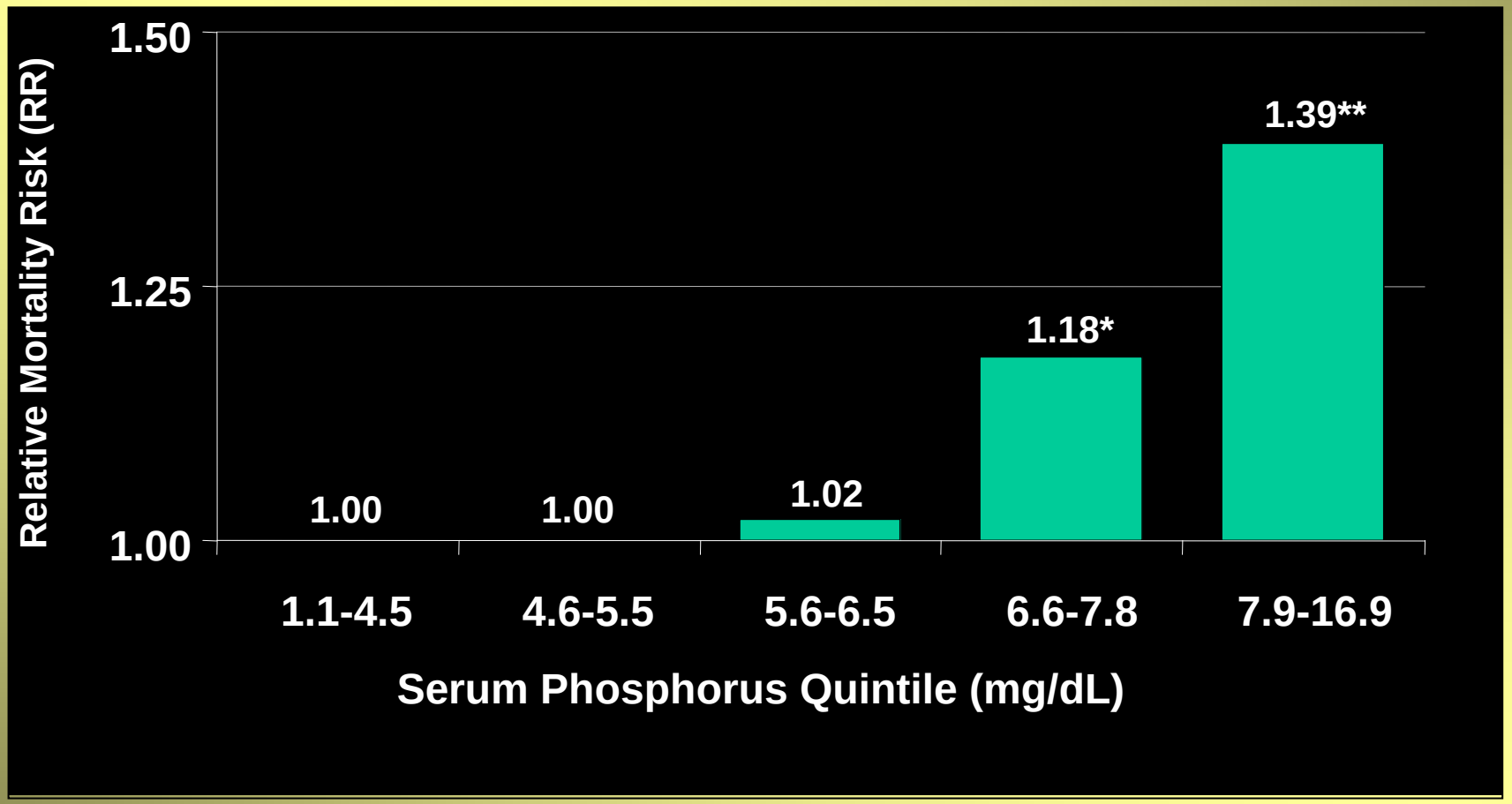
- **DEFINTIONS OF THE MODALITIES**
- INDIVIDUAL STUDIES OF EACH OF THE MODALITIES
- DAILY HEMODIALYSIS vs NOCTURNAL HEMODIALYSIS

ALTERNATIVES TO STANDARD HEMODIALSIS TREATMENTS

- SLOW LONG-DURATION HEMODIALYSIS
  - THRICE WEEKLY; BIOINCOMPATIBLE MEMBRANE; 6-8 HOURS; Q_B= 200-220 mL/min; **Kt/V>1.8**
- SHORT DURATION DAILY DIALYSIS
  - 5-6 TIMES EACH WEEK; HIGH FLUX BIOCOMPATIBLE MEMBRANE ; 1.5-2.5 HOURS; Q_B>400 mL/min; **Kt/V-.2-.8**
- NOCTURNAL HEMODIALYSIS
  - 5-7 TIMES EACH WEEK; BIOCOMPATIBLE MEMBRANE; 6-8 HOURS; Q_B= 250-300 mL/min; **K-0.9-1.2**

Elevated Serum Phosphorus Increases Mortality Risk[1]

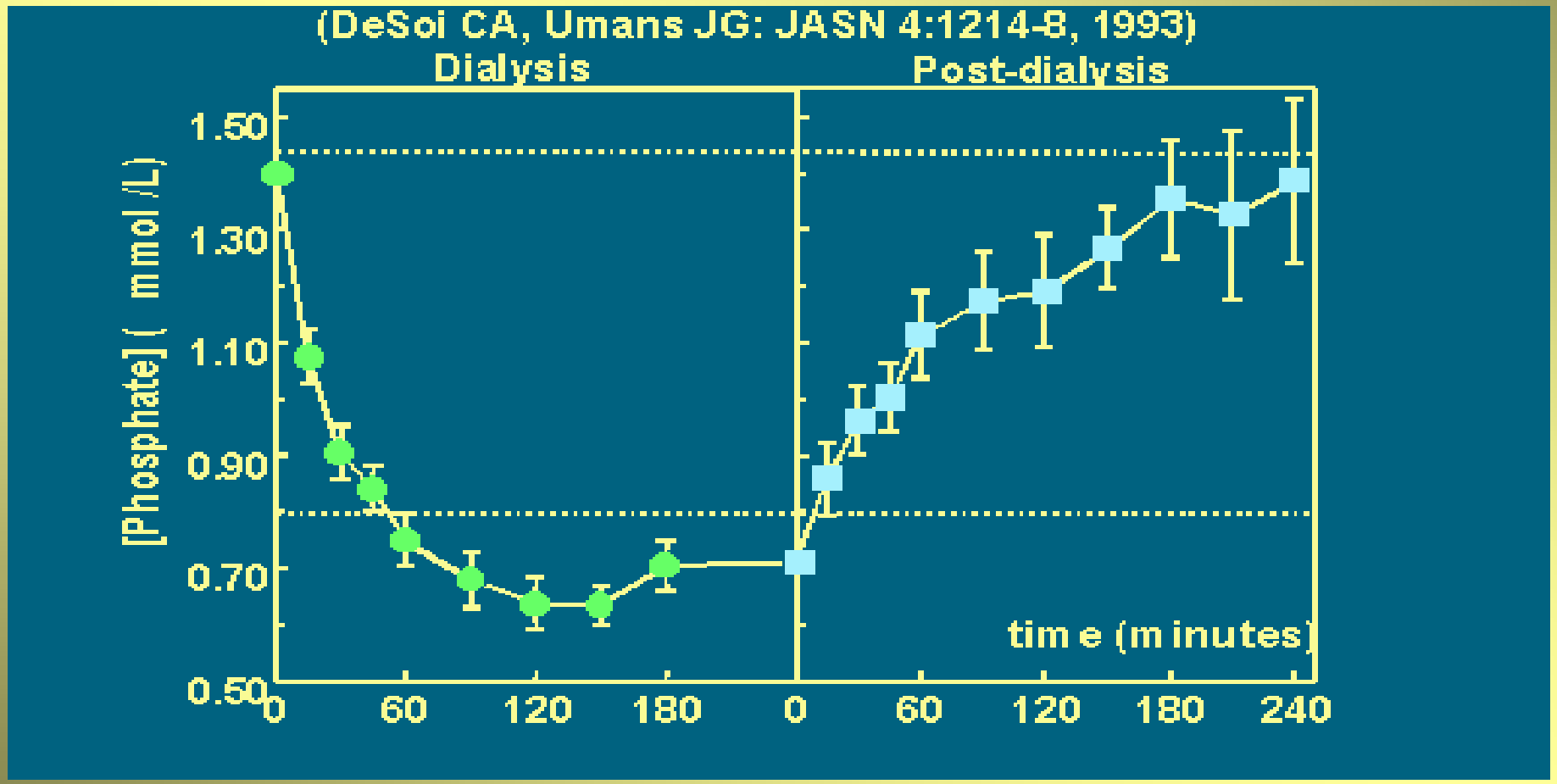
US PTS
39%> 6.5



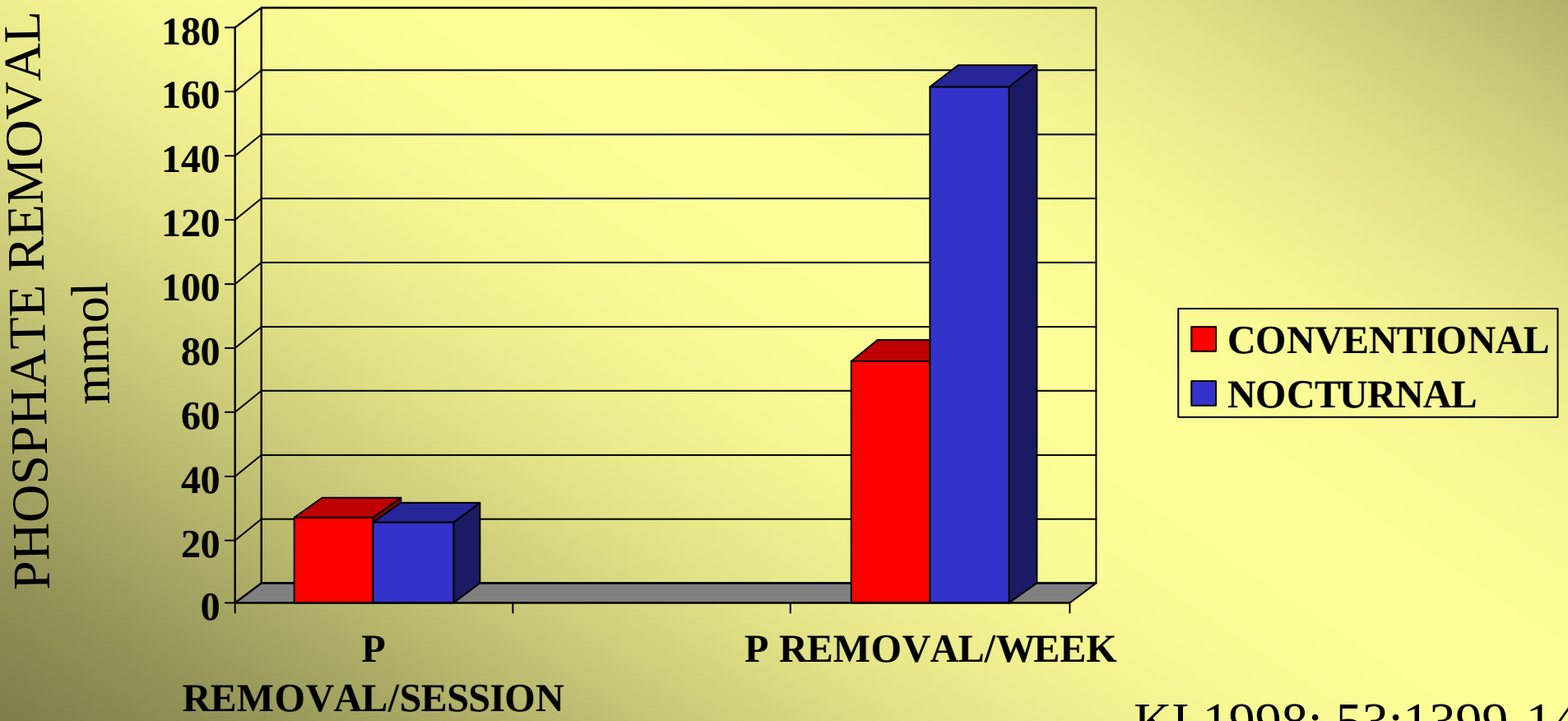
*P=0.03 **P<0.0001 (n=6407)

1. Adapted from Block GA, et al. *Am J Kidney Dis.* 1998;31:607-617.

SERUM PHOSPHORUS DURING DIALYSIS

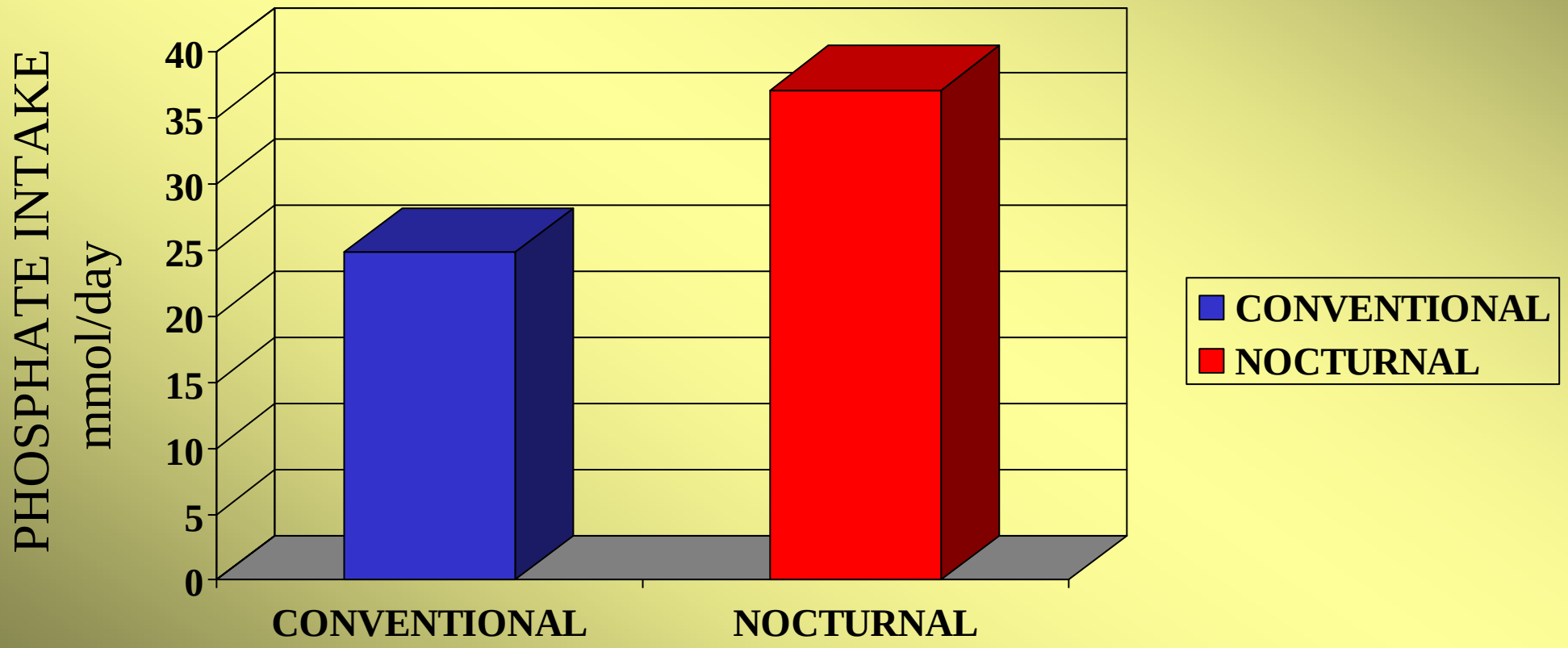


NOCTURNAL HD AND PHOSPHATE CONTROL



KI 1998; 53:1399-1404

DIETARY PHOSPHATE INTAKE: CONVENTIONAL vs NOCTURNAL HD



KI 1998; 53:1399-1404

CONVENTIONAL HD vs NOCTURNAL HD: PHOSPHATE CONTROL

- PHOSPHATE LEVELS
  - 2.1 mmol/L (~6 mg/dL) DECREASED TO 1.3 mmol/L (~3.9 mg/dL) WITH THE START OF NOCTURNAL HD
- BY THE 4th MONTH OF NOCTURNAL HD, ***NONE OF THE PATIENTS WERE USING PHOSPHATE BINDERS***

KI 1998; 53:1399-1404

NOCTURNAL vs DAILY SHORT HEMODIALYSIS

- NOCTURNAL HD
  - LONG TREATMENTS
  - PHOSHATE CONTROL IMPROVED
  - BLOOD PRESSURE CONTROL IMPROVED
  - ALBUMIN IMPROVED
  - HOME THERAPY
- DAILY SHORT HD
  - SHORT TREATMENTS
  - PHOSPHATE CONTROL NOT IMPROVED
  - BLOOD PRESSURE CONTROL IMPROVED
  - ALBUMIN IMPROVED
  - HOME OR IN-CENTER THERAPY

PRINCIPLE BEHIND THE USE OF STANDARD Kt/V

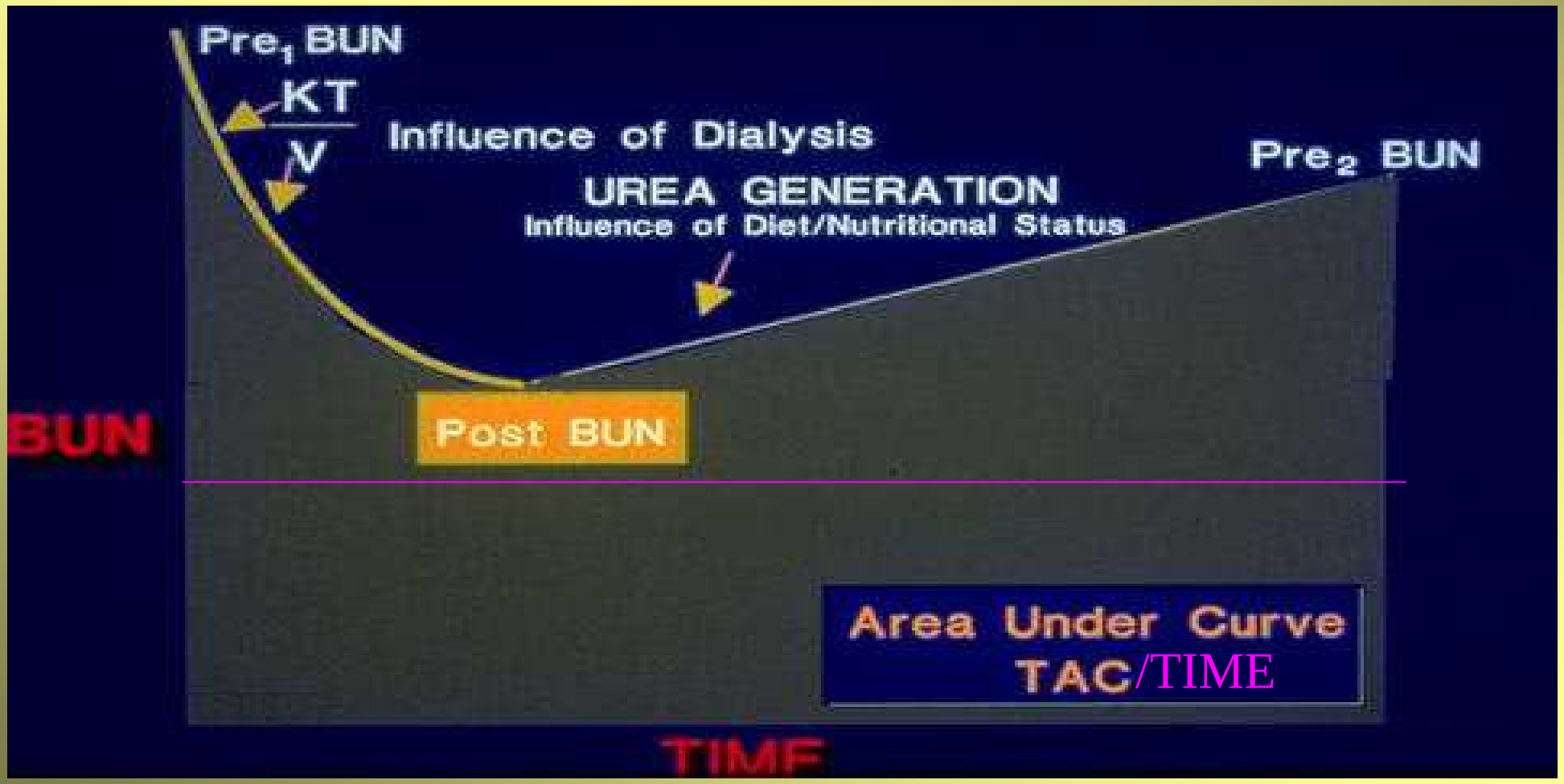
- **UREA IS REMOVED IN A MORE EFFICIENT MANNER AT THE SAME WEEKLY KT/V AS YOU INCREASE DIALYSIS FREQUENCY.**

- **REMOVAL OF LESS DIFFUSIBLE SOLUTES IS EVEN MORE EFFICIENT AT THE SAME WEEKLY KT/V.**

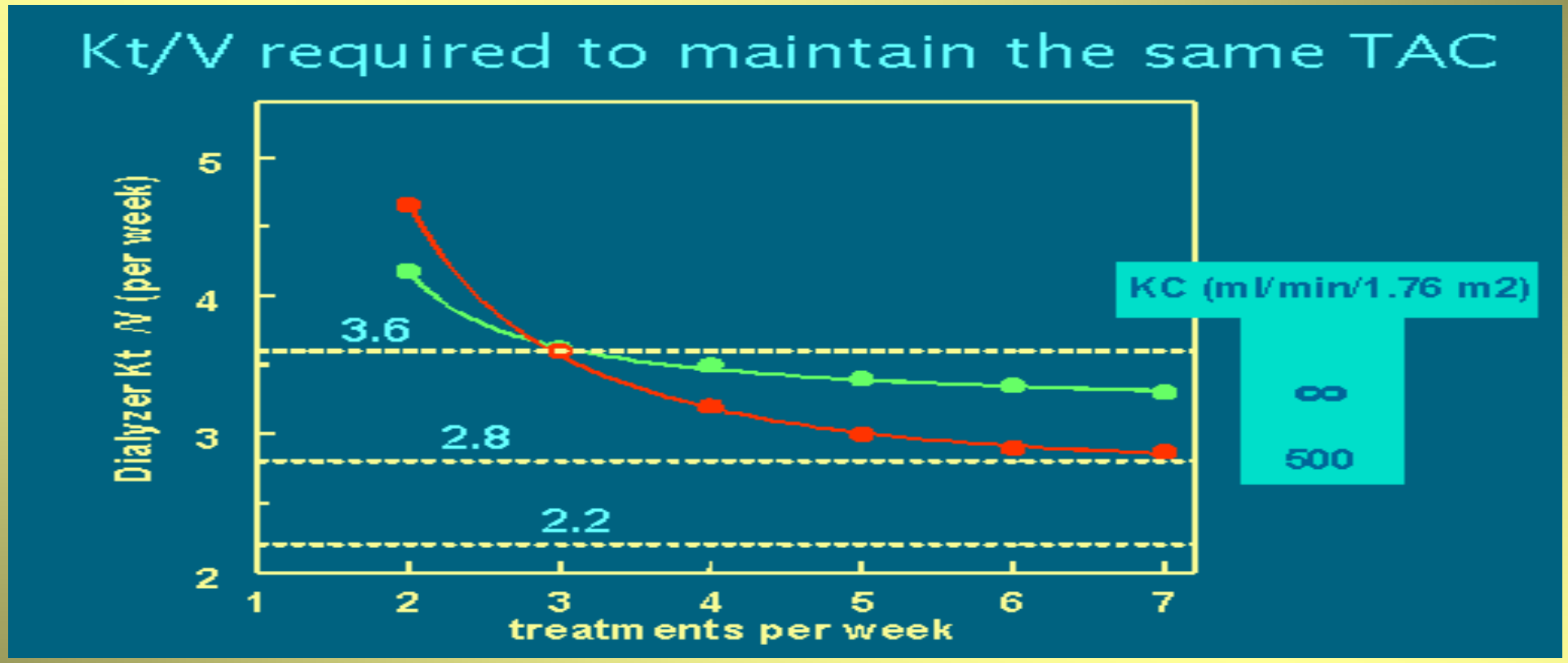
STATUS OF DAILY DIALYSIS

- NO PROSPECTIVE STUDIES OF INCIDENT PATIENTS
- PATIENT SELECTION IS NOT RANDOM
- PATIENTS NUMBER IN THE 100'S
- NO STANDARDIZATION OF REGIMENS
- NO OUTCOME STUDIES
- NOCTURNAL vs DAILY
- ACCESS FUNCTION NOT COMPROMISED

THE DIALYSIS CYCLE



THE EFFECT OF FREQUENCY ON WEEKLY Kt/V



As you increase the frequency, on the x axis here, and maintain the same time average BUN, the need for dialysis diminishes, the dose of dialysis expressed on a weekly basis is less.

RATIONALE FOR USING THE STANDARD Kt/V

- Predicts the currently accepted minimum standard for continuous urea clearance.
- Predicts the approximate level of native kidney urea clearance requiring dialysis intervention.

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STANDARD Kt/V

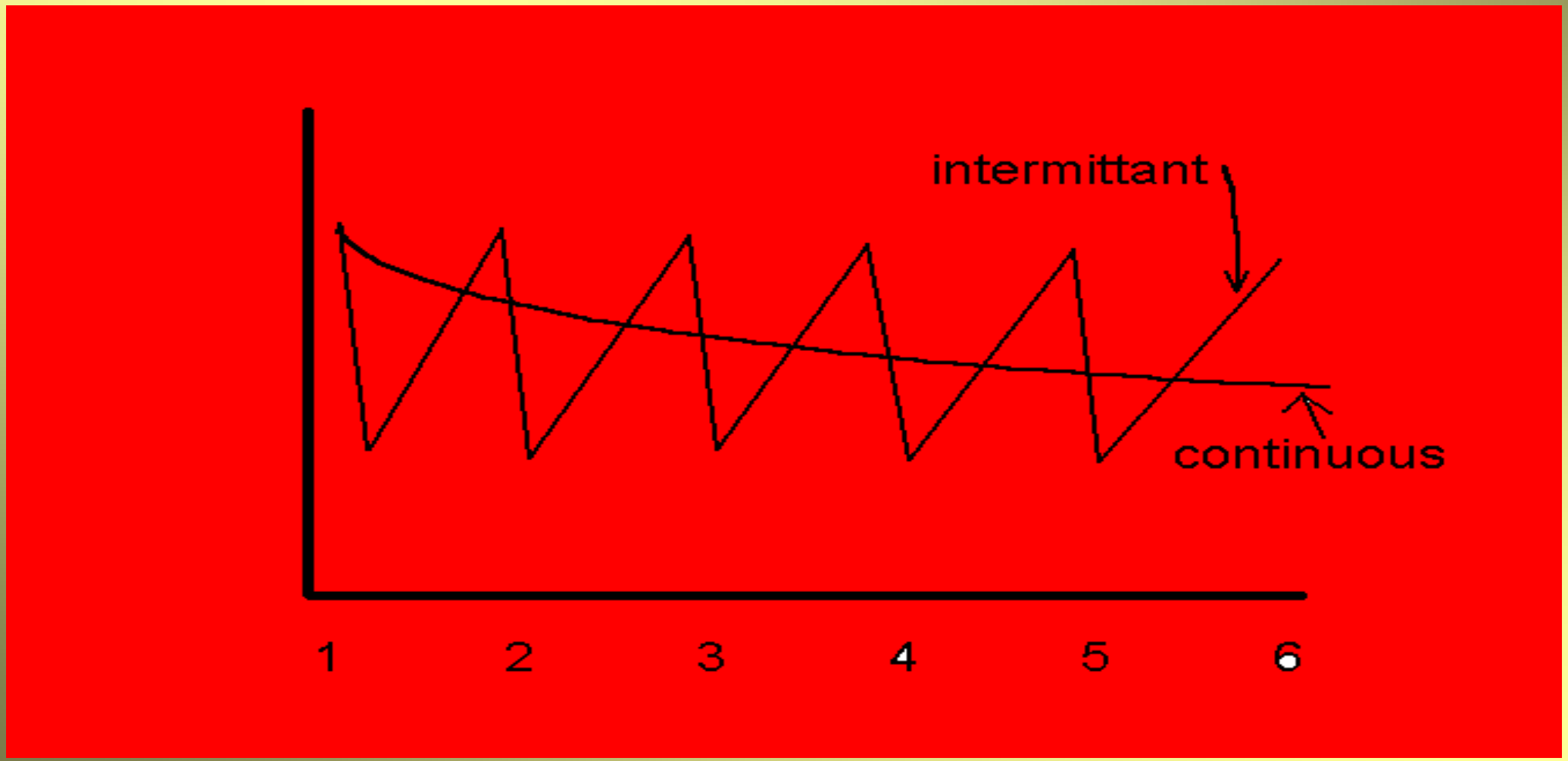
$$\text{Standard Kt/V} = \frac{\text{continuous removal rate}}{\text{average peak concentration}}$$

In a steady state, removal is equal to generation (G).

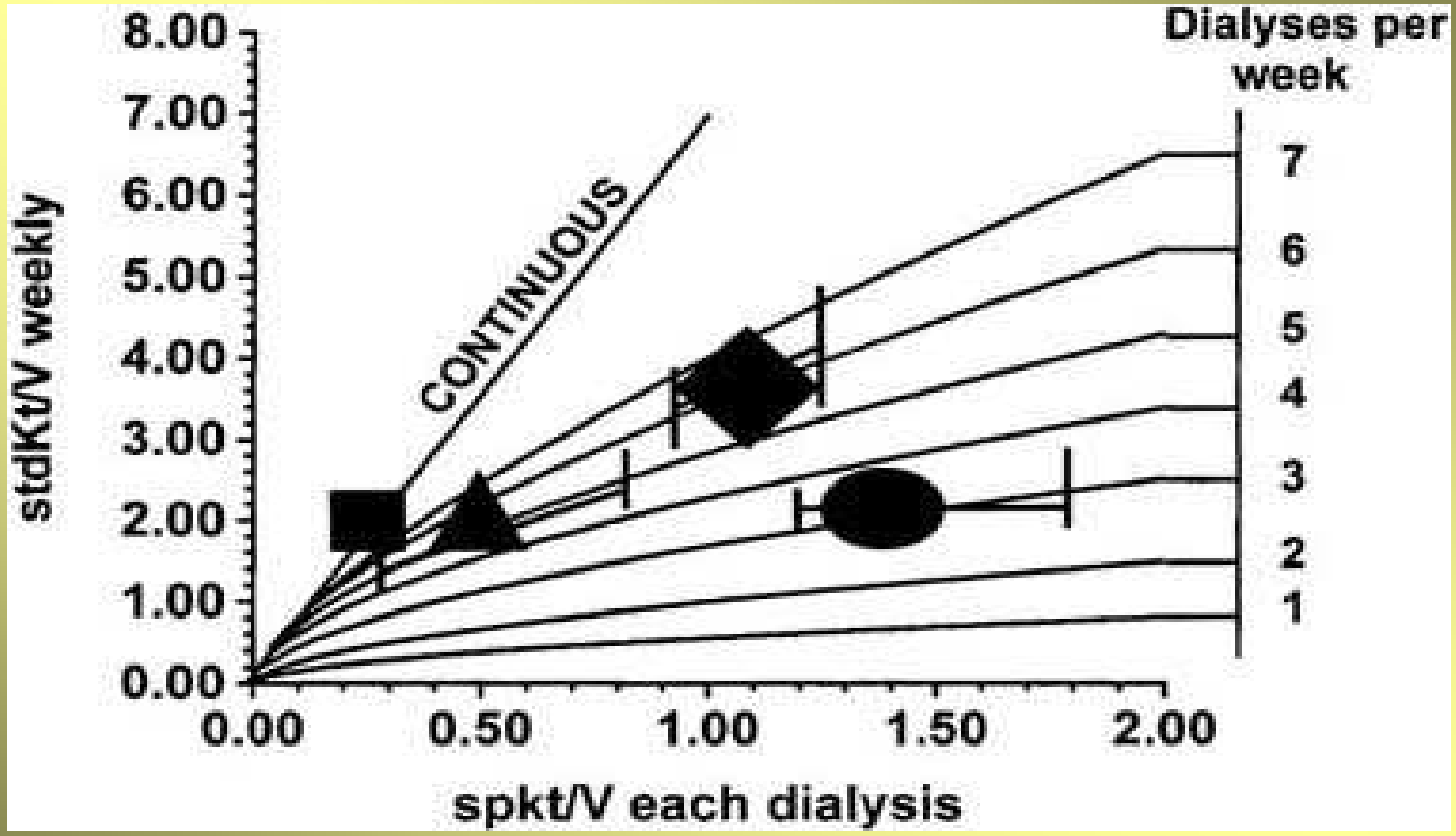
$$\text{Standard Kt/V} = \frac{G}{\text{average peak concentration}}$$

FOR A CONTINUOUS THERAPY, PEAK=MEAN

CONTINUOUS VS INTERMITTENT THERAPY



STANDARD WEEKLY Kt/V MODEL



-CAPD -IHD -SDHD -NHHD

RELATIONSHIP BETWEEN WEEKLY AND STANDARD Kt/V

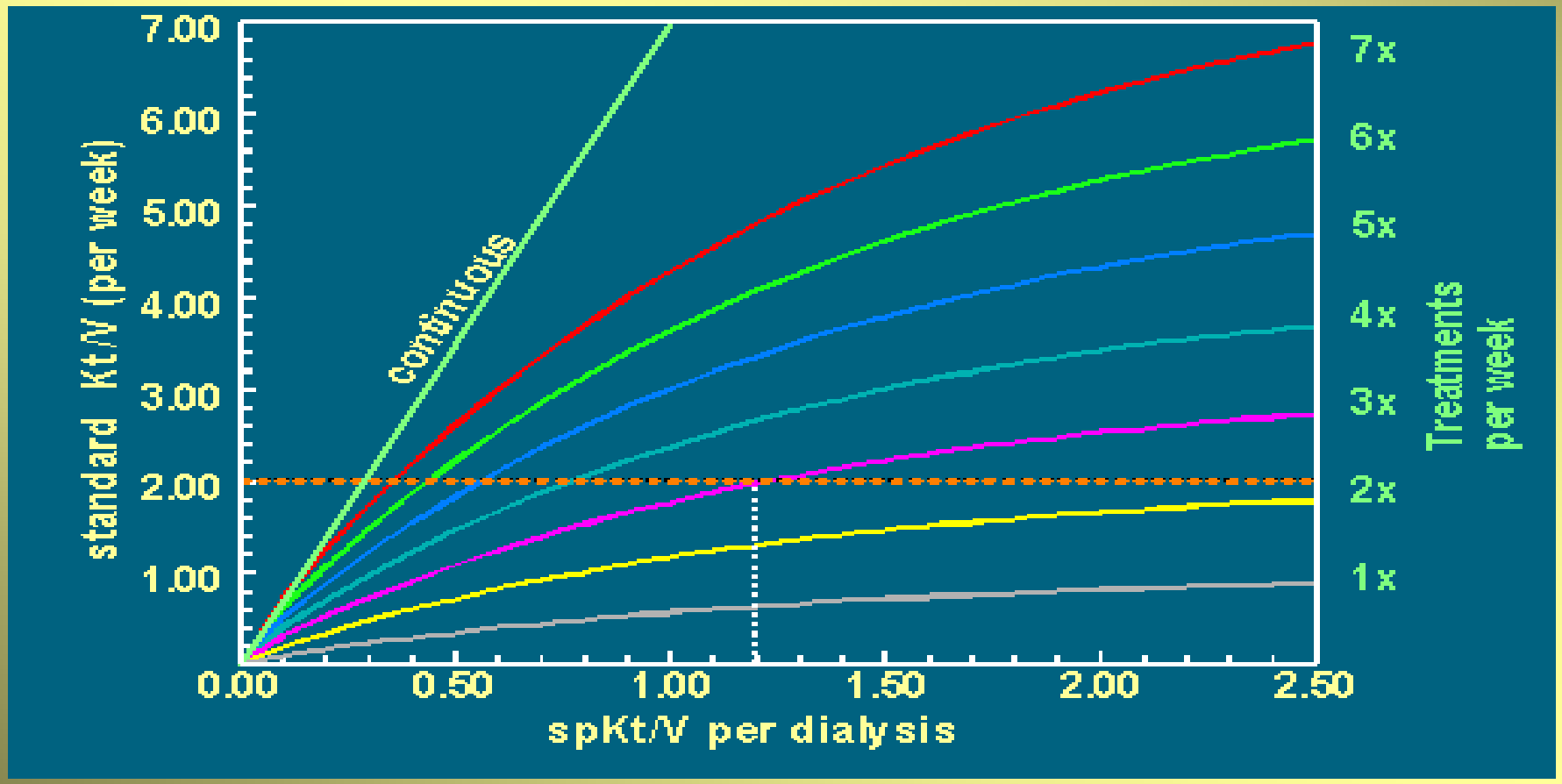
MODALITY	WEEKLY Kt/V	STANDARD Kt/V
SHORT DAILY DIALYSIS	3.5-4.5	2.7-3.2
NOCTURNAL HEMODIALYSIS	5.0-6.0	3.7-4.2

LEYPOLDT, SEMINAR DIAL, 2004

SUMMARY AND CONCLUSIONS

- MULTIPLE LINES OF EVIDENCE SUGGEST DAILY TREATMENTS IMPROVE:
  - ADEQUACY
  - BLOOD PRESSURE CONTROL
  - HOSPITALIZTION RATE
  - NUTRITION
- TRIALS OF THE MODALITIES ARE REQUIRED
- NOCTURNAL HD NEEDS TO BE INCLUDED IN SUCH TRIALS
  - LACSON AND DIAZ BUXO:NHD FIRST, DHD SUBSEQUENTLY **AM J KIDNEY DISEASE 2001; 38:225-230**

STANDARD Kt/V: A CONTINUOUS CLEARANCE EQUIVALENT



DEPNER

PLACES TO GO NEXT

DAILY/NOCTURNAL TREATMENT REGIMENS

THE REAL KEY TREATMENT VARIABLE

$$\frac{MD \times t}{COMORBIDITY}$$

AFTER DR. C RONCO

THE EYE OF GOD