

FGF-23 influence on C-V events and mortality in peritoneal dialysis patients.

Ashley Broughton, MD
Nephrology department
Cliniques de l'Europe, Bruxelles

2nd Self Care Dialysis Symposium
23/05/2014

Introduction

POLL :

Based on your current knowledge,

1. Do you believe that mortality rate in ESRD patients is too high?

Introduction

POLL :

Based on your current knowledge,

1. Do you believe that mortality rate in ESRD patients is too high?
2. Do you believe that calcium-phosphate metabolism disturbances is an important factor in overall mortality of ESRD patients?

Introduction

POLL :

Based on your current knowledge,

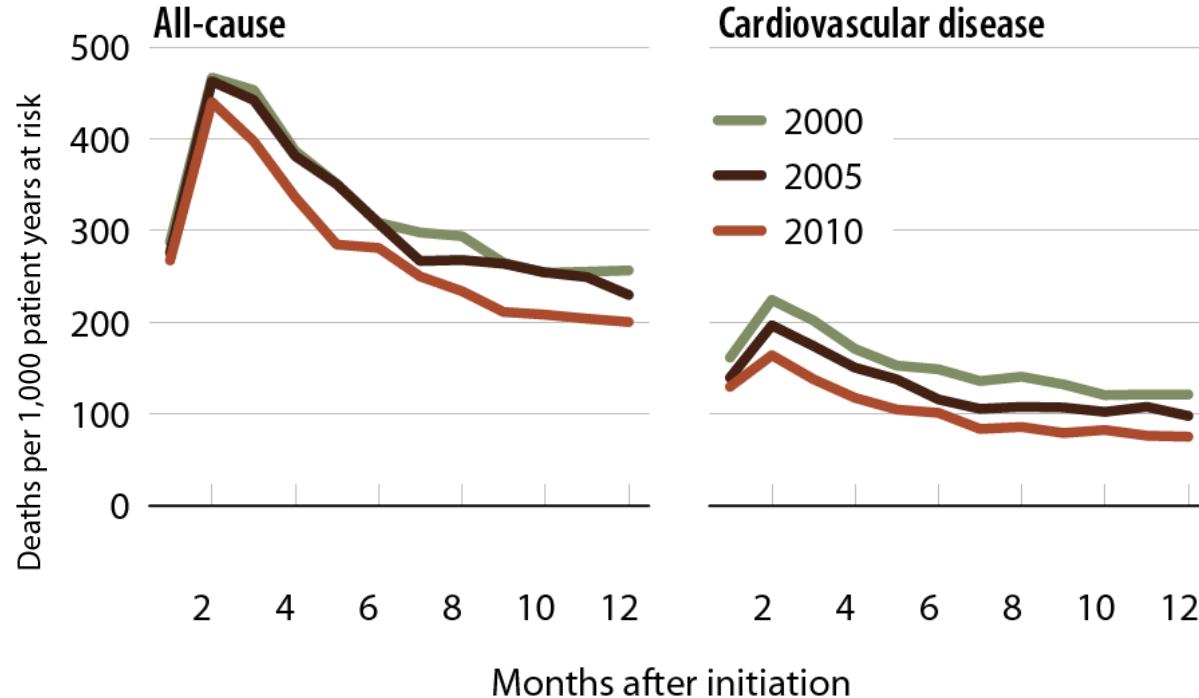
1. Do you believe that mortality rate in ESRD patients is too high?
2. Do you believe that calcium-phosphate metabolism disturbances is an important factor in overall mortality of ESRD patients?
3. Will the Belgian Red Devils win the 2014 World Cup in Brazil?

Introduction

POLL : RESULTS

1. A majority of nephrologists believe mortality is too high in ESRD patients.

⇒ First year mortality of incident dialysis patients – USRDS 2011



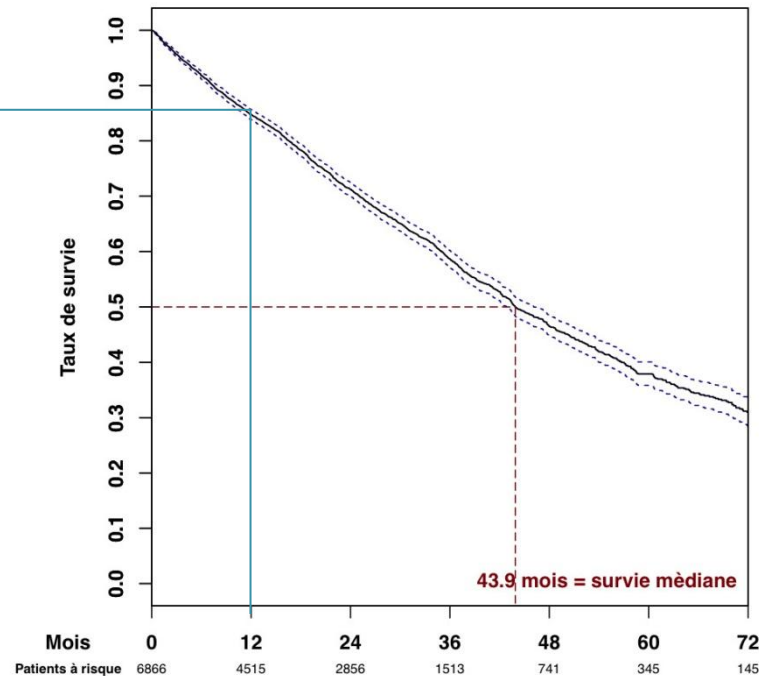
Introduction

POLL : RESULTS

1. A majority of nephrologists believe mortality is too high in ESRD patients.

⇒ Survival of incident PD patients – RDPLF 2012

Mortality = 14%



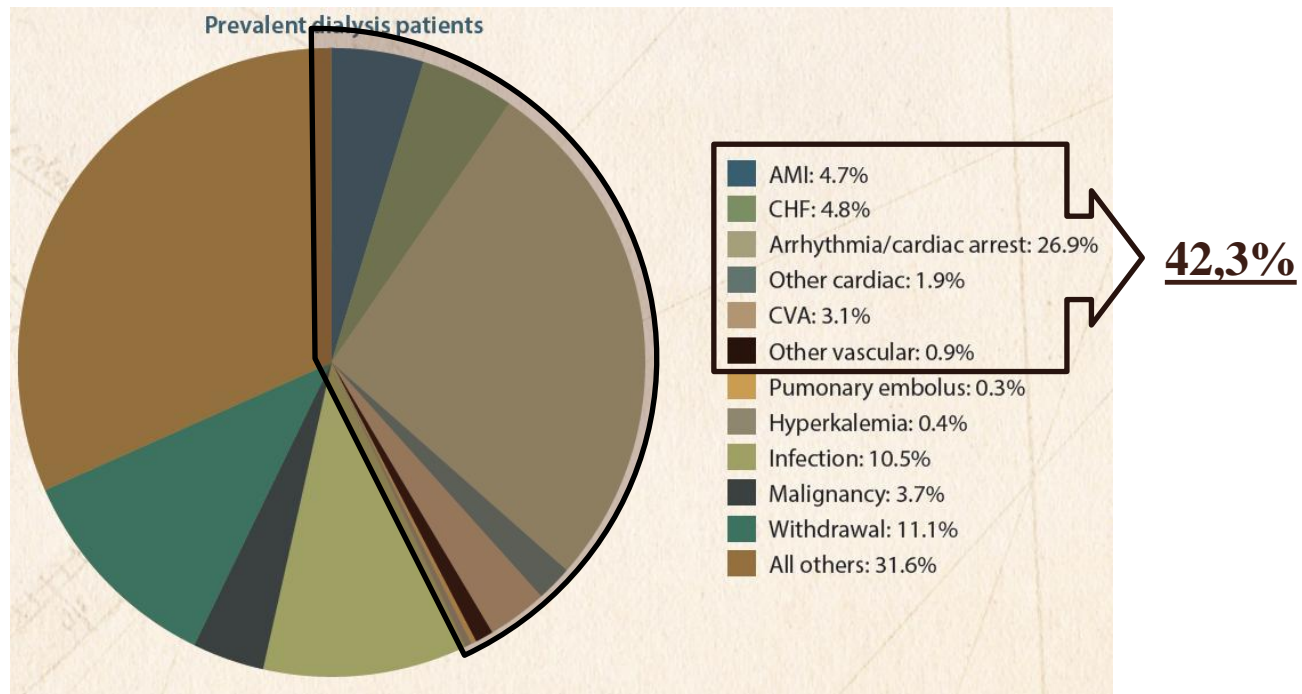
Nb. patients = 6866 Nb. centres = 143
Risques concurrents non pris en compte.

Introduction

POLL : RESULTS

1. A majority of nephrologists believe mortality is too high in ESRD patients.

⇒ Causes of death in prevalent dialysis patients – USRDS 2011

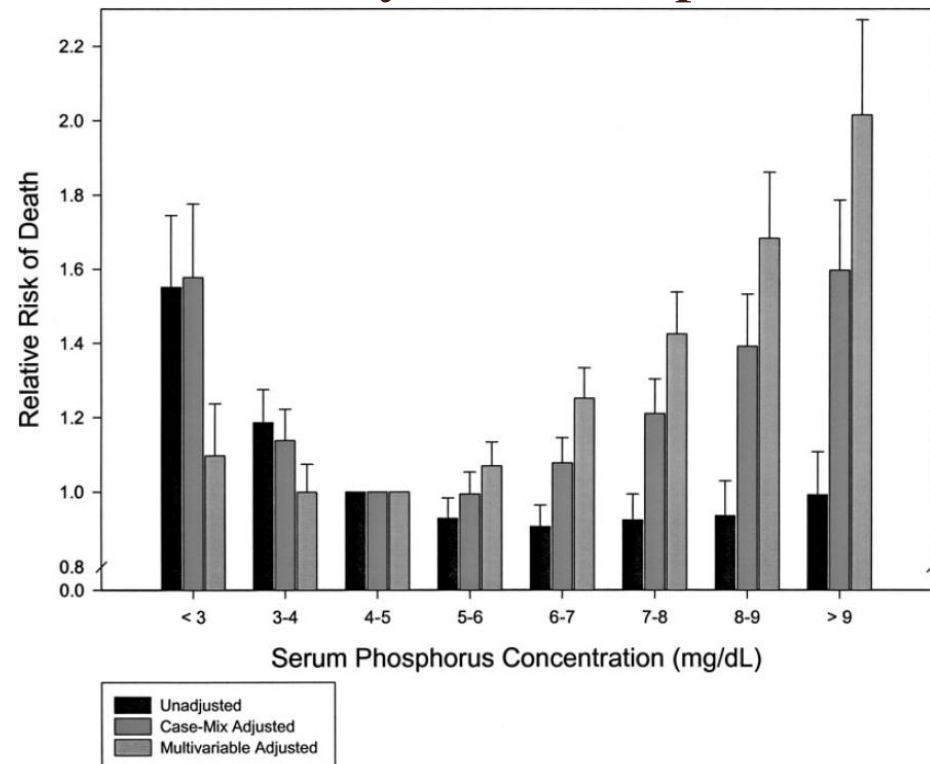


Introduction

POLL : RESULTS

1. A majority of nephrologists believe mortality is too high in ESRD patients.
2. A majority of nephrologists believe that CKD-MBD is an important factor in mortality of ESRD patients.

Mineral Metabolism, Mortality,
and Morbidity in Maintenance
Hemodialysis,
G. Block et al,
JASN 2004



Introduction

POLL : RESULTS

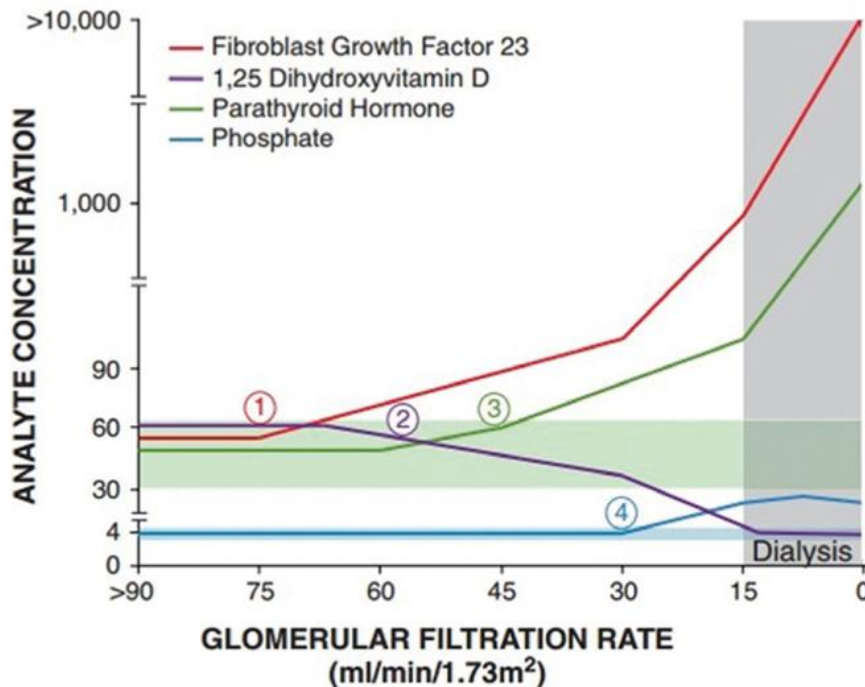
1. A majority of nephrologists believe mortality is too high in ESRD patients.
2. A majority of nephrologists believe that CKD-MBD is an important factor in mortality of ESRD patients.
3. Bookmakers opinion on Belgium's chances to win the 2014 WC :

2014 World Cup Winner Odds

	PADDYPOWER	William HILL	Ladbrokes	BETFRED	bet365	BETVICTOR	sky BET
Brazil	3	3	3	3	3	3	3
Argentina	5	9/2	9/2	9/2	4	5	5
Germany	11/2	11/2	11/2	11/2	11/2	11/2	5
Spain	7	7	6	7	7	7	6
Belgium	14	14	14	14	14	14	16
France	22	20	18	20	20	25	25
Italy	25	25	22	25	28	28	20

Introduction

- FGF-23 :
 - Phosphaturic hormone + 1,25(OH) vitamin D counter-regulation.
 - Secreted by osteoblasts and osteoclasts.
 - In CKD, rises before PTH and Ph levels.



Introduction

- FGF-23 levels are linked with:
 - Mortality in incident and prevalent hemodialysis patients,
 - Vascular calcifications, LVH, aortic calcifications of hemo patients...
 - In CKD patients, progression of renal disease, future CV events, all cause mortality...
 - In renal TP recipients, to bone density loss and hypophosphatemia.

Introduction

- FGF-23 in PD:
 - Increased serum phosphate, loss of residual renal function, longer dialysis vintage, and lower renal phosphate clearance were the main determinants of FGF-23 elevation (Isakova, CJASN 2011).
 - Lack of correlation between FGF-23 and mortality in incident dialysis patients, but differential results between dialysis modalities are not available (Olauson, NDT 2010).

Study : Methods

- Retrospective analysis, FGF-23 level at the start of PD (1998-2009).
- Bio-intact full length FGF-23 measured on frozen serum (Kainos labs ®).
- 89 patients included.

Study : Methods

- Primary end-point : relationship between FGF-23 level and a composite outcome (death or first CV event).
- A cut-off value of 730 pg/ml was arbitrary chosen based on both ROC curves and on the functional form of the predictor.
- Competing risk (TP or HD transfer) for statistical analysis.

Baseline characteristics

Table 1 : Univariate analysis : characteristics of all patients and according to FGF-23 cut off level (> or < 730 pg/ml).

Variable	All (n= 89)	FGF-23 < 730 pg/ml (n= 47)	FGF-23 > 730 pg/ml (n= 42)
Mean FGF-23	3702.2 ± 6589	302.35 ± 206.8	7506.8 ± 8066.7
Age (years)	52.5 ± 15.9	51.8 ± 16.6	53.3 ± 15.3
Sex ratio (M/F)	1.87	2.35	1.47
Active on TP waiting list	62 (69.6 %)	30 (63.8 %)	32 (76.2 %)
Race			
- Caucasian	74 (83.1 %)	38 (80.8%)	36 (85.7 %)
- Others	15 (16.9 %)	9 (19.2%)	6 (14.3 %)
Nephropathy			
- ADPKD	6 (6.7 %)	2 (4.2 %)	4 (9.5 %)
- Diabetic nephropathy	21 (23.6 %)	12 (25.5 %)	9 (21.4 %)
- Chronic glomerulonephritis	20 (22.5 %)	11 (23.4 %)	9 (21.4 %)
- Chronic interstitial nephritis	13 (14.6 %)	5 (10.6 %)	8 (19 %)
- Chronic allograft nephropathy	13 (14.6 %)	7 (14.9 %)	5 (11.9 %)
- Vascular nephropathy	10 (11.2 %)	4 (8.5 %)	6 (14.3 %)
- Others/Unknown	7 (7.8 %)	6 (12.8 %)	1 (2.4 %)
Comorbidities			
- Charlson index	4.7 ± 2.6	4.7 ± 2.6	4.7 ± 2.6
- Diabetes	24 (26.9 %)	13 (27.6 %)	11 (26.2 %)
- Hypertension	48 (53.9 %)	24 (51 %)	24 (57.1 %)
- Hypercholesterolemia	43 (48.3 %)	24 (51 %)	19 (45.2 %)
- Previous CV history	26 (29.2 %)	13 (27.6 %)	13 (30.9 %)
Biochemistry			
- eGFR (ml/min/1.73m ²)	8.3 ± 3.47	8.8 ± 3	8.3 ± 3.8
- Albumin (gr/dl)	3.22 ± 0.59	3.29 ± 0.5	3.2 ± 0.58
- Calcium (mg/dl)	9.05 ± 0.76	8.79 ± 0.74	9.05 ± 0.69
- Phosphorus (mg/dl)	4.97 ± 1.44	4.65 ± 1.41	4.97 ± 1.41
- CRP (mg/dl)	1.05 ± 1.2	1.07 ± 0.9	1.04 ± 1
- PTH (x normal value)	3.13 ± 3.23	3.64 ± 3	2.55 ± 3.39
- Total cholesterol (mg/dl)	196 ± 46.7	185 ± 53.3	201.5 ± 26.6
Peritoneal parameters			
- D/P creat 240 min	0.76 ± 0.12	0.77 ± 0.08	0.75 ± 0.15

Baseline characteristics

- In a nutshell :
 - Young patients (mean 52,5 y).
 - No difference between groups except sex ratio (more men in lower FGF-23 group).
 - Same (and relatively low) level of comorbidities and previous CV diseases.

Outcomes

Table 2 : Cardiovascular and infectious outcomes of patients followed for all patients and according to FGF-23 cut off level (> or < 730).

	All (n= 89)	FGF-23 < 730 (n= 47)	FGF-23 > 730 (n= 42)
Follow-up time (months)	29.6 ± 19.9	27.6 ± 20.3	31.93 ± 19.25
Outcomes			
- Transplantation	32 (36 %)	20 (42.5 %)	12 (28.5 %)
- Shift to hemodialysis	30 (33.7%)	15 (31.9 %)	15 (35.71 %)
- Death	14 (15.7 %)	7 (14.9 %)	7 (16.7 %)
- Remaining on PD	12 (13.5 %)	5 (10.6 %)	7 (16.7 %)
- Renal function recovery	1 (1.1 %)	0 (0 %)	1 (2.3 %)
Major CV events during follow-up			
- All	26 (29.2 %)	9 (19.1 %)	17 (40.5 %)
- 1 event	12 (13.5 %)	4 (8.5 %)	8 (19 %)
- 2 events	10 (11.2 %)	5 (10.6 %)	5 (11.9 %)
- 3 or more events	4 (4.5 %)	0	4 (9.5 %)
Type of first major CV events			
- Myocardial ischemia	12 (13.5 %)	2 (4.2 %)	10 (23.8 %)
- CVA/TIA	5 (5.6 %)	2 (4.2 %)	3 (7.1 %)
- Lower limb ischemia	7 (7.8 %)	3 (6.4 %)	4 (9.5 %)
- CABG	2 (2.2 %)	2 (4.2 %)	0
Time to first CV event (months)	16.9 ± 16.7	21.11 ± 24.33	14.7 ± 11.2
Peritonitis during follow-up			
- All	52 (58.4 %)	27 (57.4 %)	25 (59.5 %)
- 1 episode	28 (31.4 %)	14 (29.8 %)	14 (33.3 %)
- 2 episodes	12 (13.5 %)	10 (21.3 %)	2 (4.7 %)
- 3 episodes	9 (10.1 %)	1 (2.1 %)	8 (19 %)
- 4 or more episodes	3 (3.3 %)	2 (4.2 %)	1 (2.4 %)
Time to first peritonitis (months)	15 ± 14.3	16.18 ± 13.7	13.76 ± 13.3

CV : Cardiovascular; CVA : Cerebrovascular accident; TIA : Transient ischemic attack;

CABG : Coronary Artery Bypass Graft.

Outcomes

Table 3. Bivariate analysis for each outcome on peritoneal dialysis (Fine and Gray model).

Covariate	Composite		Transplantation		Transfer HD	
	sd-RH	95% CI	sd-RH	95% CI	sd-RH	95% CI
Age	1.04*	1.02-1.06	0.95*	0.931-0.969	0.99	0.964-1.03
Sex (female)	0.87	0.433-1.77	0.91	0.427-1.93	1.08	0.415-2.81
TP waiting list (Yes)	0.29*	0.15-0.565			0.75	0.3-1.85
FGF-23 cut off (>730)	2.13*	1.07-4.22	0.63	0.296-1.35	0.43	0.153-1.24
Charlson score	1.36*	1.19-1.55	0.59*	0.472-0.742	1.02	0.846-1.22
Phosphorus (mg/dl)	1.13	0.894-1.42	0.86	0.645-1.15	0.93	0.696-1.25
eGFR (ml/min/1.73m ²)	0.99	0.88-1.12	0.96	0.863-1.07	1.09	0.957-1.24
Calcium (mg/dl)	0.97	0.676-1.38	0.85	0.453-1.59	1.18	0.621-2.24
Albumine > 30 (gr/dl)	0.48*	0.245-0.928	2.46	1.01-5.97	1.22	0.46-3.22
CRP (mg/dl)	1.05	0.873-1.27	0.78	0.517-1.18	0.94	0.582-1.52

* = $p < 0.001$.

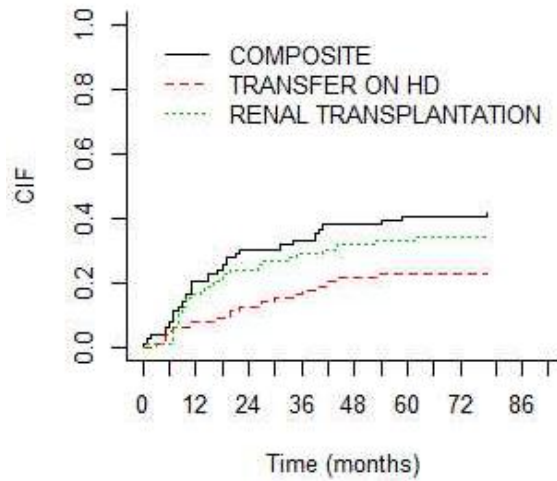
Outcomes

Table 4. Multivariate analysis: event of interest (composite of death or major CV event). Fine and Gray model (sd-RH).

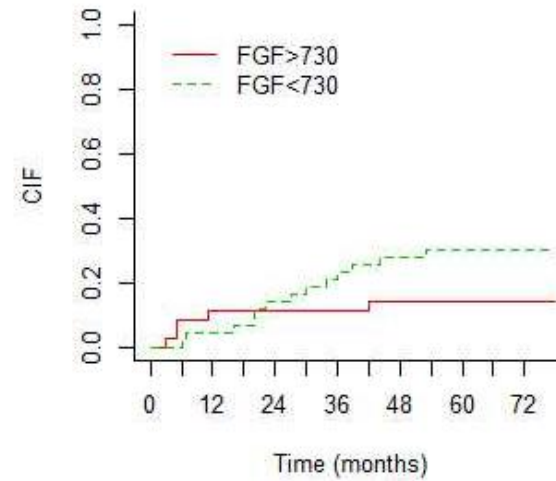
Covariate	Composite of death or major CV event		
	sd-RH	95% CI	<i>p</i> value
Charlson score	1.36	1.090-1.71	< 0.01
eGFR (ml/min/1.73m ²)	0.98	0.873-1.11	0.81
TP waiting list (Yes)	0.78	0.255-2.38	0.66
FGF-23 cut off (> 730)	2.85	1.355-5.98	< 0.01

Outcomes

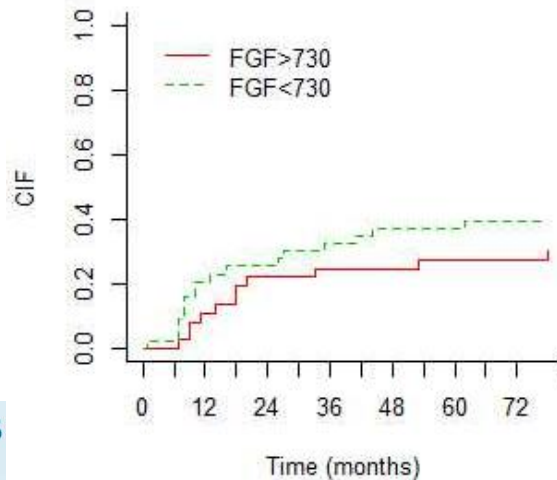
CIF of each outcome on PD



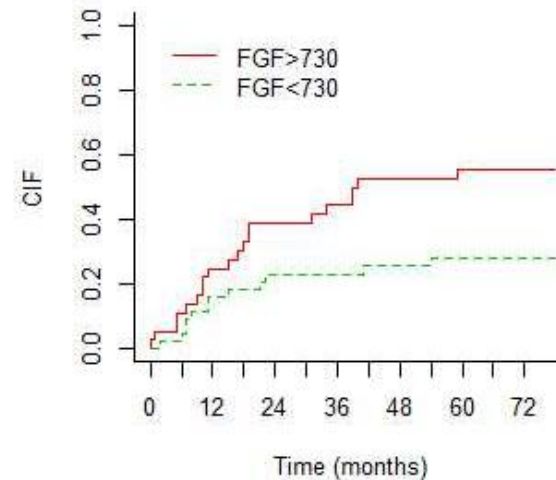
CIF of transfer on HD



CIF of renal transplantation



Composite



Conclusion

- FGF-23 level > 730 pg/ml :
 - Is statistically linked with an almost 3x higher risk of death or first major CV event in incident PD patients.
 - Incidence of AMI was particularly influenced.
 - First CV event occurred faster.
 - Higher rate of multiple CV events.

Conclusion

- FGF-23 level > 730 pg/ml :
 - Not influenced by sex in our cohort.
 - Residual kidney function comparable between groups : incident patients.
 - Phosphate slightly higher (4.97 mg/dl versus 4.65 mg/dl in lower FGF-23) groups but again, incident patients, starting RRT.

Limitations

- Small amount of patients (it's a PD study!).
- Retrospective, risk of residual confounding factors...
- Specific study population :
 - Young,
 - Low level of comorbidities...
- Prospective studies on larger cohorts needed.

THANK YOU FOR YOUR ATTENTION

