Method and duration of hemodialysis

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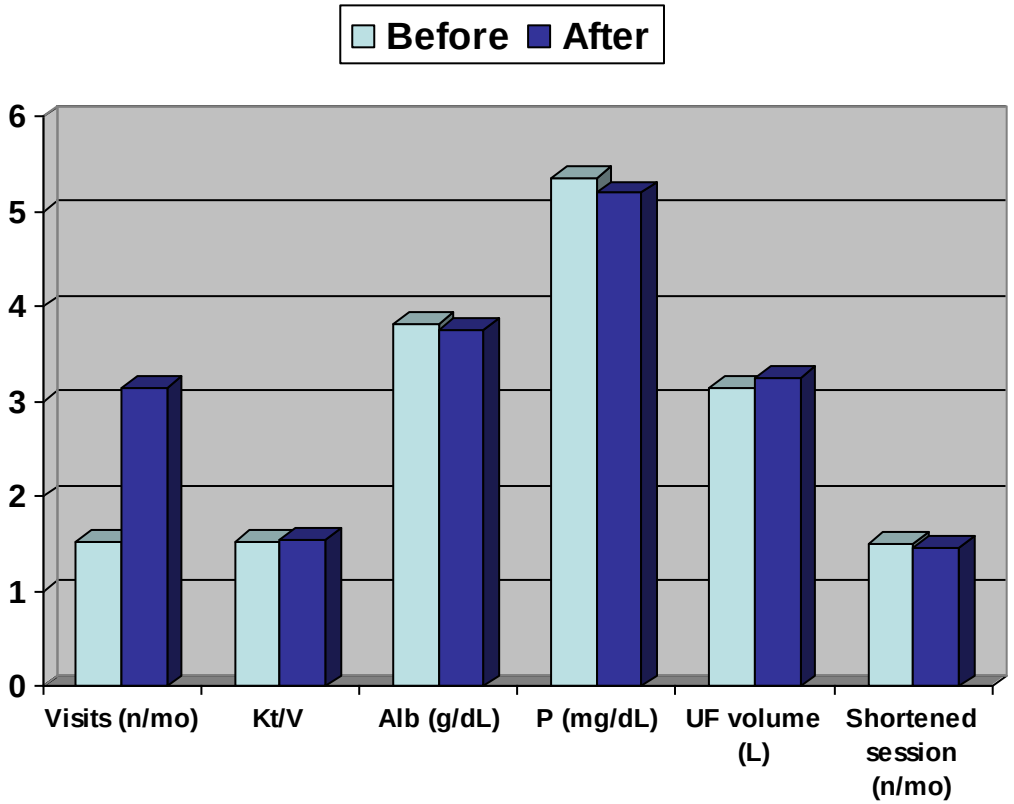
How to improve outcomes in hemodialysis

- After a change in payment policy in the US, number of nephrologist visits per month markedly increases in HD pts
- Results: In the comparison of 12 months before and 7 months after,



- They concluded that **"no clinically important change in surrogate markers despite doubling of nephrologist visit number per month"**

Mentari EK, Am J Kidney Dis 2005, 46: 621-7

Do we really have efficient tools to improve outcomes in hemodialysis ?

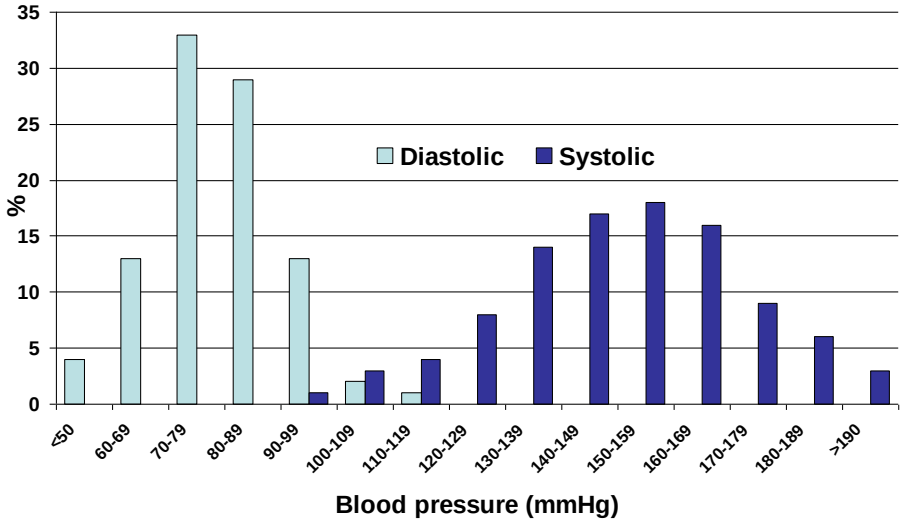
- ACE-I: No survival benefit – FOSIDIAL
- Statins: No survival benefit – 4D, AURORA
- Non-Ca based PO_4-binders: No better PO_4 control, no survival benefit – CARE, D-COR
- Erythropoietin: Good or bad ? – CHOIR, CREATE
- Folic acid: No survival benefit – HOST
- High flux membrane, high blood flow: No survival benefit – HEMO (advantage only in some subgroups, MPO)
- Ultra-pure dialysate: Unknown
- Hemodiafiltration: Unknown

Any missing ones ?

- MORE INTENSIVE DIALYSIS
- SALT RESTRICTION & VOLUME CONTROL

SALT RESTRICTION & VOLUME CONTROL

50-90% of dialysis patients are hypertensive despite several anti-hypertensive medications

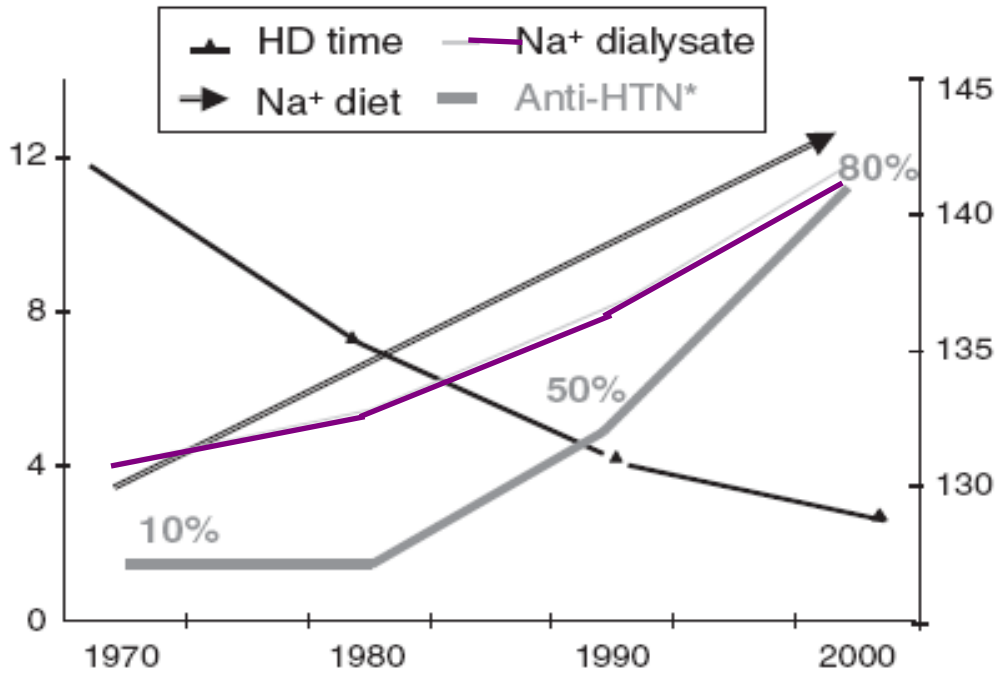


Mailloux LU, Am J Kidney Dis 1998

Whereas almost no hypertension in early years of HD

- Blood pressure was normal in 91% of patients without anti-hypertensive medications in 1960s (9 reports)

What has changed in the last 30 years ?



* Anti-HTN= % of patients using antihypertensive medications

- **Duration of HD sessions ↓**
- **Dialysate Na concentration ↑**
- **Dietary Na intake ↑**
- Use of anti-HT medication ↑
- Blood pressure ↑

Charra B, Hemodial Int 2007

Salt intake-interdialytic weight gain and mortality

- Higher IDWG & overall mortality in diabetics

Kimmel PL, Kidney Int 2000

- Higher left atrial volume & mortality in HD patients

Tripepi G, J Hypertens 2006

- Higher UF rate & overall mortality

Movilli E, Nephrol Dial Transplant 2007

- Higher IDWG & CV and overall mortality

Kalantar-Zadeh K, Circulation 2009

- Predictive role of LA volume for mortality is dependent on IDWG

Ozdogan O, Am Heart J 2010

Implementation of “volume control strategy” in Ege University Dialysis Center

Before 1993,

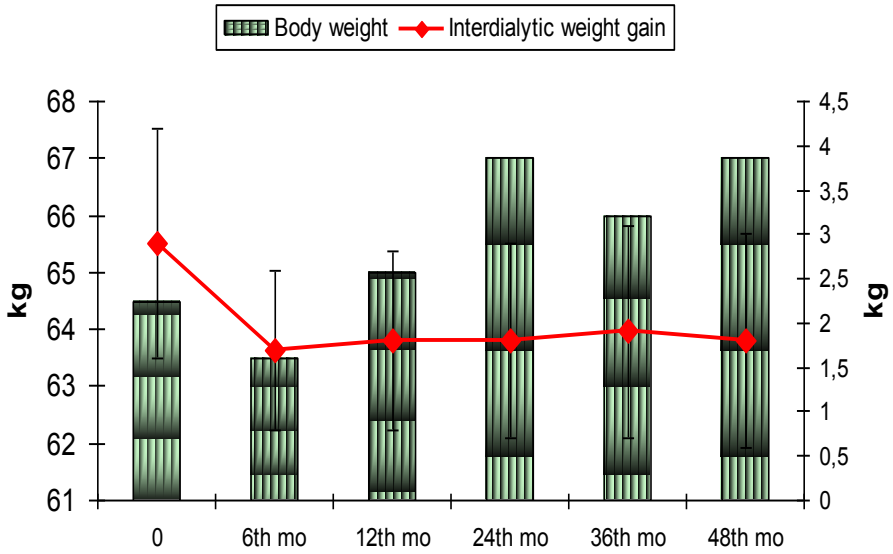
- 65% of patients were using anti-hypertensive medications
- Interdialytic weight gain over 3 kg
- Heart failure frequent, cardiothoracic index above 0.5 in 75%
- Intradialytic hypotension and cramps frequent
- Some patients diagnosed as uremic cardiomyopathy
- Many patients requested to stop earlier dialysis because of hypotension and cramps in the last hours of dialysis

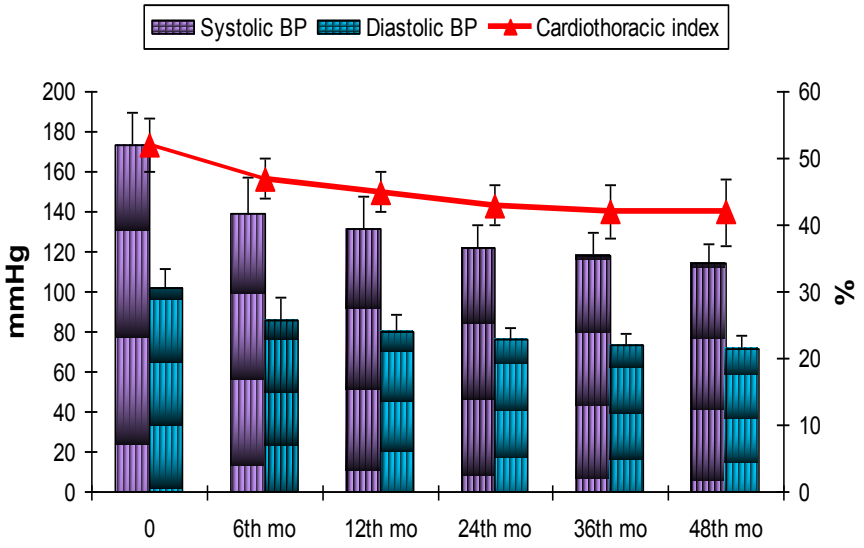
Volume control policy implemented by Dr Evert J Dorhout Mees in Ege University

- 12 - 15 hours HD per week
- Dialysate Na concentration 135-138 mmol/L
- Discontinuation of anti-hypertensive medications
- **Strict dietary salt restriction** (as lower as possible with aim of 50 mmol/day) **to reduce interdialytic weight gain below 2 kg**
- Recommendation for fluid intake: **“not to drink more or less than thirst feeling indicated”**

- **Insistent UF for dry weight reduction until blood pressure becomes below 140/90 mm Hg and cardiothoracic index below 0.50** (CTi: calculated as the largest inner diameter of the rib cage divided by the largest diameter of the heart shadow on the chest X-ray)
- If needed, temporarily additional UF sessions
- If in doubt for renin-dependent hypertension, if BP becomes normal after a test dose of 25 mg PO captopril, start an ACE-I

The results of switch from conventional approach to volume control strategy





- **67 hypertensive HD patients**, stop anti-hypertensive medications, insistent UF, dietary salt restriction; **4 years follow-up**
- At the end, only 4% in need of anti-HT medication
- No edema, no heart failure
- Intradialytic hypotension and cramps decreased
- Hemoglobin and serum albumin levels increased

Ozkahya M, Am J Kidney Dis 1999

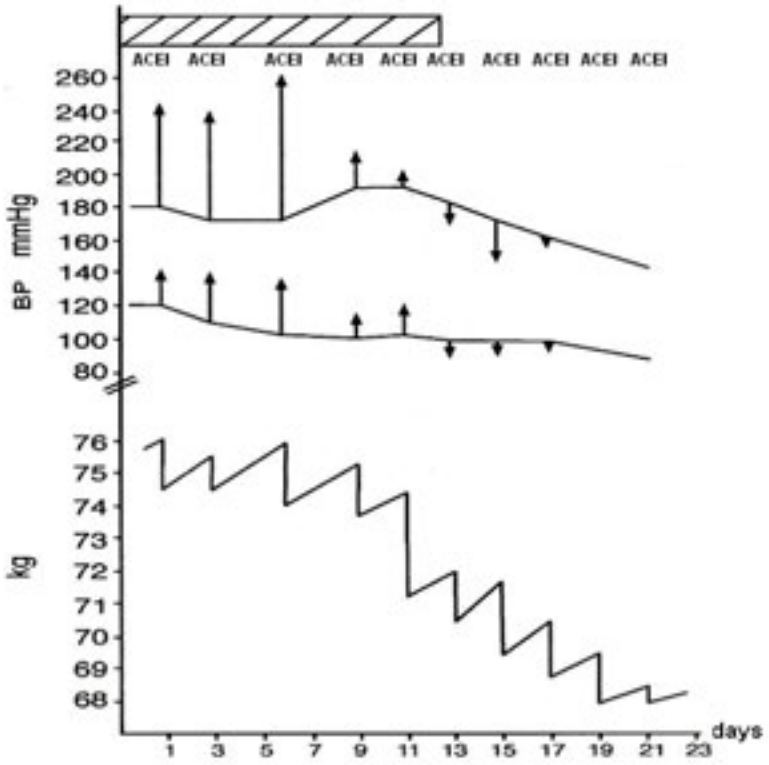
Regression of left ventricular hypertrophy with volume control

- Two echocardiographies in 15 prevalent HD patients with a mean interval of 37 11 months after implementation of volume control policy

	First	Second
• Systolic BP (mmHg)	136 11	101 14
• Diastolic BP (mmHg)	119 8	82 12
• CTi	0.48 0.03	0.43 0.04
• Left atrial diameter (mm/m^2)	22.5 3.1	19.9 4.4
• **LV mass index (g/m^2)**	**175 60**	**105 11**

Ozkahya M, Nephrol Dial Transplant 1998

Treatment of paradoxical hypertension by ultrafiltration



- Seven patients with paradoxical hypertension who were not responsive to medications (no edema but cardiac dilatation)

- After reduction of body weight below a threshold value (6.7 3.0 kg), paradoxical BP increases during HD disappeared

- CTi decreased; EF increased; valvular regurgitations regressed; serum albumin increased

Cirit M, Nephrol Dial Transplant 1998

Disappearance of mitral and tricuspid regurgitation by ultrafiltration in HD patients

- 21 patients with valvular insufficiency (no sign of heart failure but cardiomegaly)
- Dry weight reduction with slow ultrafiltration in long term (months) (mean decrease in body-weight 5.4 ± 2.7 kg)

	Before UF	After UF
Mitral regurgitation (n)	**20** →	**7**
Tricuspid regurgitation (n)	**18** →	**4**
Mean arterial pressure (mmHg)	126 ± 15	95 ± 11
Cardio-thoracic index (%)	57	47
Mitral annular diameter (mm/m^2)	23	19
Left ventricul systolic diameter (mm/m$^{2)}$	25 ± 5	21 ± 5
Left ventricul end-diastolic diameter (mm/m$^{2)}$	31 ± 5	27 ± 5

Cirit M, Nephrol Dial Transplant 1998

Hypervolemic hemodialysis patients with low ejection fraction

- 12 prevalent HD patients with heart failure who had ejection fraction ≤45% (mean EF 31 9%) (mean age 43 9 years)

- 7 of 12 were diabetics

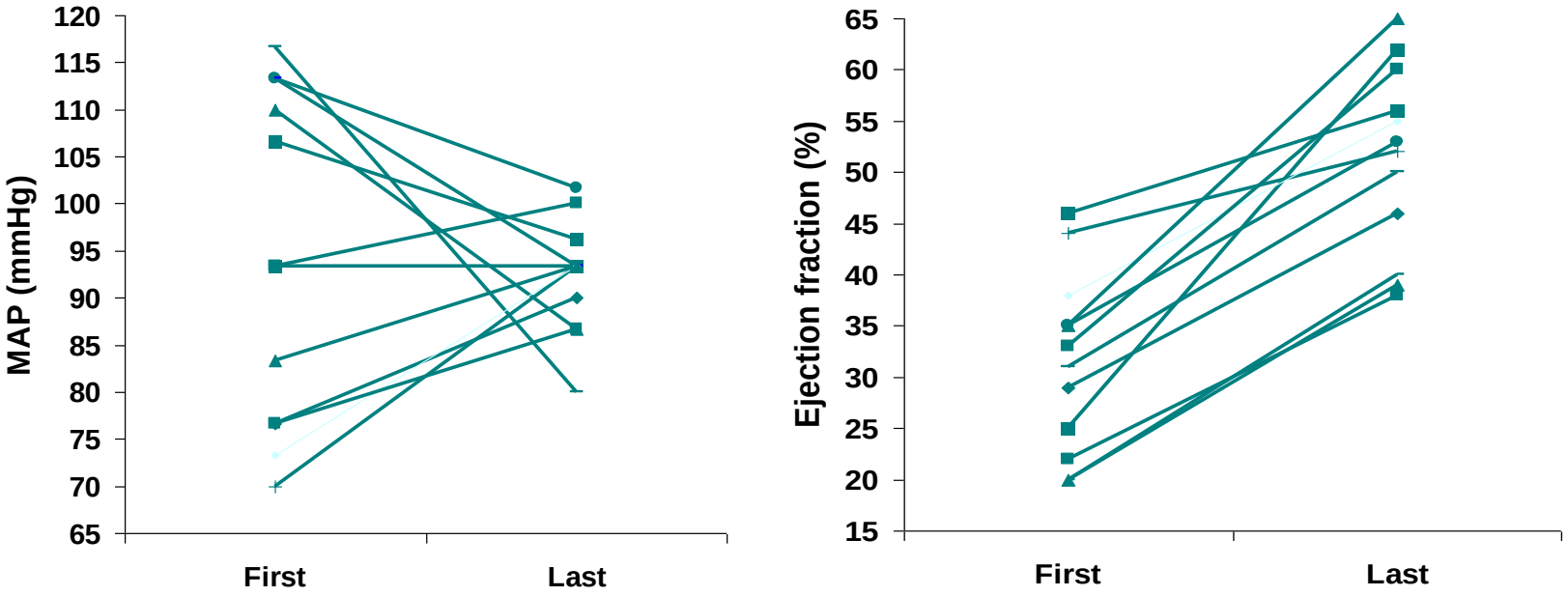
- BP low in half of them, valvular regurgitation present in all cases

Treatment

- Prolonged sessions or additional isolated UF sessions
- Slow UF (0.2–0.5 L/h)
- Mean decrease in body weight 12 10 kg (corresponding to 19% of baseline body weight) in 20-120 days

Toz H, Hemodial Int 2007

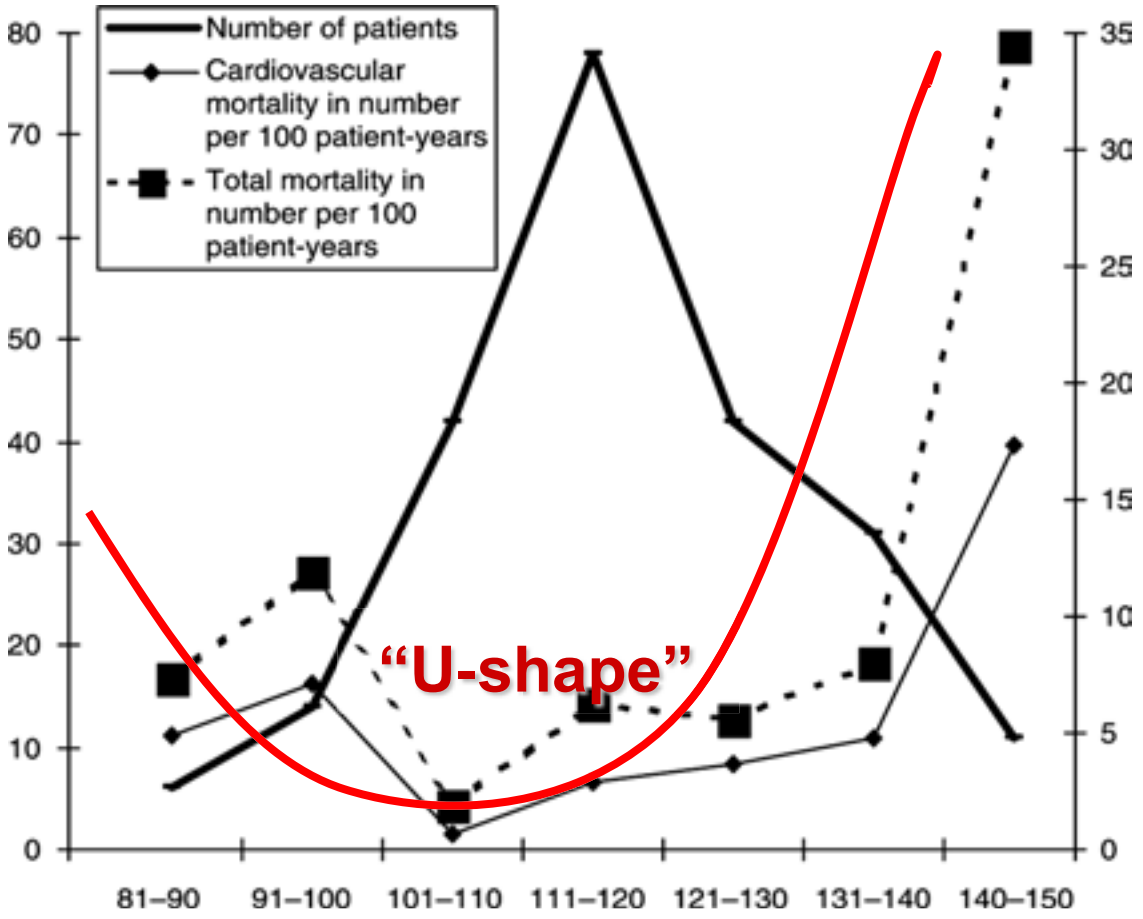
Significant improvement of low ejection fraction by ultrafiltration



- Heart failure findings disappeared in all patients
- **Ejection fraction increased in all, from 31 9% to 50 9%**
- BP increased in cases with low BP at baseline
- Valvular regurgitations disappeared or improved

Toz H, Hemodial Int 2007

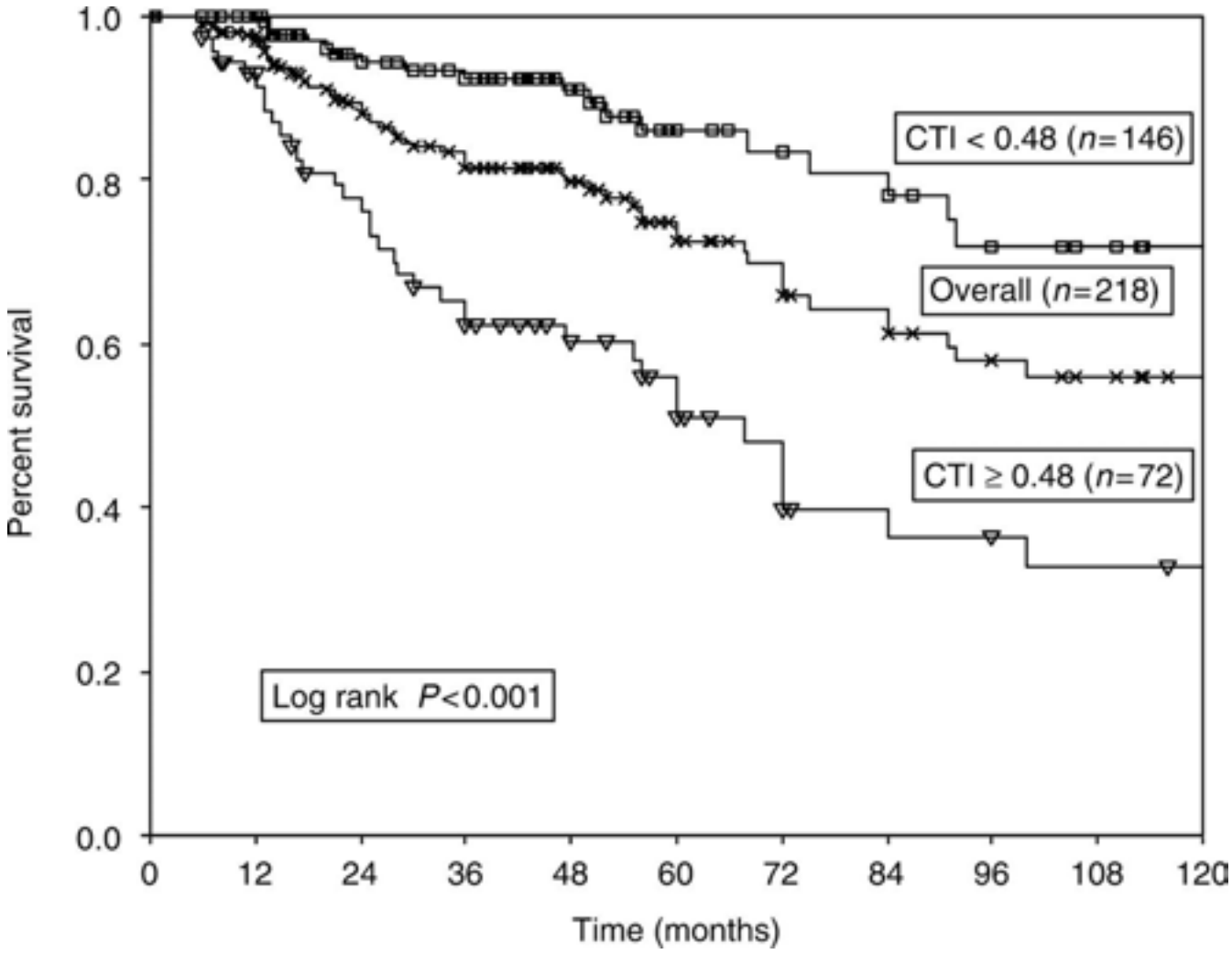
Relationship between blood pressure and mortality in patients treated with volume control policy



- Patients with SBP between 101-110 mmHg had lowest mortality rate

Ozkahya M, et al Nephrol Dial Transplant 2006

Relationship between overhydration determined by chest x-ray and survival



Ozkahya M, Nephrol Dial Transplant 2006

Independent predictors of mortality

	Risk Ratio	95% CI	*P*-value
Age at start of HD			
<45 years	Reference		
≥45 years	**5.01**	**1.98–12.67**	**0.001**
SBP in follow up (mmHg)			
100–130	Reference		
<100	1.37	0.57–3.28	0.472
130–140	1.90	0.83–4.35	0.125
>140	**10.33**	**3.87–27.60**	**<0.001**
CTI in follow-up			
<0.48	Reference		
≥ 0.48	**3.84**	**2.05–7.18**	**<0.001**

Ozkahya M, et al Nephrol Dial Transplant 2006

A cross-sectional study

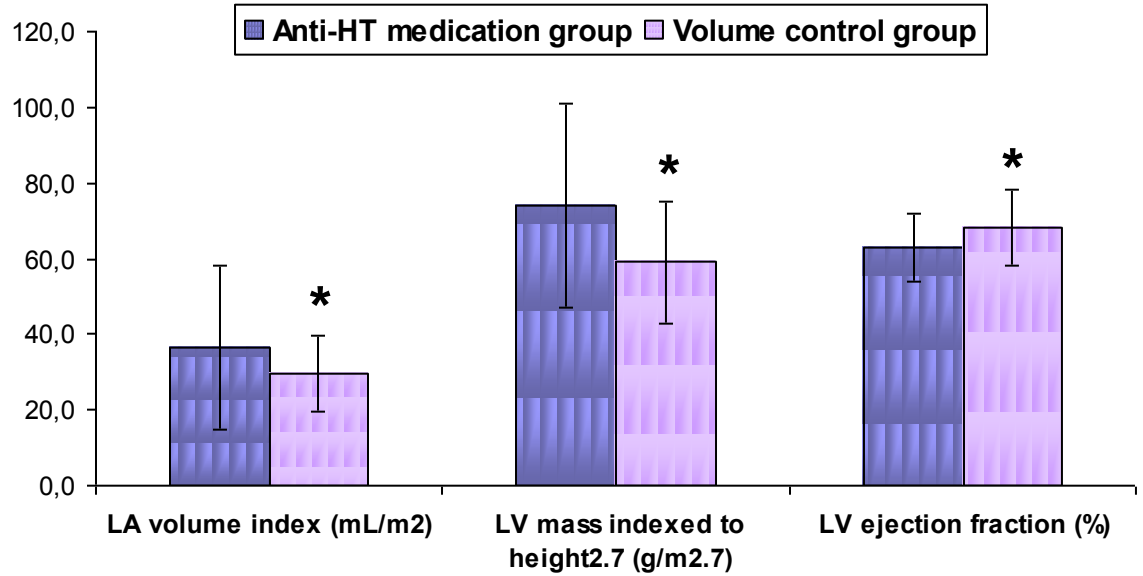
- Comparison of the two dialysis centers regarding BP and cardiac geometry and functions
- Center A practiced volume control strategy, Center B anti-hypertensive medication - based strategy

	Center A (n: 190)	Center B (n: 204)	p
Anti-hypertensive use (%)	7	42	<0.01
IDWG (kg)	2.29 0.83	3.31 1.12	<0.001
Systolic BP (mmHg)	126 15	126 21	ns
Diastolic BP (mmHg)	75 12	76 11	ns
Intradialytic hypotension episode per 100 sessions	11	27	<0.01

• No difference regarding age, sex, diabetes, HD duration, dialysate composition

Kayikcioglu M, Nephrol Dial Transplant 2009

Cardiac aspect



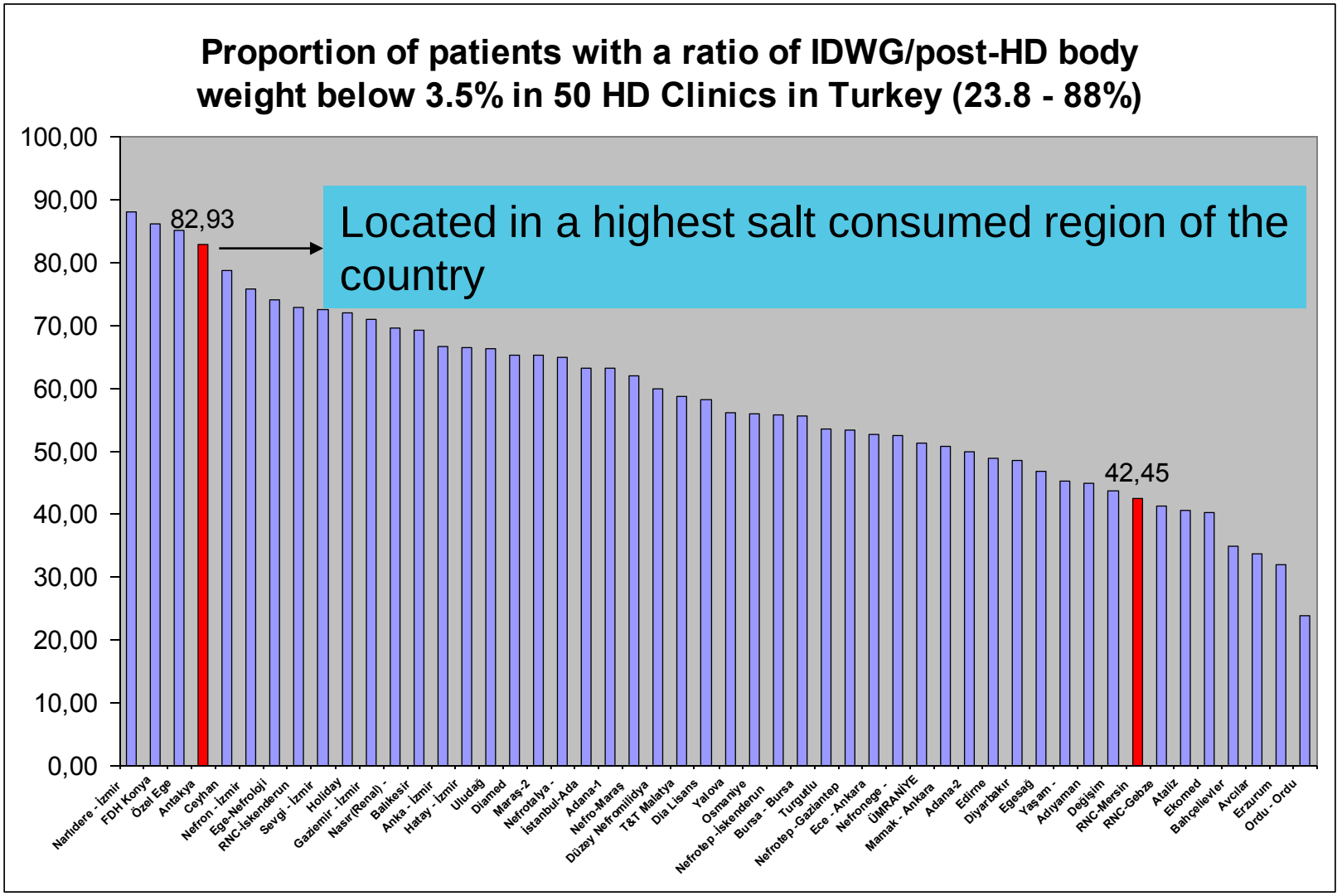
* p<0.001

- Despite similar BP control, volume control strategy is associated with
  - lesser cardiac dilatation
  - lower left ventricular mass
  - better preserved systolic and diastolic functions

How to achieve successfull salt restriction ?

- **Are physicians convinced** on the followings ?
  - Salt intake leads to irresistible thirst and fluid intake
  - **Interdialytic weight gain is due to salt intake not water intake** (predialysis serum Na <130 mmol/L in only 0.3% of 7179 HD patients with normoglycemia)
  - **Intradialytic hypotension does not indicate that dry weight has been reached but an ultrafiltration rate higher than refill rate**
  - **Do not forget that nurses who are the key persons for success must be convinced**

Large differences of IDWG in the same country: Determinant role of dedicated health professionals



Patients and their families

- How can we help our patients for this “**addiction**” ?
  - To tell these facts **again and again**
  - To talk their **family members**
  - To explain that **adaptation to salt-free diet takes approximately one month** (if he/she does not consume salty food in this period, then salt sensing of his/her tongue will be changed)
  - To organize **common information and discussion sessions**
  - To provide opportunities for compliant patients to **share their positive experiences with other patients**

Dietary recommendations

- In our country-our condition, we suggest:
  - **No salt** during cooking and eating
  - Salt-free bread
  - Diminish to consume processed food
- If it is an obligation to consume **processed food**,
  - Solution is **more difficult**
  - To find / prefer salt-poor products
  - **GOVERNMENTS ARE EXPECTED TO GRADUALLY RESTRICT SALT CONTENT OF FOODS**

Conclusion

- Hypertension can be treated by volume control policy in patients treated with conventional hemodialysis regimen without anti-hypertensive medications.
- Overhydration even in the absence of hypertension is important and should be treated.
- Dietary salt restriction is essential and it can be achieved.

DURATION OF HEMODIALYSIS

History

- **In the early era of chronic dialysis with 20-40 h/week HD**
  - Excellent BP control, rare intradialytic BP drop
  - Satisfactory nutritional status
  - Sufficient RBC production
  - Nearly full rehabilitation, almost no neuropathy
    - *Ann Intern Med 1967; 67: 1149*
- **Later…**

Short dialysis

- **“Intensive utilisation of a dialysis unit”**
  - From 27 hour/week in 1971 to 12 hour/week in 1972
  - *Successful adaptation, s*imilar biochemical results “***except phosphate***”

Cambi V, Proc Eur Dial Transplant Assoc 1973; 10: 342

- Short dialysis schedules – “**Finally ready to become a routine ?”**

Proc Eur Dial Transplant Assoc 1973; 10: 342-8

  - Although **“*bilateral nephrectomy is required* in 2 cases for BP control!”**

- *Why dialyze more than 6 hours a week?*

  Rotellar E, ASAIO Trans 1985; 31:538

- How long should it be ? Need for a scale ?

- ***"God sent Kt/V for short hemodialysis"***

  Twardowski ZJ, University of Missouri

- **Despite presence of hypertension, hyperphosphatemia, anemia, *"dialysis is adequate if Kt/V is above …"***

- **And now we face:**

Problems in patients treated with three times weekly four-hour hemodialysis

- **High mortality and morbidity, low QOL**
- **Numerous troubles**
  - *High/low BP, LV hypertrophy, heart failure, arrhythmia*
  - *Anemia, malnutrition, inflammation*
  - *Hyperphosphatemia, vascular calcification*

USRDS, Am J Kidney Dis 2003; 42 (Suppl 5): S103

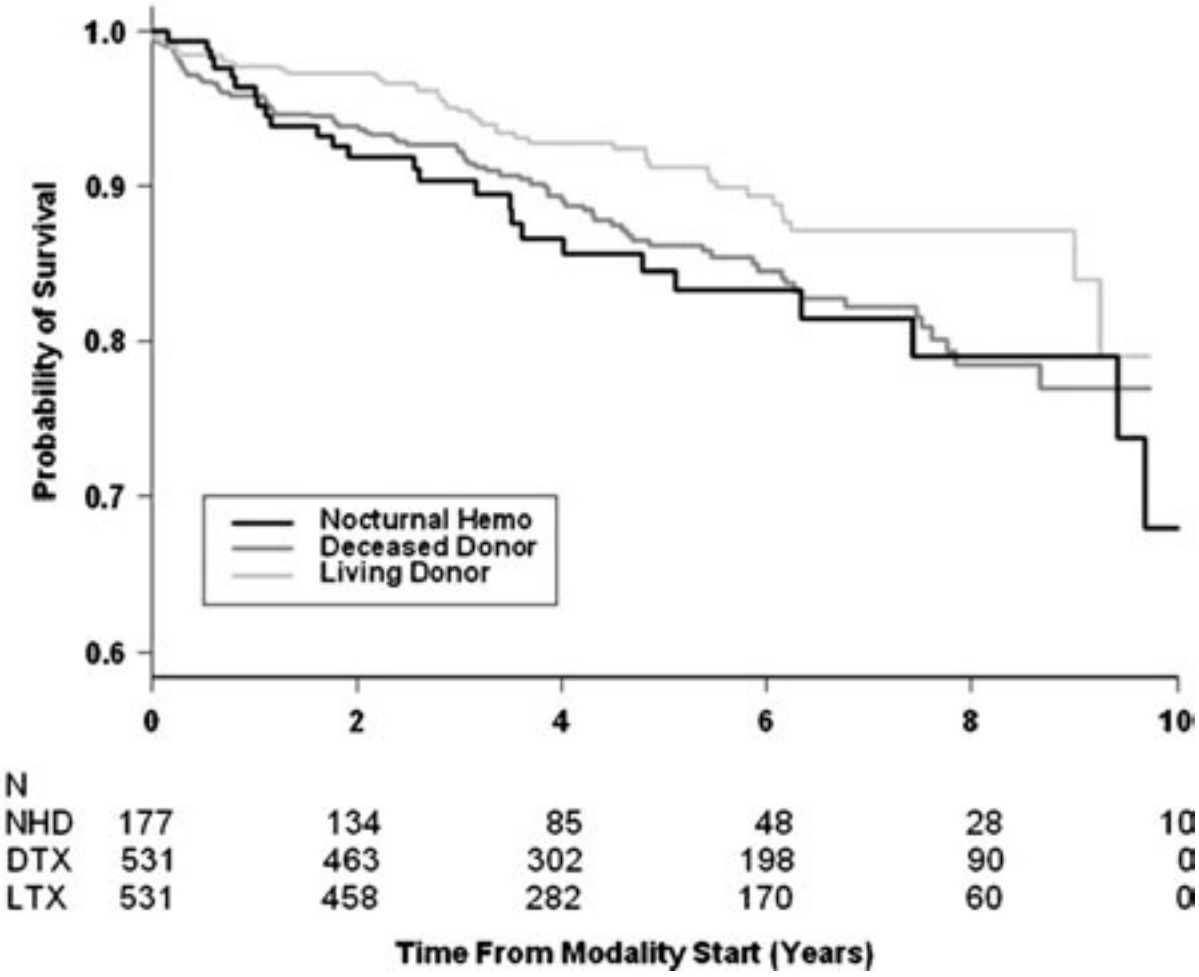
- **Introduction of several medications to solve these problems** *(Epo, P-binders, ACE-I, carniten, Na-modelling, gabapentin, etc)*
- **Extra cost (equal to 1/4 to 1/2 of dialysis cost)**
- **No survival benefit with these medications**

Clinical benefits of intensive HD

	Nocturnal HD	Short daily HD
Blood pressure control	+++	++
Left ventricle hypertrophy	+++	++
LV systolic function	+++	Not shown
Arterial compliance	+++	Not shown
Sleep apnea	Correction	Not shown
Cardiac autonomic abnormalities	Restoration	Not shown
Phosphate control	+++	Depends on duration
Anemia	++	+
Malnutrition	++	++
Inflammation	CRP and IL-6 ↓	CRP ↓
Cognitive function	+	Not shown
Fertility	++	Not shown

Perl J, Am J Kidney Dis 2009

Survival in NHD similar to cadaveric RTx



Pauly RP, Nephrol Dial Transplant 2009

- Best survival data with three times weekly HD from Tassin: 8-h in-center HD
  - Excellent patient survival (5-year survival 87%)
  - Very few hypertension, good phosphate control, less anemia

Kidney Int 1992; 41: 1286

- No prospective study to compare hemodialysis regimens applied in the past and now

- Frequent Hemodialysis Network randomized trials: conventional HD versus in-center short daily HD and versus home nocturnal HD

Suri RS, Kidney Int 2007

Long Dialysis Study

- Prospective, matched-controlled study to compare 8-h and 4-h in-center HD; follow-up one year

  ClinicalTrials.gov Identifier: NCT00413803

- 224 prevalent conventional HD patients were assigned to 8-h three times weekly in-center nocturnal HD (NHD) and

- 224 age-, sex-, diabetic status-, and HD vintage-matched control cases to 4-h conventional HD (CHD)

- No difference in baseline parameters

	NHD (n: 224)	CHD (n: 224)
▪ **Mean age (years)**	45 ± 12	45 ± 12
▪ **Female**	32%	
▪ **Diabetes**	20%	
▪ **HD vintage (months)**	58 ± 44	58 ± 44
▪ **Duration of HD session** (min)	455 ± 20 *	236 ± 8
▪ **Blood flow** (ml/min)	240 ± 36 *	291 ± 31

Time-averaged data; * p<0.0001

Overall mortality

	NHD	CHD	p
12 month-survival (%)	98.7	93.8	0.009
Death rate (n/100-pt-yr)	1.29	6.03	<0.05

- Multivariate analysis

NHD vs CHD	0.23 (0.06-0.80)	0.02
Age (per 1 year)	1.07 (1.03-1.11)	<0.001

* Adjusted for age, gender, diabetes, and HD duration

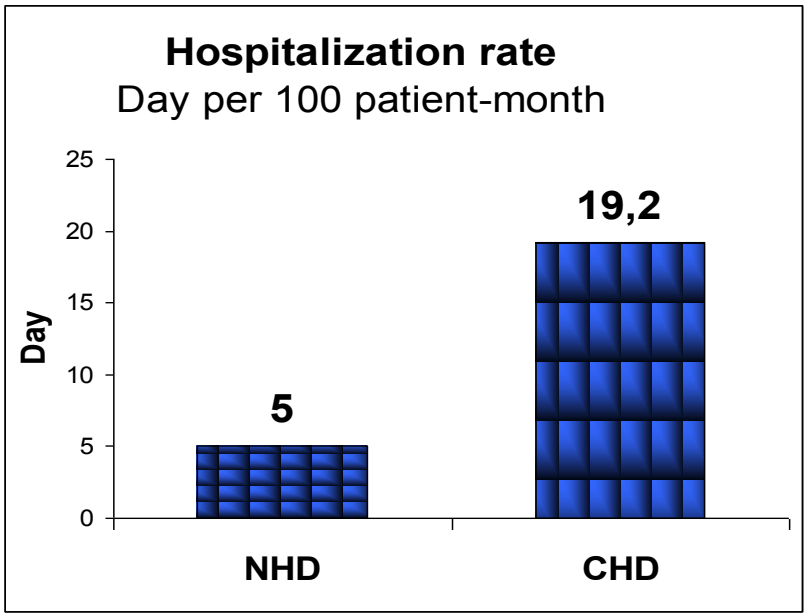
Model Chi-square:24.3, p<0.001

Time-averaged laboratory values

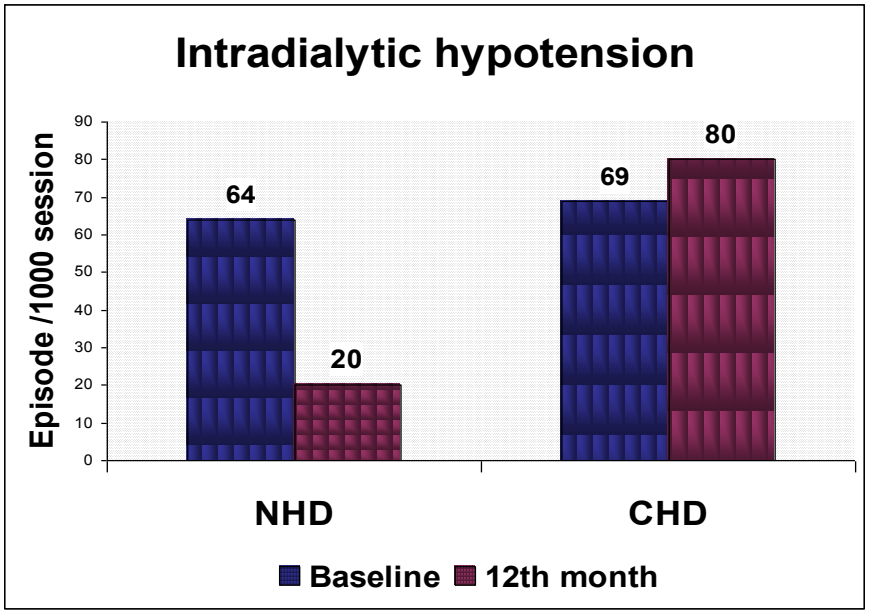
	NHD		CHD		p value
spKt/V	1.86	0.33	1.38	0.25	<0.001
Pre-dialysis K (mEq/L)	5.00	0.55	5.11	0.55	0.042
Phosphate (mg/dl)	3.89	1.20	4.95	1.14	<0.001
CaxP product (mg^2/dl^2)	35.0	11.3	43.6	10.9	<0.001
Albumin (g/dl)	4.03	0.25	3.93	0.29	<0.001
Total cholesterol (mg/dl)	174	42	166	40	0.040
Triglyceride (mg/dl)	210	137	181	107	0.021
Hemoglobin (g/dl)	11.8	1.4	11.5	1.6	0.030
Ferritin (ng/ml)	788	618	921	728	0.045
Transferrin saturation (%)	27	14	32	16	0.004
Bicarbonate (mEq/L)	23.8	1.7	23.2	1.8	<0.001
hsCRP (mg/dl)	1.41	1.38	1.70	1.74	0.055

- **Higher Kt/V, albumin, Hb, HCO_3, triglyceride, total cholesterol in NHD**
- **Lower K, PO_4, ferritin, transferrin saturation in NHD**

Hospitalization

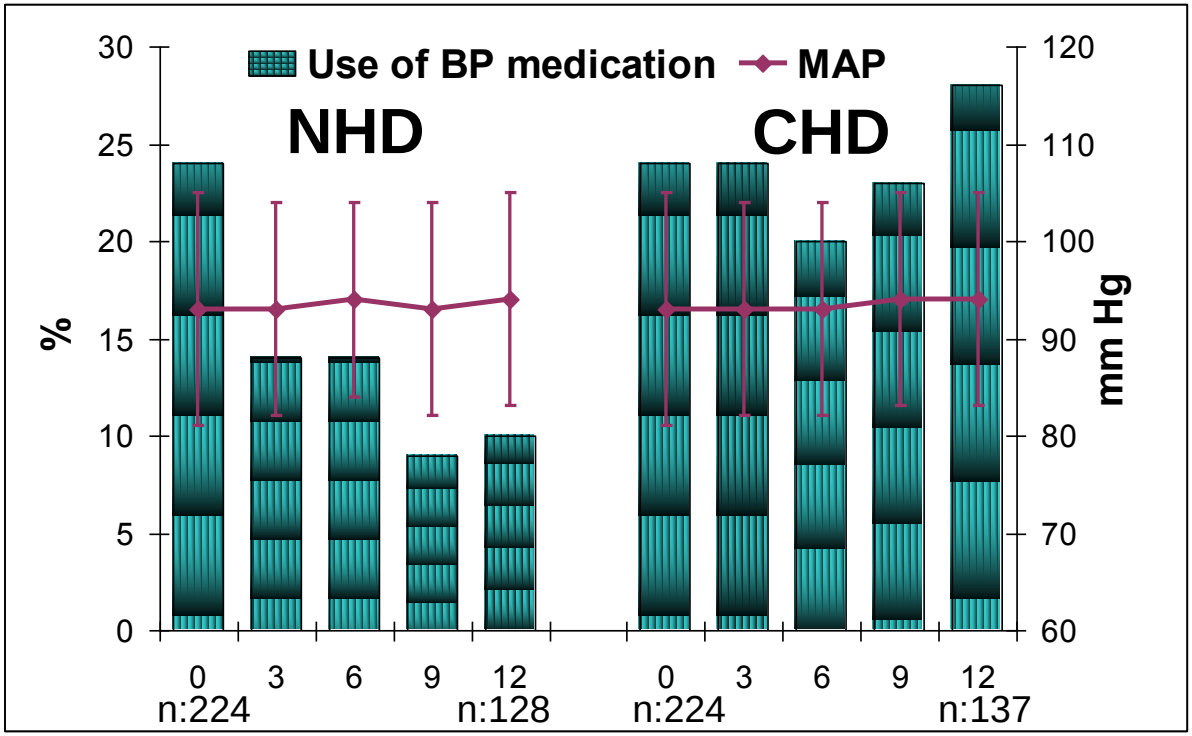


Intradialytic hypotension



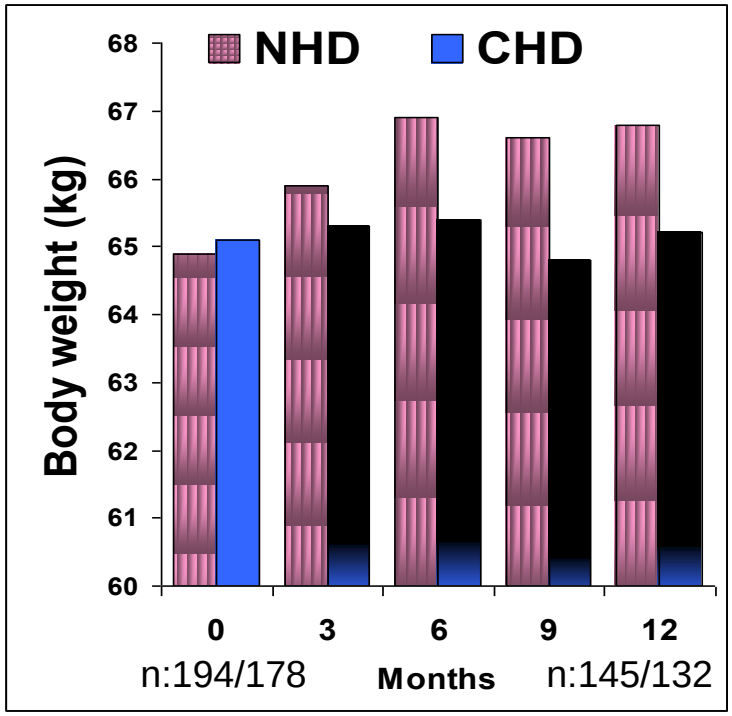
- 73% less all-cause hospitalization rate in the NHD arm ($p<0.05$)
- Marked decrease in intradialytic hypotension episodes in the NHD group ($p<0.01$)

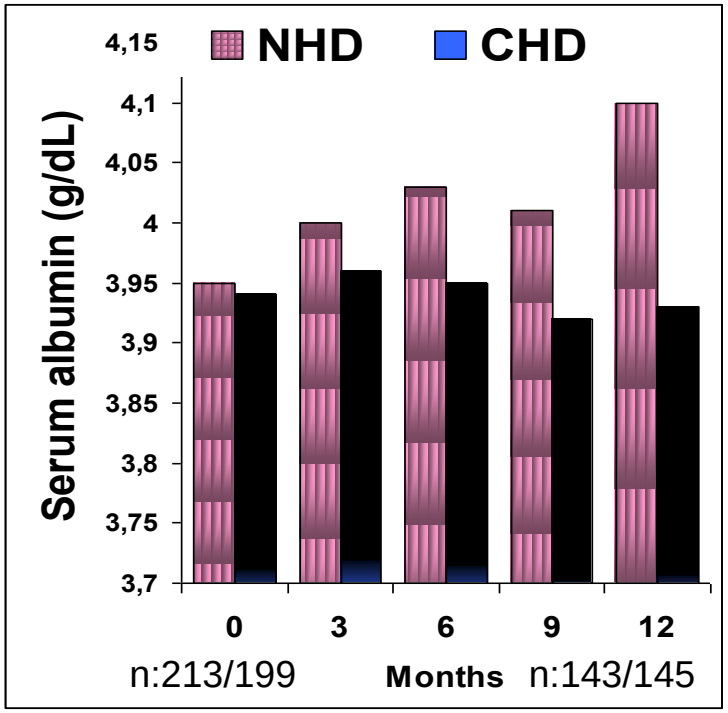
Blood pressure control



- No change in mean arterial BP in both arms
- Requirement of anti-hypertensive medication decreased from 24% to 8% in the NHD group

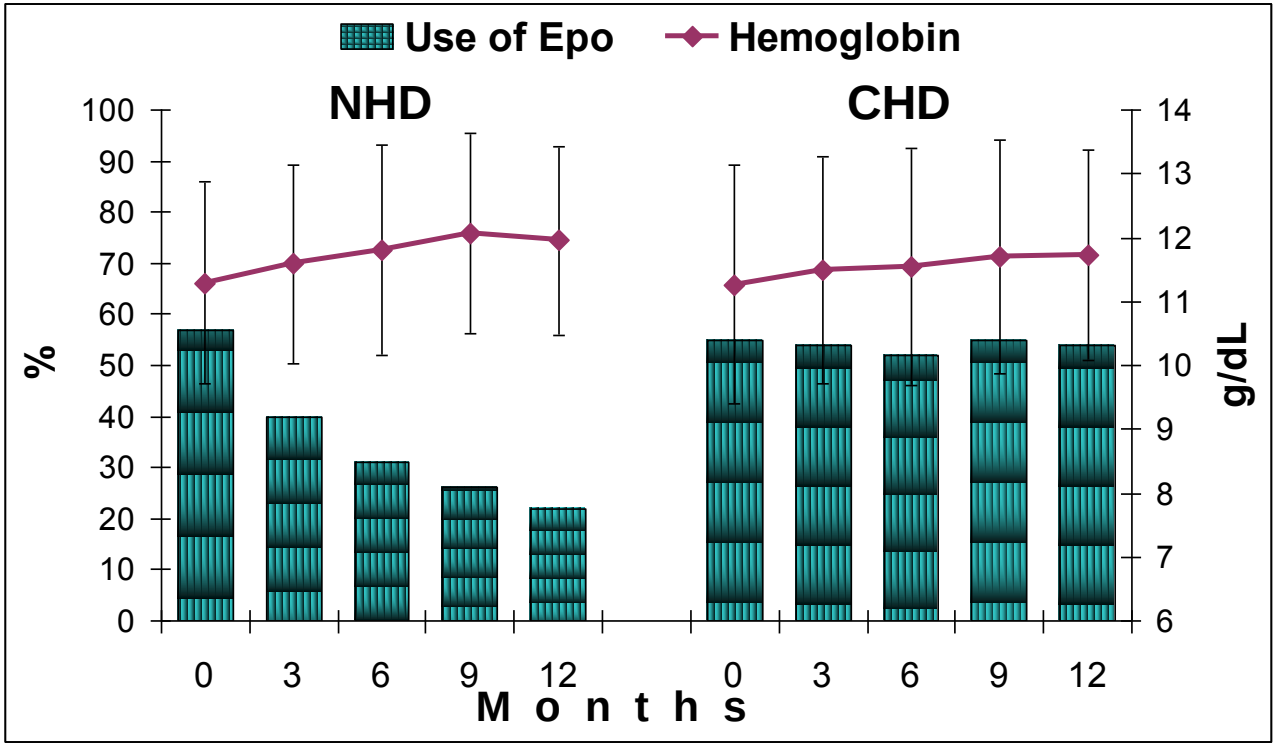
Nutritional status





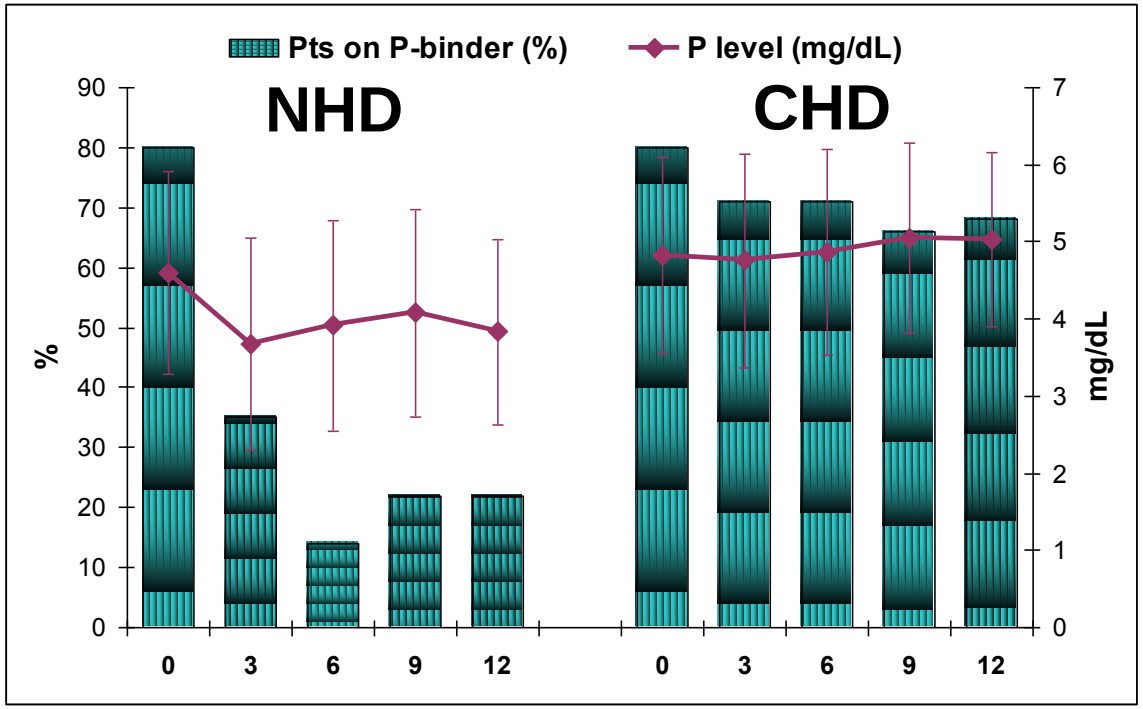
- Increase in post-dialysis body weight in NHD group, with stable blood pressure (from 65 14 to 67 15 kg, p<0.001)
- Increase in serum albumin level (from 3.95 0.29 to 4.10 0.29 g/dL, p<0.0001)

Anemia management



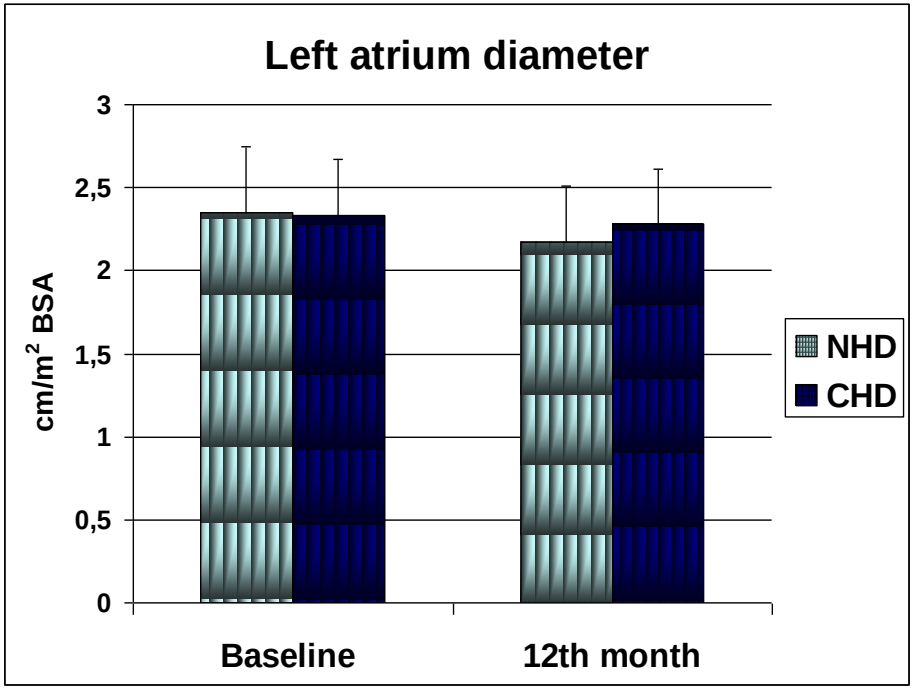
- Hemoglobin levels slightly increased in both arms ($p<0.01$)
- Proportion of patients on Epo declined from 57 to 22% in the NHD group ($p<0.0001$)

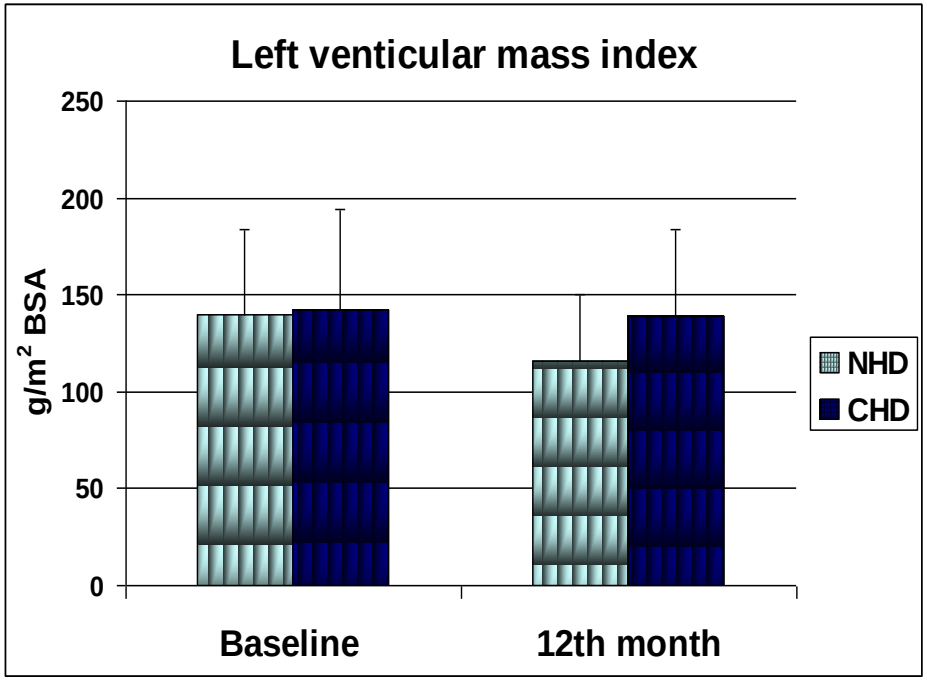
Phosphate control



- Serum P levels decreased from 4.59 1.31 to 3.83 1.2 mg/dl at 12th month in NHD patients (p<0.0001)
- Use of P-binder declined from 81 to 22% (72% reduction)

Cardiac structure



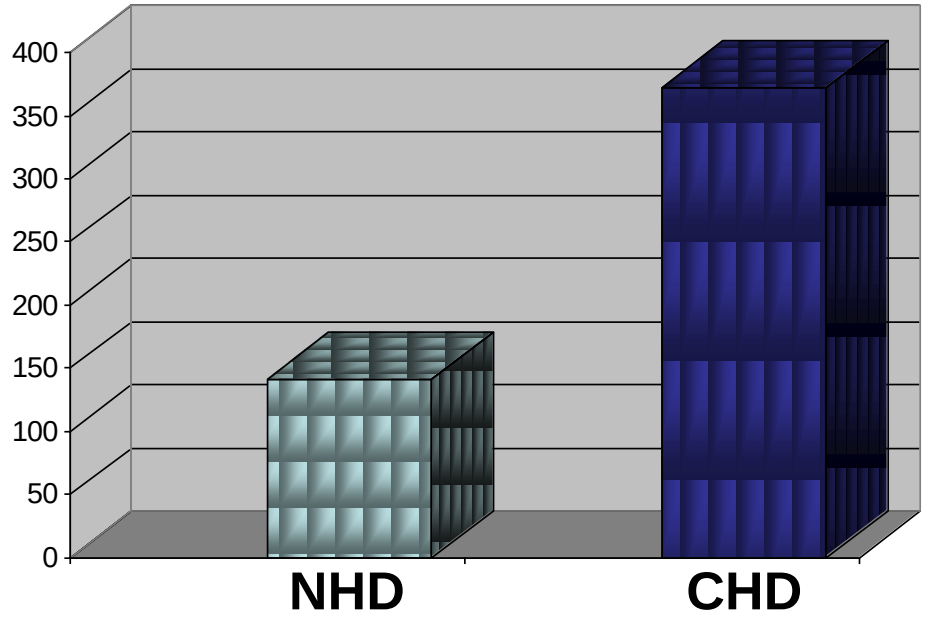


- Decrease in LA diamater in the NHD group (from 2.35 0.40 mm/m^2 BSA to 2.17 0.34, p<0.001)
- Regression in LV mass index in the NHD group (from 140 44 g/m^2 BSA to 116 34, p<0.001)

The effect of longer HD on progression of coronary artery calcification

- **Two multi-slice CTs in 89 patients with an interval of 10 months** (43 NHD, 46 CHD)
- **Followed for at least 6 months in the Long Dialysis Study**
- Baseline demographical, clinical, laboratory data similar
- In follow-up serum P, CaxP product, use of P-binder and BP medication were lower in the NHD group

Change in median CAC score in patients with baseline score >200



	NHD	CHD	p
Delta median CACs (interquartile range)	141 (67-291)	372 (142-695)	<0.01

- Lower progression rate with NHD in patients with moderate to severe vascular calcification

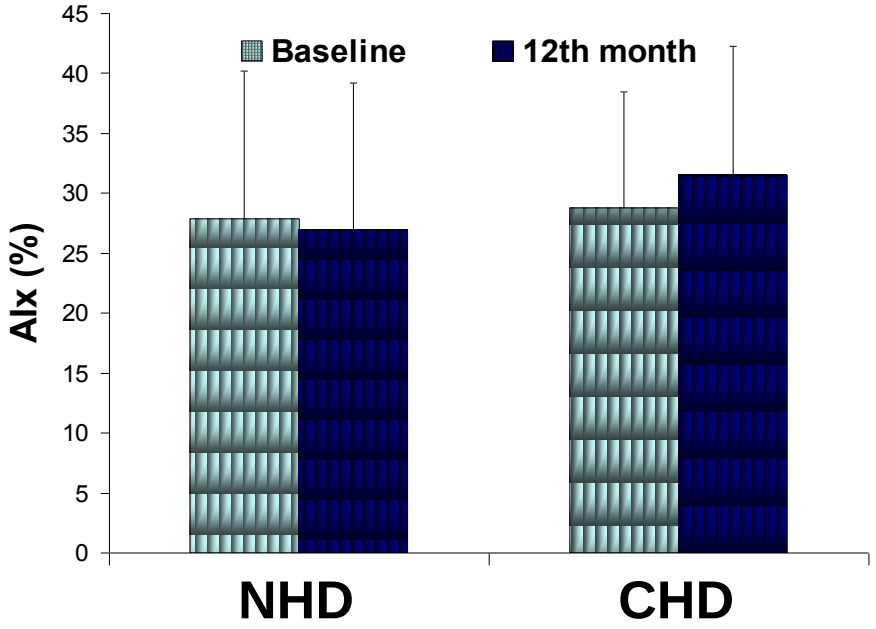
- Serum phosphate was predictor for CAC progression

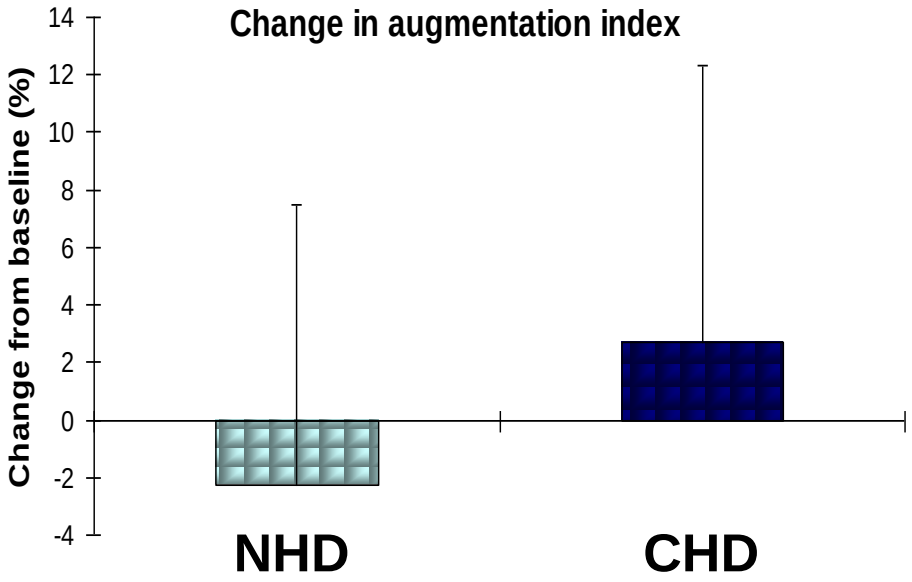
(Exp-B 2.05, 95% CI 1.46-2.90, p <0.001)

The effect of longer HD on arterial stiffness

- **Pulse wave analysis and pulse wave velocity** (from carotid to radial arteries) **in 115 patients at baseline and 12 months** *(AtCor®,PWV Inc., Westmead, Sydney, Australia)* (55 NHD, 60 CHD)
- Baseline demographical, clinical, laboratory data similar
- In follow-up serum P and CaxP product were lower in the NHD group

Augmentation index



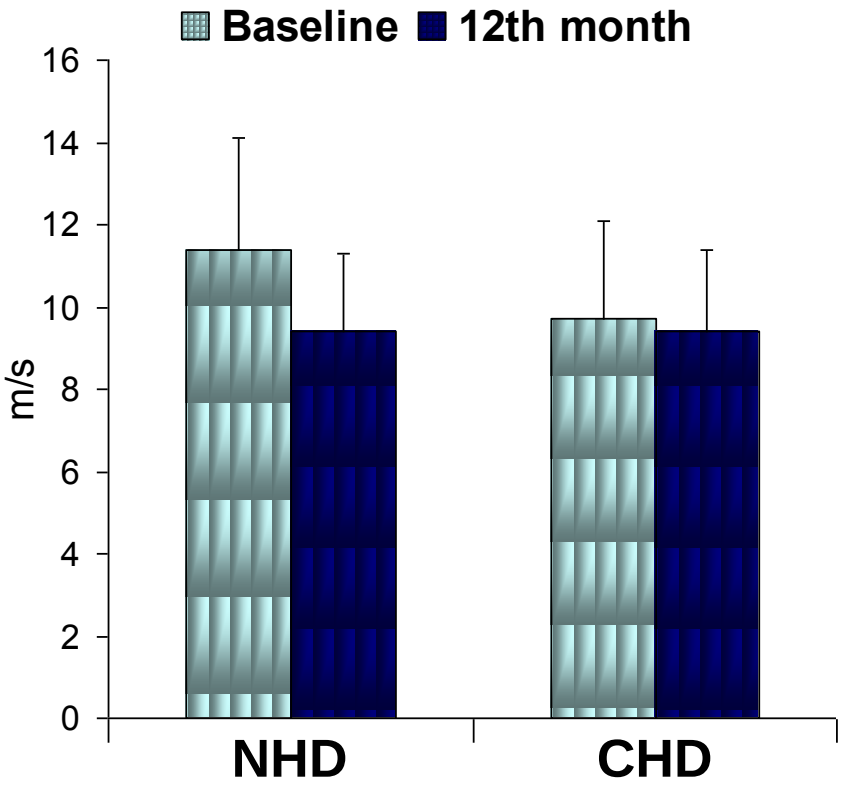


	NHD		CHD	
Baseline	27.9	12.3	28.8	9.7
12th mo	27.0	12.2	31.5	10.8
p	0.09		0.03	

	NHD		CHD	
Δ AIx	**2.6**	**9.7**	**-2.2**	**9.8**
p	**<0.01**			

- AIx increased in CHD arm, slightly decreased in NHD
- Change in AIx significantly different between two arms
- Serum P predictor for delta AIx *(ß-coefficient 0.349, t 2.58, p <0.01)*

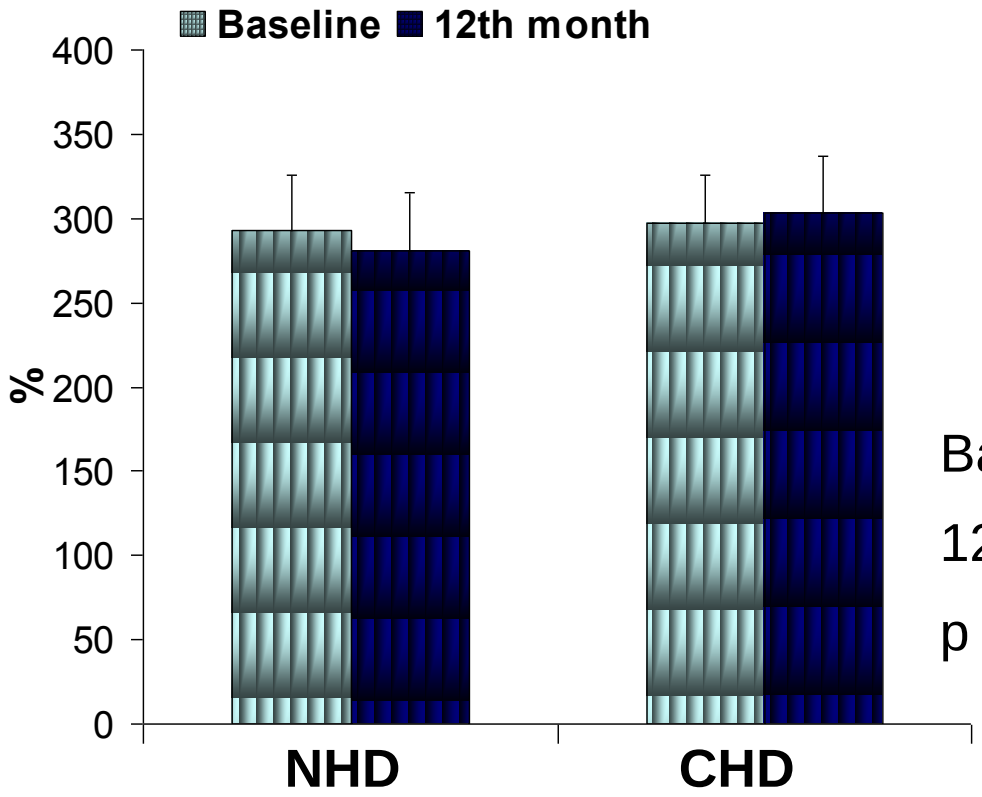
Pulse wave velocity



	NHD	CHD
Baseline	**11.4 2.7**	9.7 2.4
12th month	**9.4 1.9**	9.4 2.0
p	**<0.001**	0.368

- Pulse wave velocity decreased in the NHD group

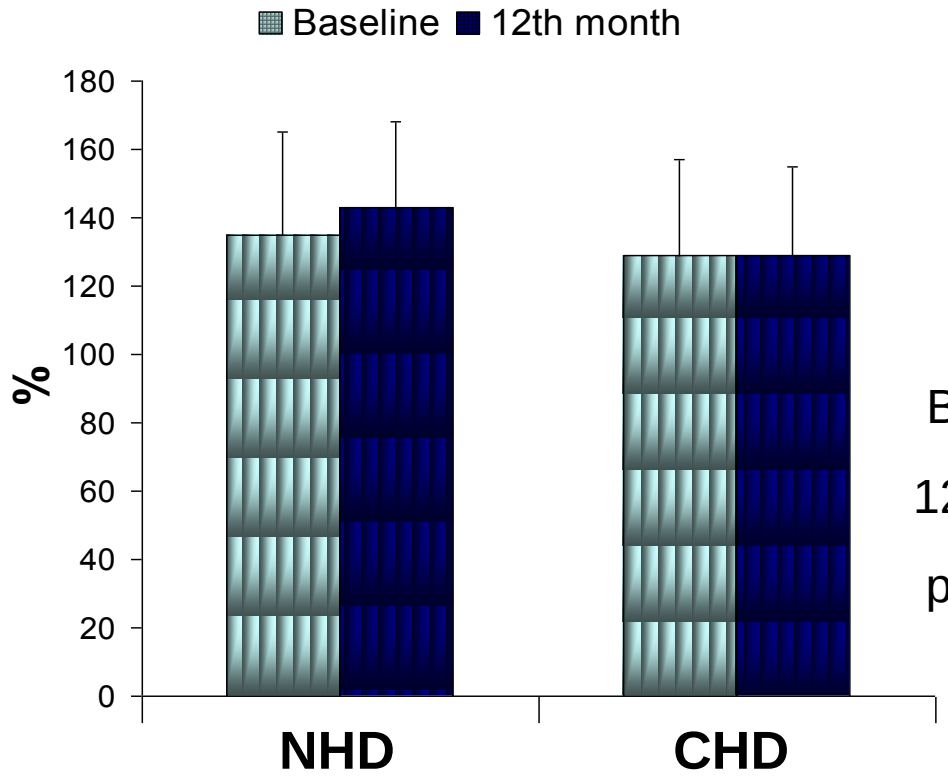
Ejection duration



	NHD	CHD
Baseline	**295 33**	297 29
12th month	**282 34**	303 34
p	**0.007**	0.155

- Diastolic dysfunction assessed by “ejection duration” improved in the NHD group
- Serum P was predictor for change in ejection duration *(ß-coefficient 0.415, t 3.25, p <0.01)*

Subendocardial perfusion



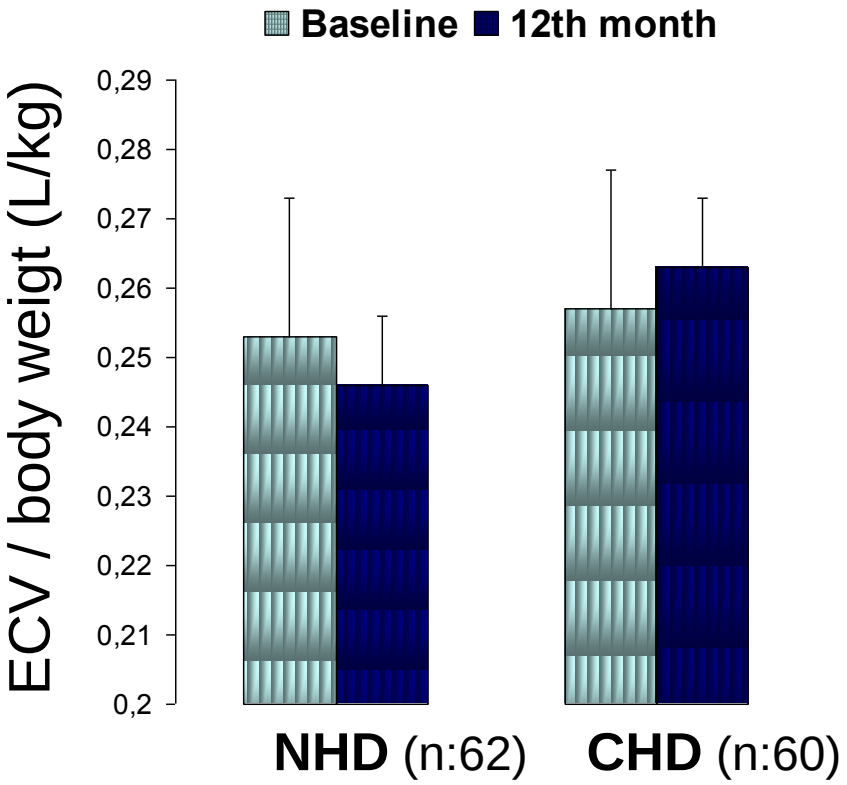
	NHD	CHD
Baseline	**135 30**	129 28
12th month	**143 25**	129 26
p	**0.041**	0.996

- Subendocardial perfusion reflected by “subendocardial viability ratio” increased in NHD
- Predictors for improvement were lower CRP and NHD *(ß-coefficient -0.397, t -3.45, p <0.01) (ß-coefficient 0.314, t 2.70, p <0.01)*

The effect of longer HD on volume and nutrition status - BIA

- **Multi-frequency bio-impedance analysis in 122 patients at baseline and 12th month** (5, 50, 100, 200 kHz) (62 NHD, 60 CHD)
- Baseline demographical, clinical, laboratory data similar
- In follow-up, higher eKt/V and serum albumin, lower serum P and hsCRP in the NHD arm

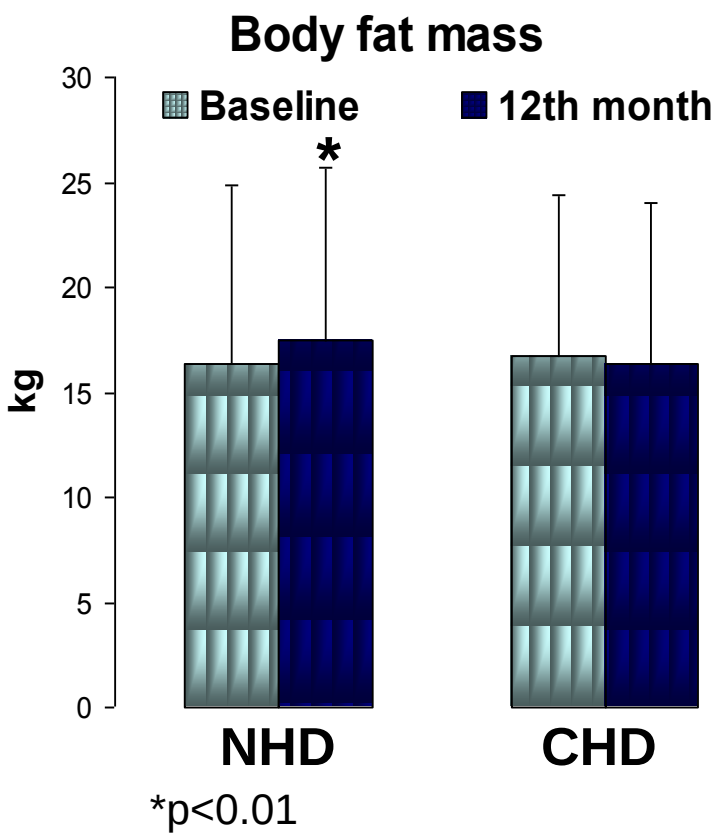
Extracellular fluid volume measured by bio-impedance analysis

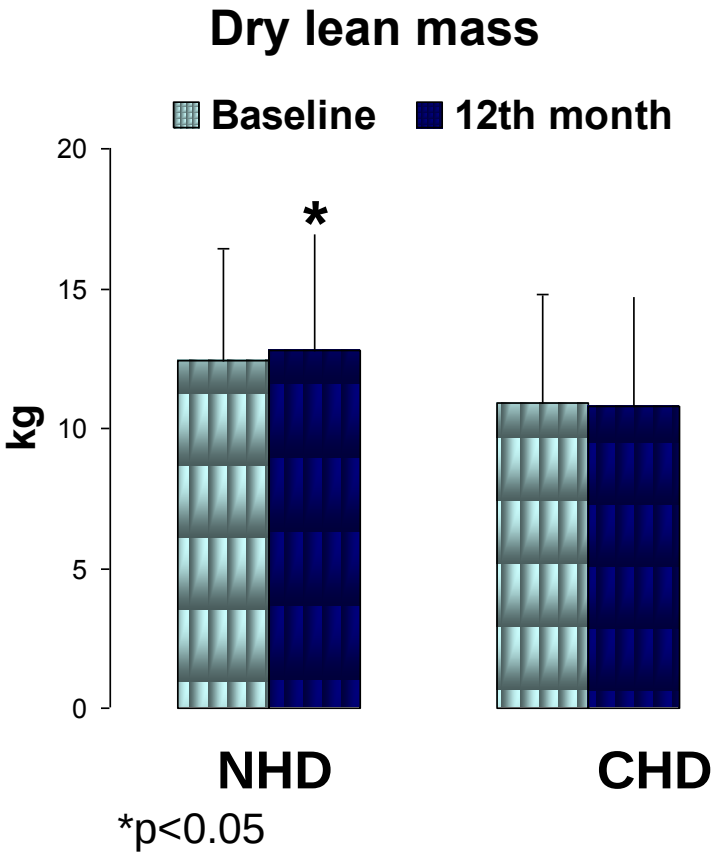


	NHD		CHD	
Baseline	**0.25**	**0.02**	0.25	0.02
12th month	**0.24**	**0.01**	0.26	0.01
p	**<0.01**		<0.05	

- ECV decreased in the NHD group, increased in the CHD group

Body fat mass and dry lean mass measured by bio-impedance analysis



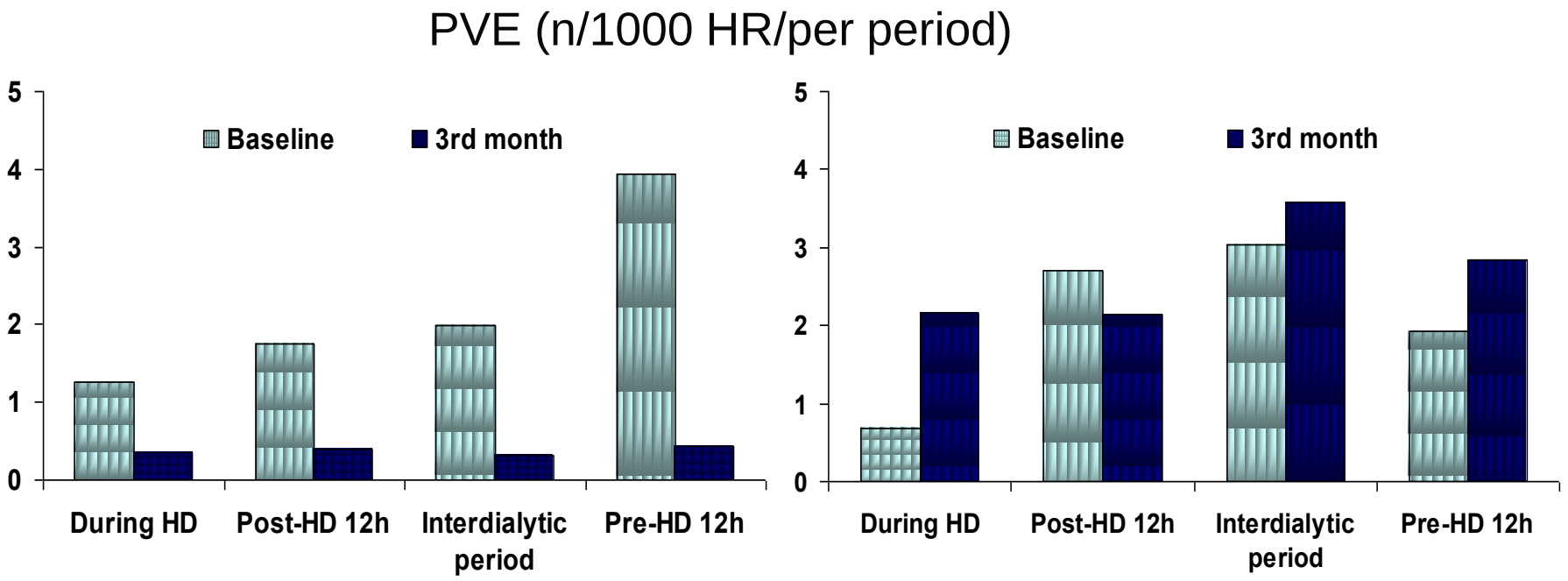


- Increase in body fat mass and dry lean mass in the NHD group

The effect of longer HD on ventricular arrythmias

- **Holter ECG in 60 patients at baseline and at 3rd month**; **midweek 48-h recording** (30 NHD, 30 CHD) (mean duration 2714 60 min)
- Baseline demographical, clinical, laboratory data similar; EF and LVMI not different
- In follow-up, lower use of anti-hypertensive medication and hypotension episode in the NHD arm

Premature ventricular ectopia



- Decrease in PVE at all time-points in the NHD group, no change in CHD patients

Conclusion

Implementation of longer HD sessions may improve several outcomes:

- Better phosphate control, slow down in progression of vascular calcification, improvement in arterial stiffness
- Better volume and blood pressure control, regression of cardiac enlargement and left ventricular hypertrophy
- Improvement in anemia, reduction of Epo requirement; decrease in ventricular arrythmia

Conclusion

- Improvement in nutritional status
- Decrease in intradialytic complications and hospitalization
- Decrease in mortality

Limitations of the presented studies

- Non-randomized
- Relatively small numbers of study cases
- Relatively short follow-up
- Methods not most accurate ones (echo instead of MRI for LV geometry)

SALT RESTRICTION & VOLUME CONTROL AND MORE INTENSIVE DIALYSIS

- It seems that we have some effective **but underutilized** tools to improve cardiovascular outcomes in dialysis patients.
- Problems are those:
- Compared to drug studies, difficulties in conducting randomized studies on both subjects, which are asked by nephrology community to be convinced
- Both requires serious enforcement from not only nephrologists but also governmental health authorities

- **Dialysis, as longer as possible**
  - **Salt, as lower as possible**

Thank you