

Effect of very low-protein diet vs. standard low-protein diet on renal death in patients with CKD: a pragmatic, randomized, controlled, trial

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Background

- ❖ Lowering of dietary proteins has been considered an effective clinical tool to reduce the negative progression of CKD
- ❖ Though a significant effect of dietary protein restriction in slowing down the GFR decline was not definitely demonstrated a reduction of protein intake has been shown to delay the start of renal replacement therapy in non diabetics
- ❖ No randomized clinical trial tested whether striking dietary protein restriction delays start of dialysis and affects survival in patients with advanced CKD

Aim

Compare the effects of a very low versus a standard low protein-diet on the outcome of patients with moderate to advanced CKD (stages 4 and 5) by means of a randomized, pragmatic, clinical trial

Subjects & Groups

- ❖ Unselected CKD 4-5 patients naïve for very low protein diet followed from at least 6 mts in renal clinics
- ❖ No severe undernutrition or severe active diseases
- ❖ No acute kidney injury in the previous 3 months
- ❖ Randomly (centralized and stratified by center and CKD stage) assignment to a dietary protein intake:
 - very low-protein diet, **VLPD group**, 0.35 g/kg ideal Body wt/day plus ketoacids
 - standard low-protein diet, **LPD group**, 0.60 g/kg ideal Body wt/day
- ❖ RCT registered ClinicalTrials.gov n° [NCT00323713](https://doi.org/10.1186/1745-7581-13-13)

Measurements

Registration:

- Start of chronic dialysis, end stage renal disease, ESRD
- All-cause death before and after dialysis start

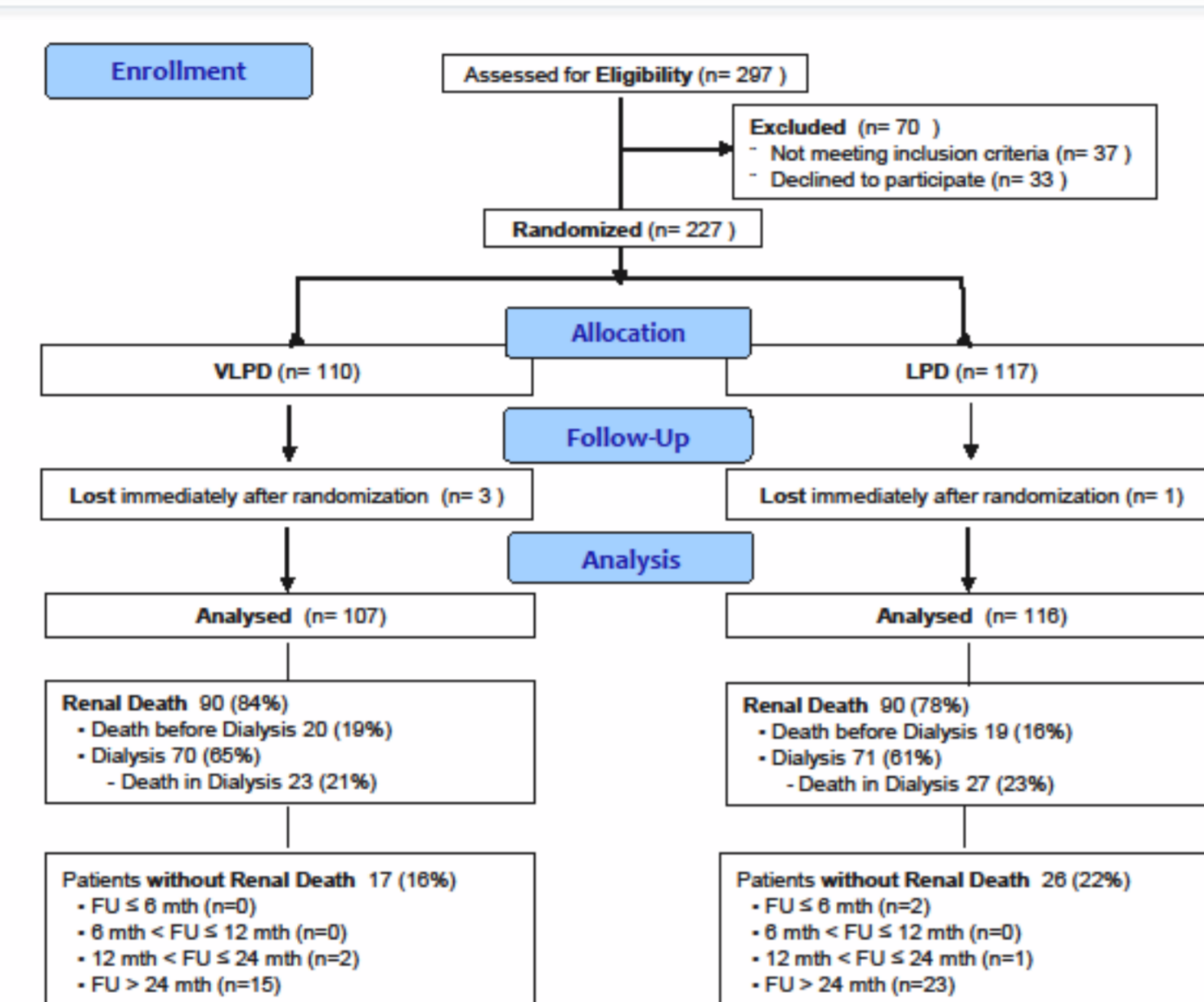
Outcomes:

- Primary outcome** was time to renal death, defined as the first event between ESRD or patient death
- Secondary outcomes** were:
 - ESRD
 - overall mortality
 - adherence to diet

ERIKA study

- **AIM** – compare effect sVLPD vs. LPD on renal outcome in advanced CKD
- **DESIGN** – pragmatic, multicenter, randomized, controlled trial
- **PARTICIPANTS** – adult, unselected, CKD stage 4-5
- **ESCLUSION** – severe undernutrition, severe active diseases
- **PRIMARY END-POINT** – renal death (first event between ESRD or patient death for all causes)
- **SECONDARY END-POINT** – ESRD, patient death for all causes

Flow diagram



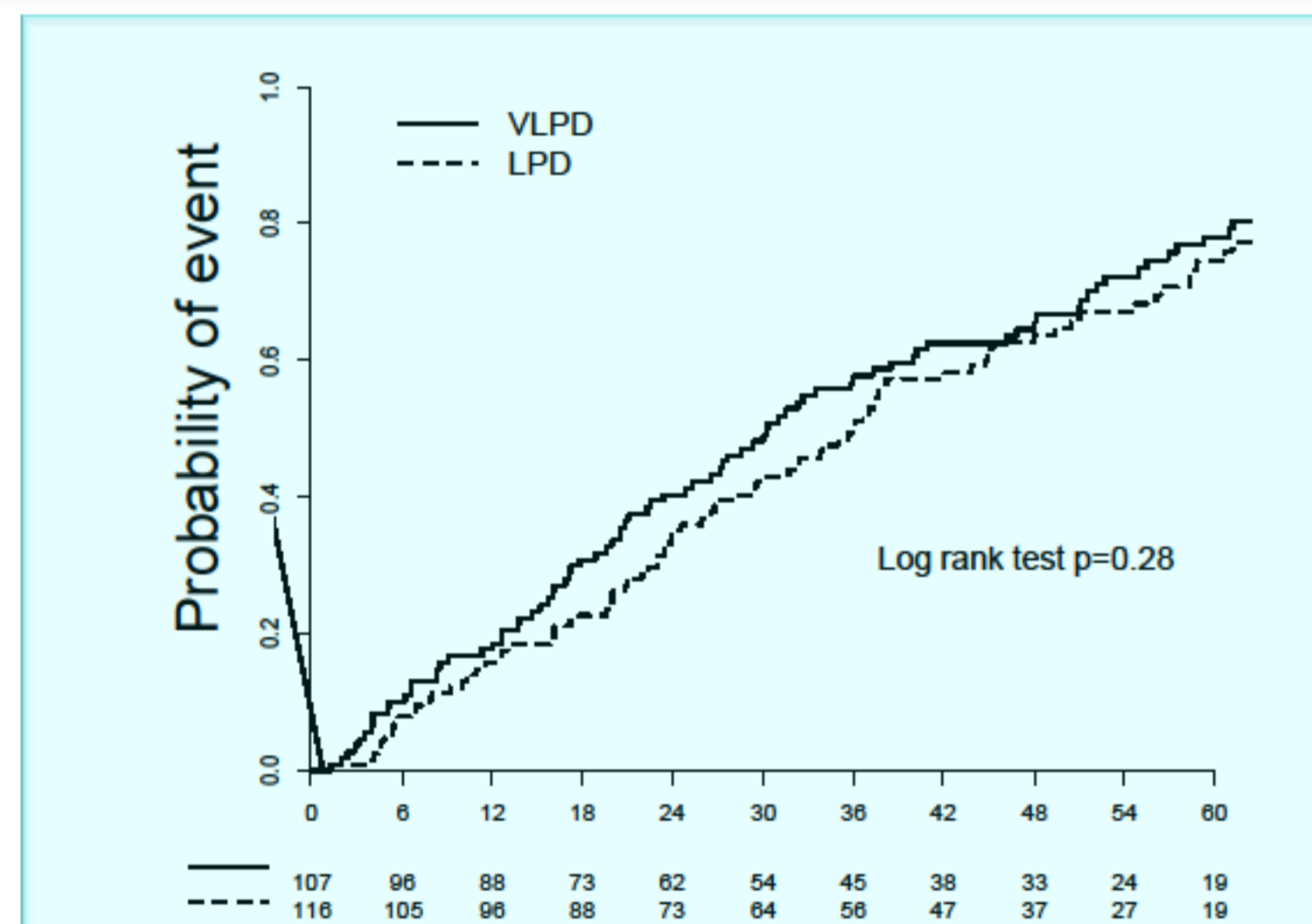
Clinical Characteristics

Variable	VLPD (N=107)	LPD (N=116)
Male gender, n (%)	65 (61%)	72 (62%)
Age, yrs (SD)	63.8 (14.8)	63.8 (14.2)
Diabetes, n (%)	33 (31%)	45 (39%)
Previous CV events:		
Yes, n (%)	32 (30%)	38 (33%)
No, n (%)	59 (55%)	65 (56%)
Missing, n (%)	16 (15%)	13 (11%)
BMI, kg/m ² (SD)	27.1 (4.4)	26.9 (4.7)
Weight, kg (SD)	72.4 (13.0)	70.2 (14.0)
Systolic blood pressure, mmHg (SD)	135 (18)	130 (20)
Diastolic blood pressure, mmHg (SD)	80 (12)	77 (11)
Diuretics:		
Yes, n (%)	62 (58%)	71 (61%)
No, n (%)	39 (36%)	40 (35%)
Missing, n (%)	6 (6%)	5 (4%)
Number of antihypertensive drugs, mean (SD)	2.7 (1.2)	2.9 (1.5)
ACE/ARB:		
Yes, n (%)	80 (75%)	89 (77%)
No, n (%)	21 (20%)	21 (18%)
Missing, n (%)	6 (6%)	6 (5%)

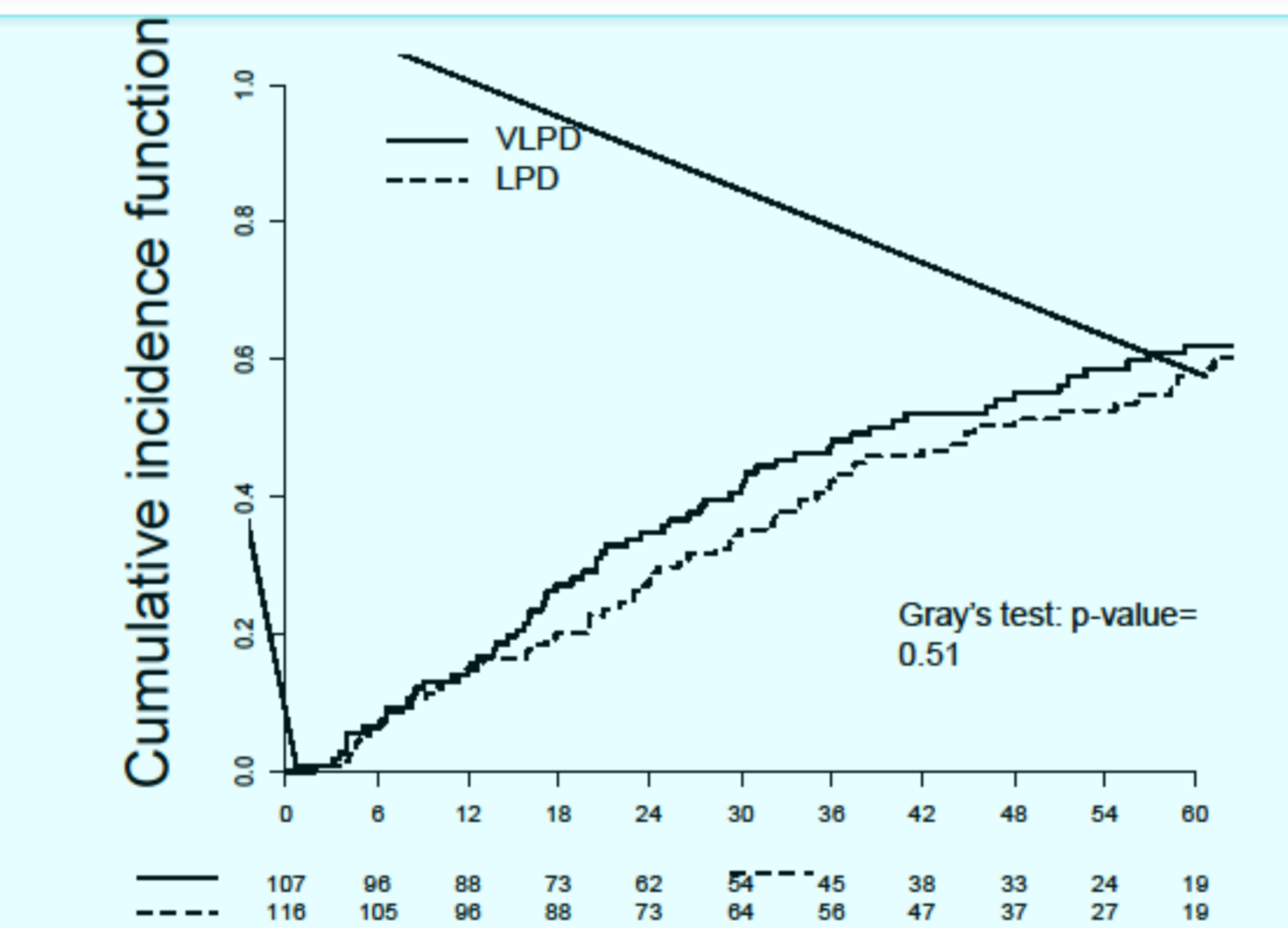
Laboratory Data

Variable	VLPD (N=107)	LPD (N=116)
Creatinine, mg/dL (SD)	3.9 (1.3)	3.7 (1.2)
GFR _{MDRD} , ml/min (SD)	17.1 (6.6)	18.3 (6.9)
Creatinine Clearance, ml/min/1.73m ² (SD)	21.3 (9.9)	22.1 (10.6)
Cholesterol, mg/dL (SD)	188 (41)	185 (37)
LDL, mg/dL (SD)	108 (34)	106 (33)
HDL, mg/dL (SD)	47 (13)	48 (15)
Triglycerides, mg/dL (IQR)	136 (98-188)	138 (99-185)
Hemoglobin, g/dL (SD)	11.9 (1.5)	11.9 (1.4)
Transferrin, mg/dL (SD)	217 (60)	224 (53)
Albumin, g/dL (SD)	3.9 (0.5)	4.0 (0.5)
Potassium, mEq/L (SD)	5.1 (0.7)	5.1 (0.8)
Calcium, mg/dL (SD)	9.3 (0.8)	9.4 (0.7)
Azotemia, mg/dL (SD)	133 (43)	130 (45)
Phosphate, mg/dL (SD)	4.4 (1.0)	4.4 (0.8)
PTH, pg/mL (IQR)	153 (89-267)	154 (77-246)
Proteinuria, g/die (IQR)	0.72 (0.30-1.89)	0.88 (0.20-1.84)
Protein intake, g/kg i.b.w./day (SD)	0.88 (0.23)	0.89 (0.28)
Creatinine excretion, mg/kg/die (SD)	16.3 (7.0)	16.0 (6.9)
Salt intake, g/die (SD)	8.5 (4.4)	9.4 (6.9)
Phosphate intake, mg/die (SD)	903 (642)	966 (501)

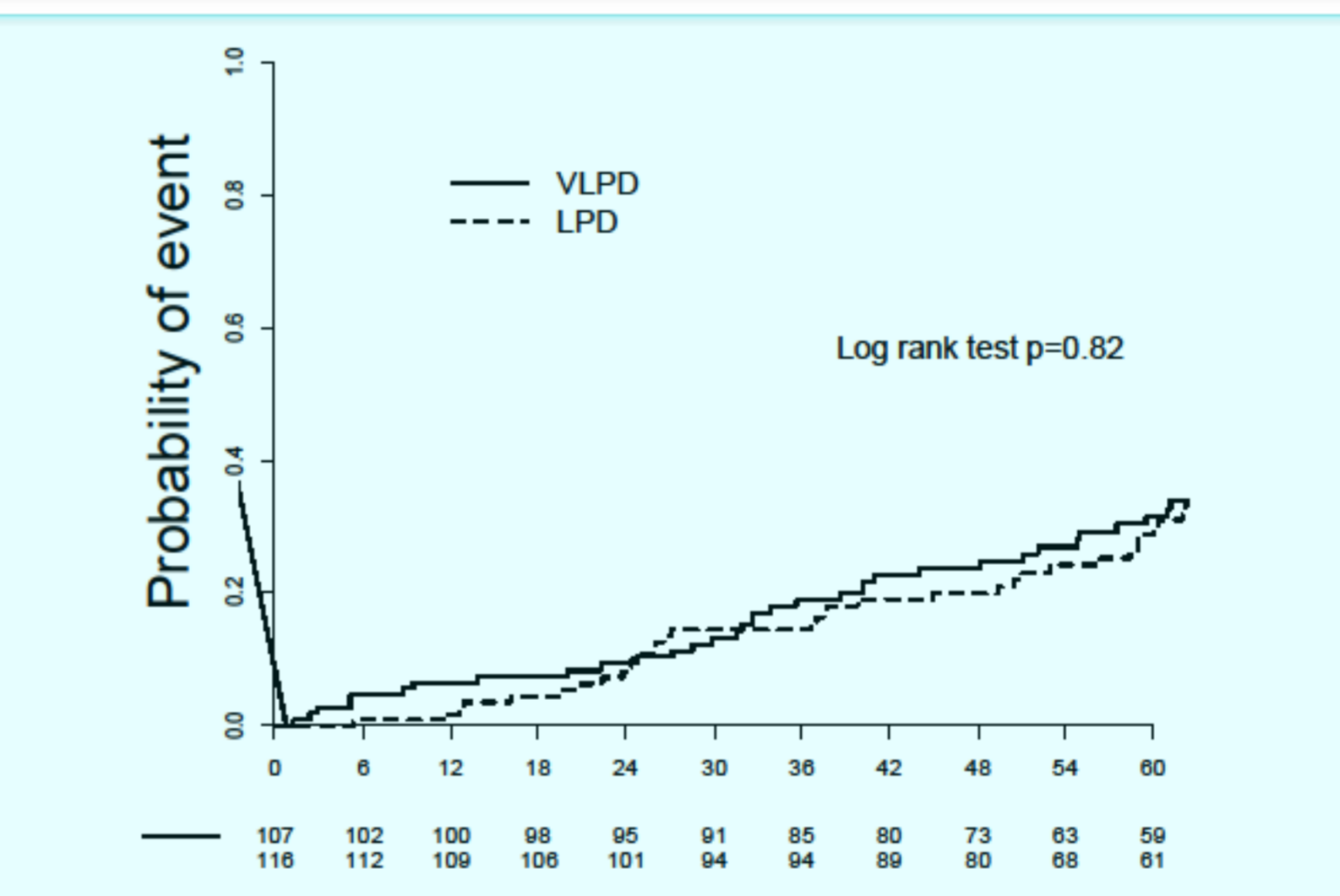
Renal Death



Dialysis



Overall Death

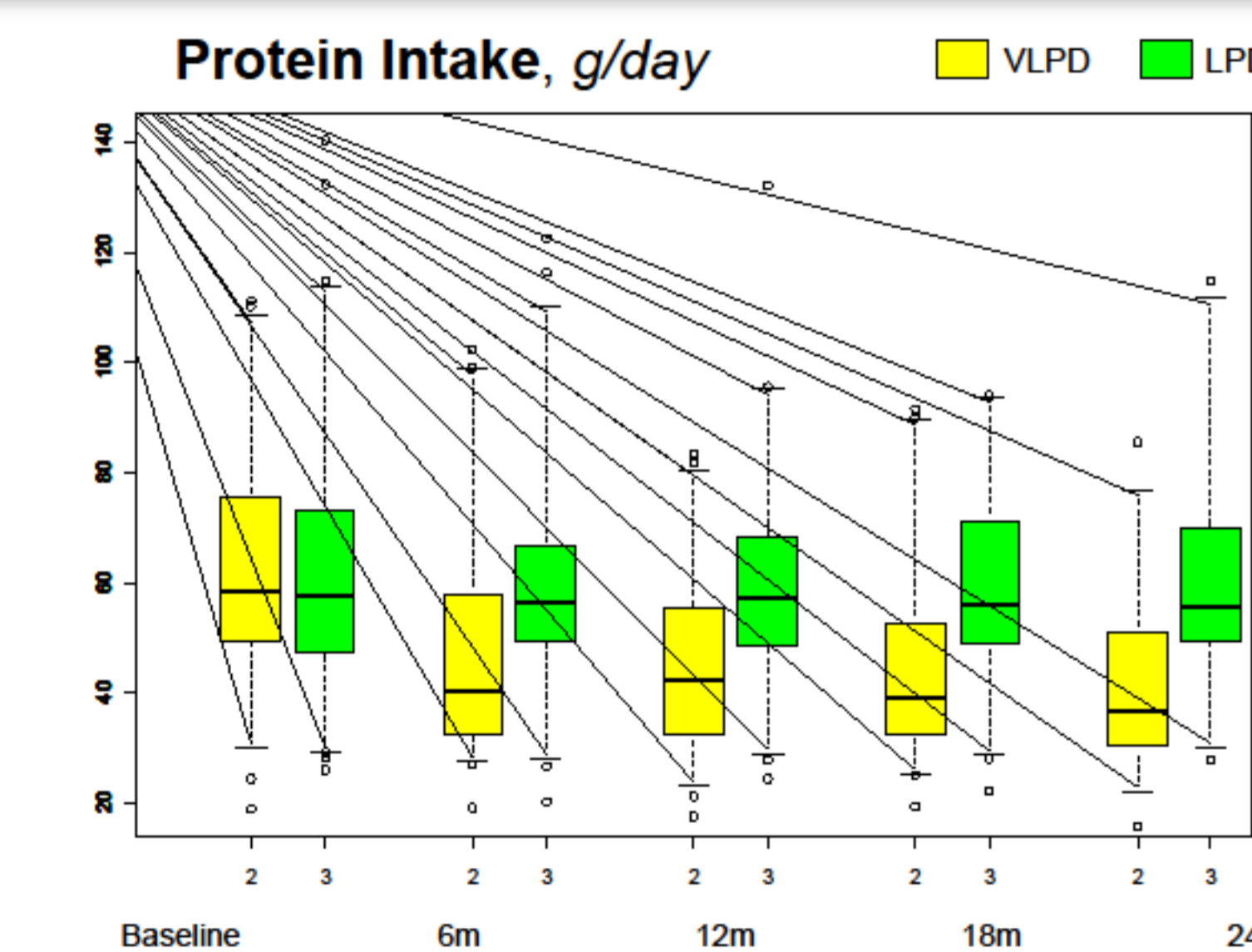


Efficacy Outcomes

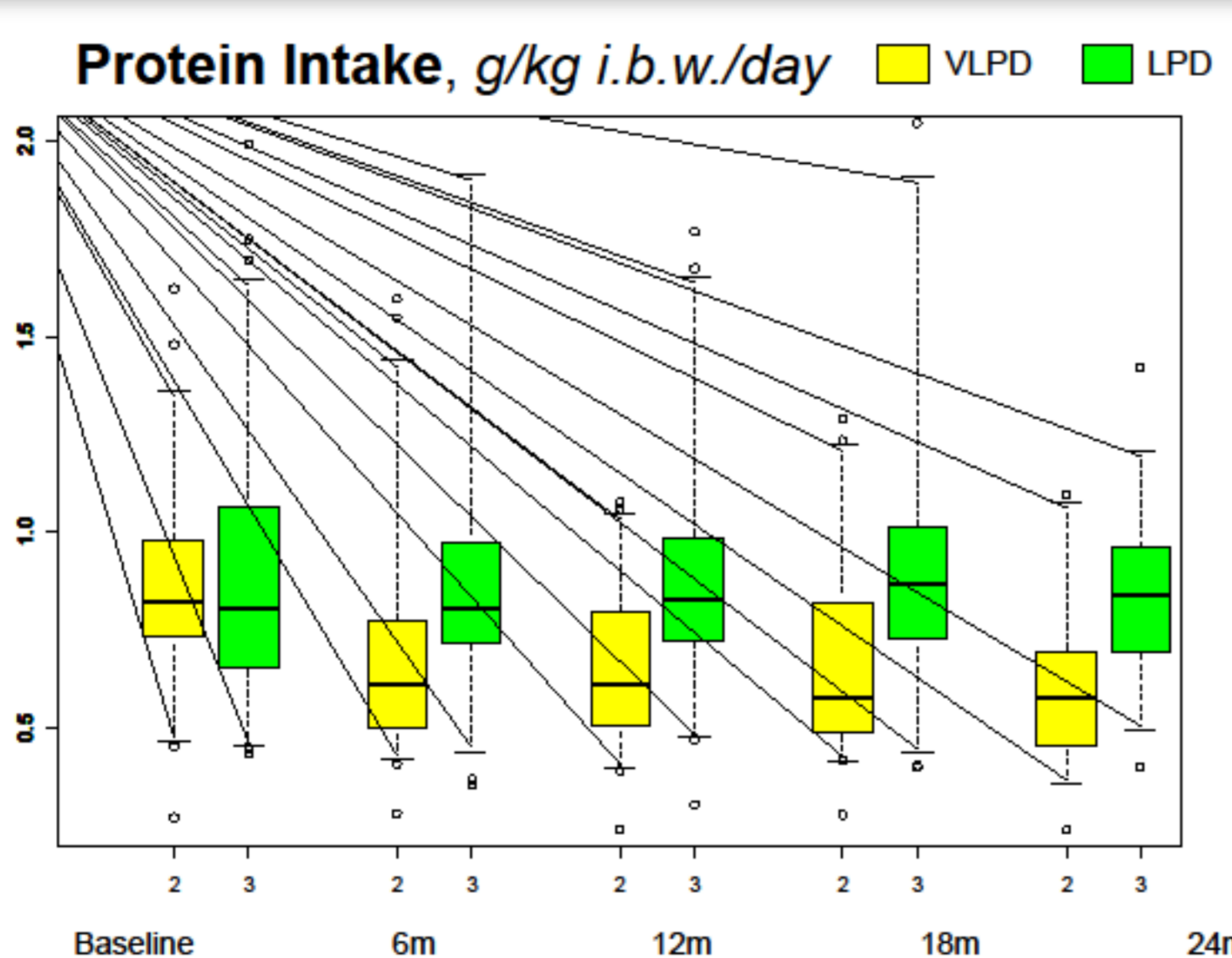
	HR (95%CI)	HR** (95%CI)
Renal Death	1.17 (0.88-1.57)	1.09 (0.76-1.57)
Dialysis*	1.12 (0.81-1.56)	1.03 (0.70-1.51)
Overall Death	0.95 (0.62-1.45)	0.96 (0.58-1.60)
Renal Death adherent pts	0.66 (0.40-1.09)	0.58 (0.31-1.07)

* after adjustment by age, sex, CKD stage, protein intake, diabetes and proteinuria
** considering Death as competing event
*** after adjustment by age, sex, CKD stage, diabetes and proteinuria

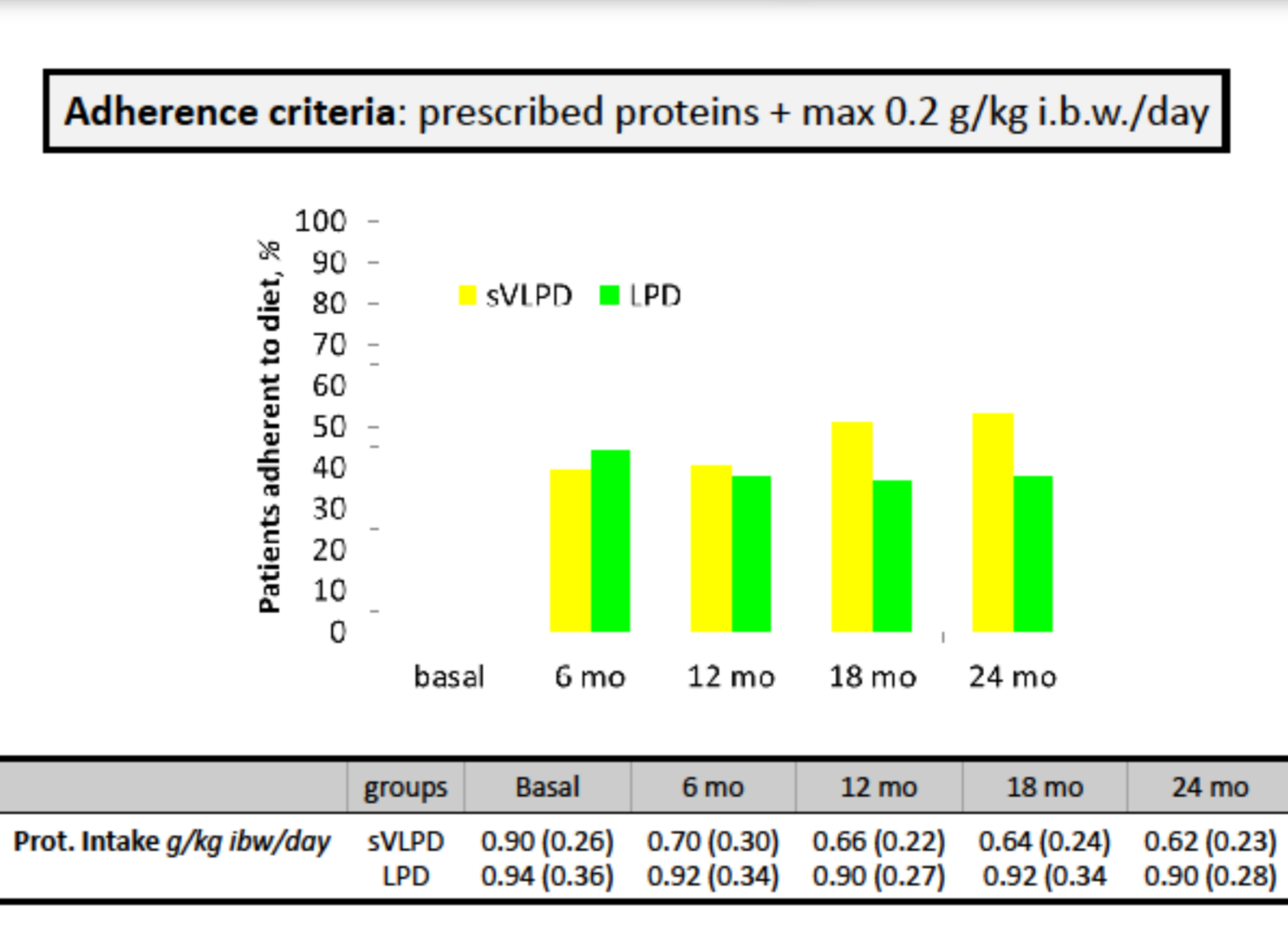
Protein Intake



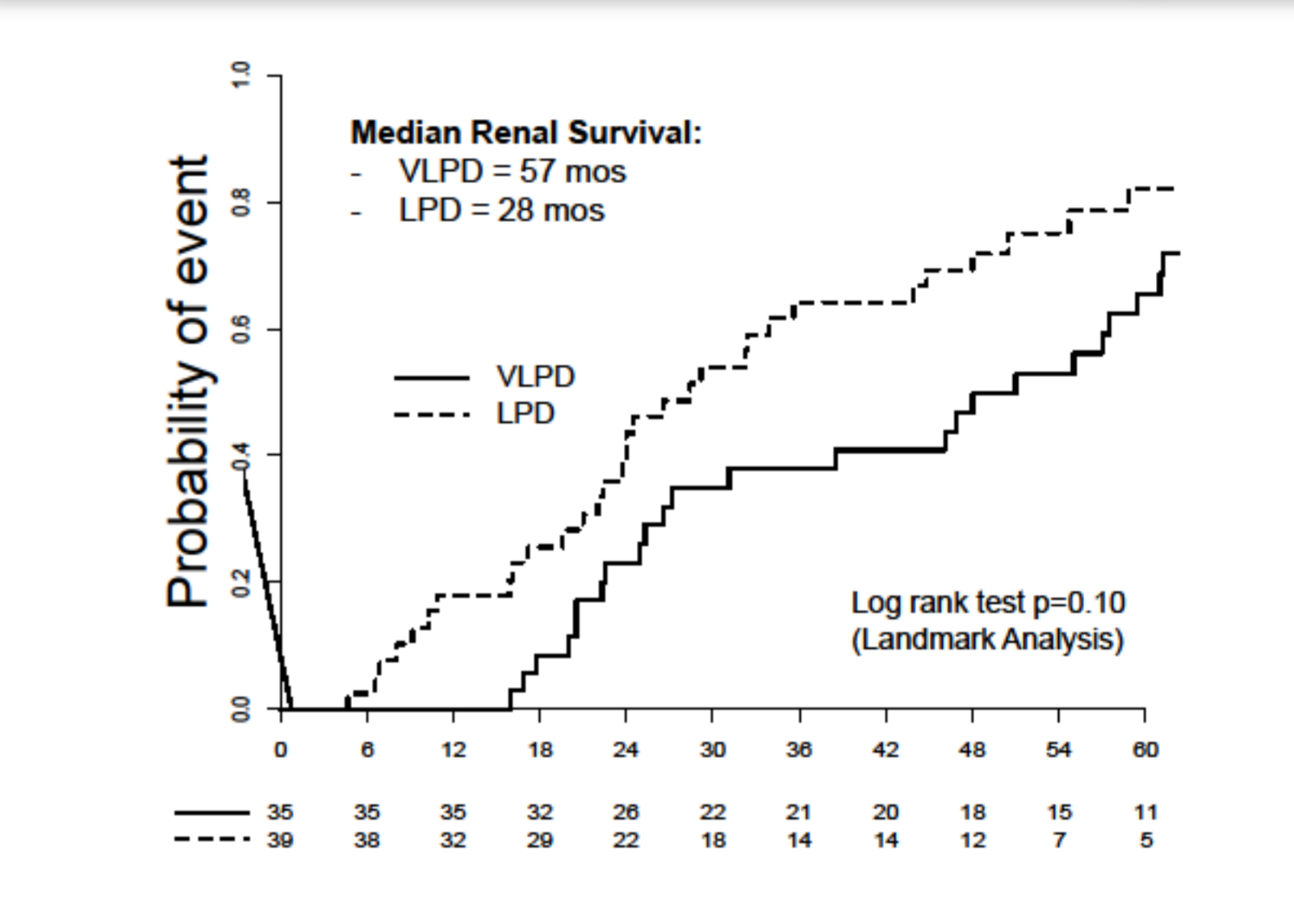
normalized Protein Intake



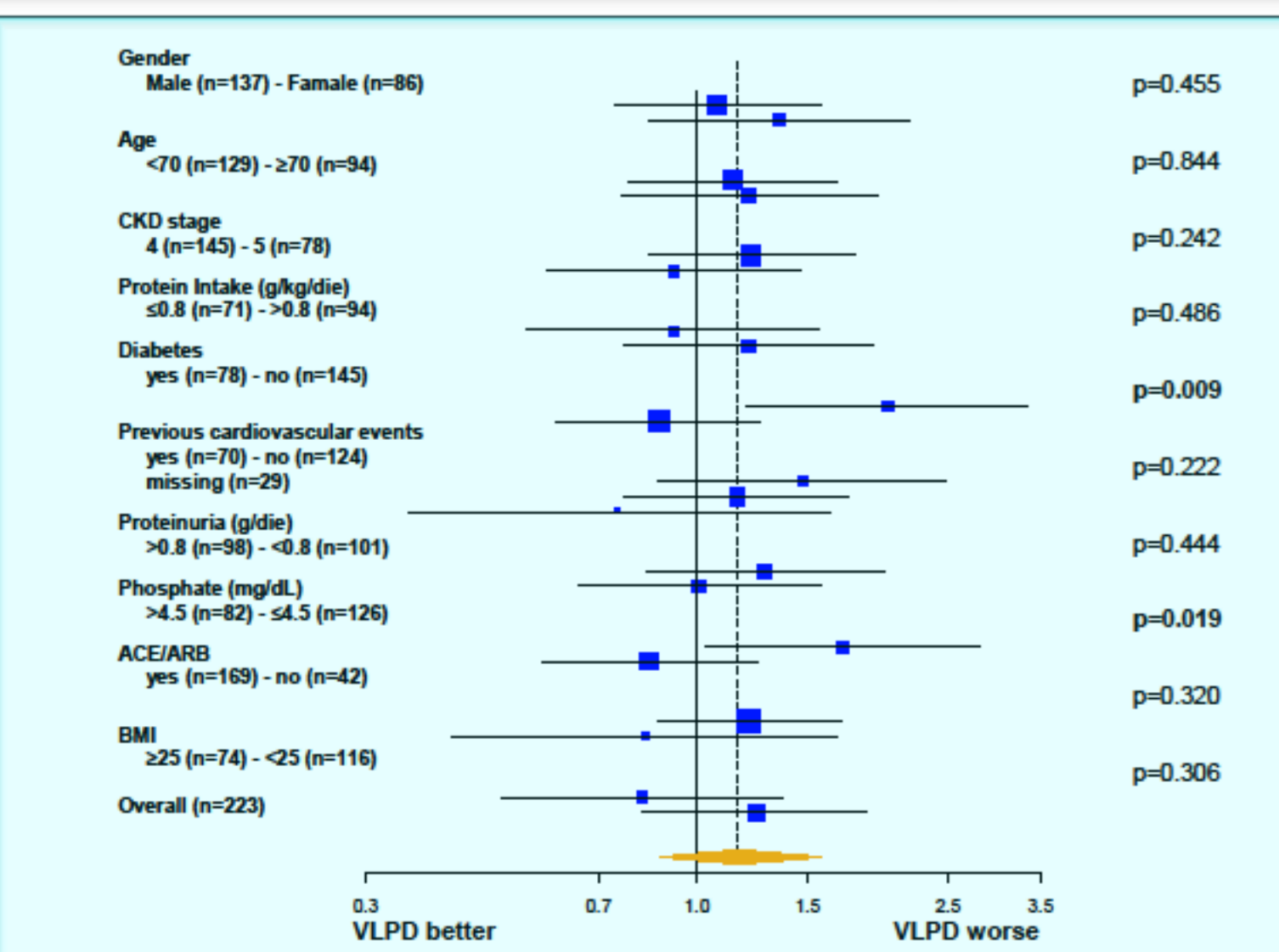
Adherence to proteins



Renal Death adherent pts



Renal Death sub-groups



Renal & Pts Outcomes

	sVLPD	LPD
Δ GFR, ml/min	-1.08 [-3.44-0.65]	-1.38 [-3.87-0.23]
Death rate, %/year	6 [4-10]	5 [3-8]
ESRD rate, %/year	16 [12-20]	19 [12-19]

ERIKA study - conclusions

- In unselected CKD stage 4-5 patients, VLPD, as compared with standard LPD, does not reduce the risk of renal death
- Adherence to VLPD, and LPD as well, in unselected CKD patients is low and this may have influenced the results
- Other factors may have an impact on the effect of VLPD on renal death (i.e. previous rate of GFR decline; intensive nephrology care)
- In selected conditions, VLPD may work better (i.e. low phosphate) or may be even associated with a worst outcome (i.e. diabetes), but these conditions remain to be better evaluated

ERIKA study - limitations

- **SELECTION** – prevalent patients on tertiary, intensive nephrology care with good control of comorbidities
- **CONTROLS** – intensive treatment
- **PROGRESSION** – very slow GFR declining rate (including patients non progressor) and reduced renal death (power analysis)
- **OUTCOME** – lower mortality rate (power analysis)
- **PROTEIN INTAKE** – already low-normal protein intake at baseline
- **ADHERENCE** – low adherence during the study (yes education at baseline; no adherence trial; no intensive re-counselling during the follow-up; semi-personalized diet) and low actual reduction of protein intake