At what eGFR should we start dialysis?

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No conflict of interest

This presentation is **dedicated to all our patients** and their families who come to our clinic with statements like:

- ❑**‘’Doctor, mum said I might need to start dialysis now. I am afraid and I don’t really want to…”** (5 years old, CAKUT)
- ❑**‘’Doc, when will we start dialysis? I cannot wait any more! I am really fed up…”** (13 years old, FSGS)

Background

Criteria to start dialysis

Aim when starting dialysis

Early vs. Late

Background

Criteria to start dialysis

1. **Uremic symptoms** (pericarditis, encephalopathy….)
2. **Abnormal biochemical findings** (severe hyperK+ and/or acidosis)
3. **Diuresis-resistant fluid overload** (pulmonary oedema)
4. **Failure to growth**

Aim when starting dialysis

1. **Prolong life**
2. **Improve life**

Poll Question (1) : A clinician should base their decision to initiate maintenance dialysis on a child on the presence of…

a) Biochemical abnormalities difficult to control by medications, diuresis-resistant fluid overload and growth, but not eGFR

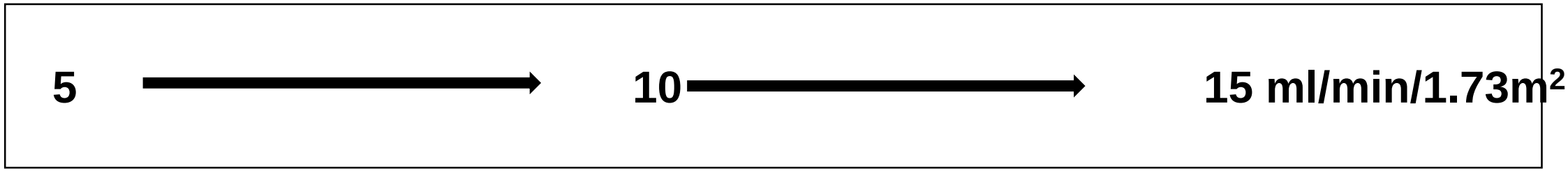
b) Answer (a) including eGFR. The primary renal disease(PRD) should not affect our decision.

c) Answer (a) including PRD. The eGFR should not affect our decision.

d) Biochemical abnormalities difficult to control by medication, diuresis-resistant fluid overload, PRD, growth, HTN, eGFR, patient-related QoL and a shared decision making with parents/families.

When should children be considered to start dialysis ?

European Paediatric Peritoneal Dialysis Working G. Guidelines, Perit Dial Int 2001 < 10-15 mL/min/1.73m^2



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european society for paediatric nephrology

5 → **10** → **15 ml/min/1.73m²**

RRT in children should be **recommended** when the eGFR further falls **< 8 mL/min/1.73m²**

RRT in children should be **considered** when the eGFR falls **< 14 mL/min/1.73m²**

National Kidney Foundation® | KDOQI® Kidney Disease Outcomes Quality Initiative

2006

When should children be considered to start dialysis ?

Canadian Society of Nephrology, 2014

Start dialysis if
< 6 mL/min/1.73m²

European Paediatric Peritoneal Dialysis Working G. Guidelines, Perit Dial Int 2001 **< 10-15 mL/min/1.73m²**

Close monitoring if **< 15 mL/min/1.73m²**

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Update KDOQI 2015: symptoms & signs

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NICE National Institute for Health and Care Excellence

2018: **5-7 mL/min/1.73m²** if no symptoms

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5

1.73m²

RRT in c

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min/1.73m²

KDIGO 2019:
There is no specific eGFR for initiation of dialysis in the absence of symptoms and current data do NOT support pre-emptive dialysis initiation.

NICE
National Institute for Health and Care Excellence

2018: **5-7 mL/min/1.73m²** if no symptoms

National Kidney Foundation® KDOQI® Kidney Disease Outcomes Quality Initiative

2006

Update KDOQI 2015: symptoms & signs

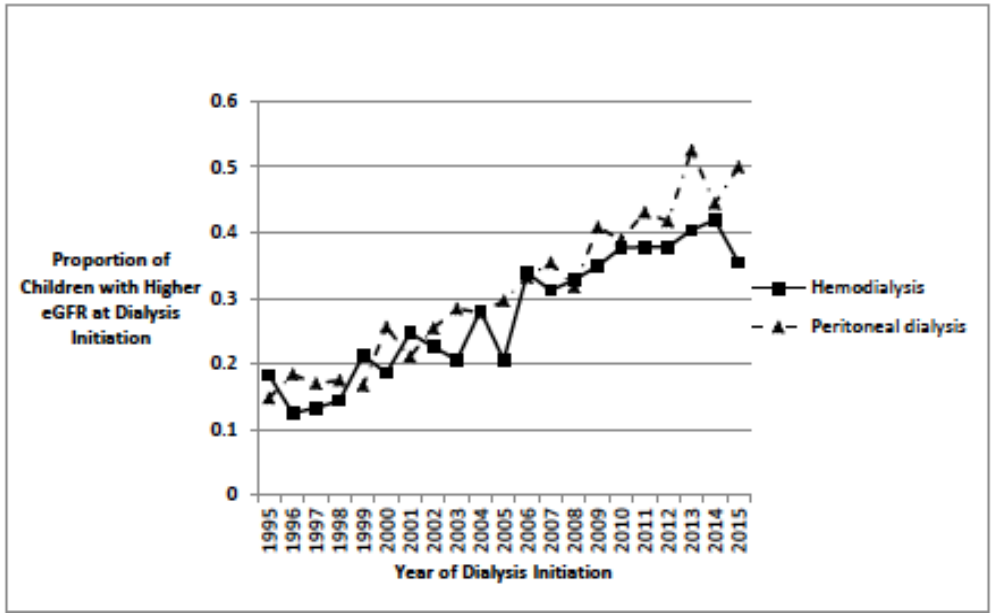
When are children currently starting dialysis ?

1) ESPN/ERA-EDTA Registry for children, Preka et al, Nephrol Dial Transplant 2019

Median eGFR at start of RRT was **8.2 mL/min/1.73m²**
(IQR 6.2-10.7 mL/min/1.73m²)

2) US Renal Data System Registry in children, Okuda et al, AJKD 2019

Median eGFR at start of RRT was **7.8 mL/min/1.73m²**
[IQR 5.6-10.5 mL/min/1.73m²]



Winnicki et al, JASN 2019, Increase in children who start dialysis at higher eGFR > 10 → Median eGFR 12.8 (IQR 11.1-16.0)

Poll Question (2) : According to the only RCT in adults and the 3 largest paediatric registry observational studies, what is the main conclusion regards the optimal time to start maintenance dialysis?

a) ‘’The earlier the better’’
b) ‘’The later the better”
c) There is no evidence supporting benefit from early initiation. However, decisions in children should be made on a case-by-case basis.
d) There is no evidence supporting benefit from early initiation. However, when eGFR is between 5 and 7 ml/min/1.73m2 dialysis should always be initiated.

Only one RCT in 2010, the "IDEAL study"

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 12, 2010 VOL. 363 NO. 7

A Randomized, Controlled Trial of Early versus Late Initiation of Dialysis

Bruce A. Cooper, M.B., B.S., Ph.D., Pauline Branley, B.Med., Ph.D., Liliana Bulfone, B.Pharm., M.B.A., John F. Collins, M.B., Ch.B., Jonathan C. Craig, M.B., Ch.B., Ph.D., Margaret B. Fraenkel, B.M., B.S., Ph.D., Anthony Harris, M.A., M.Sc., David W. Johnson, M.B., B.S., Ph.D., Joan Kesselhut, Jing Jing Li, B.Pharm., B.Com., Grant Luxton, M.B., B.S., Andrew Pilmore, B.Sc., David J. Tiller, M.B., B.S., David C. Harris, M.B., B.S., M.D., and Carol A. Pollock, M.B., B.S., Ph.D., for the IDEAL Study*

RCT between 2000-2008
828 adults
- 404 early-starters (eGFR 10-14ml/min/1.73m^2)
- 424 late-starters (eGFR 5-7 ml/min/1.73m^2)
- Median follow-up: 3.59 years

Cooper et al, IDEAL Study, NEJM 2010 :

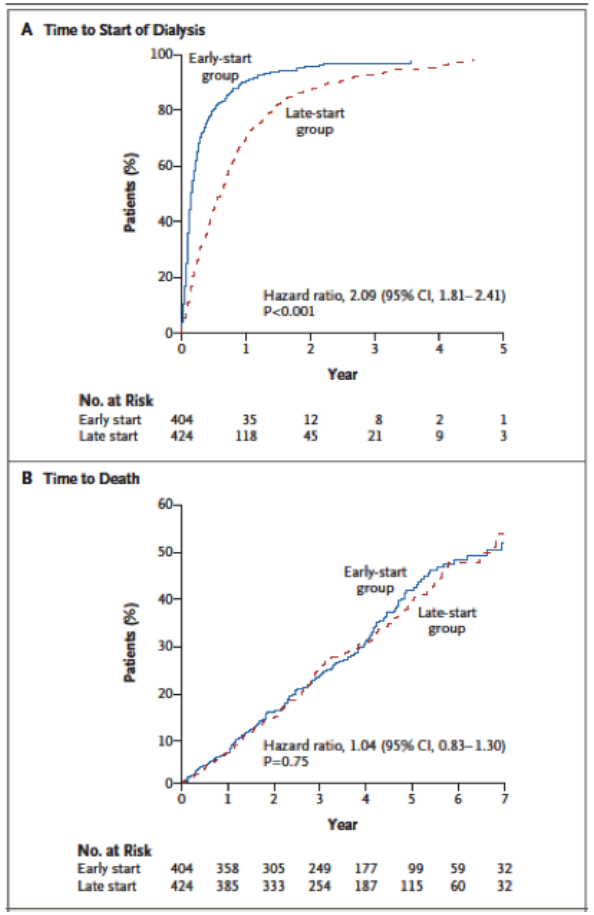


Table 2. Primary and Secondary Outcomes, Including Adverse Events.

Outcome	Early-Start Group (N=404)		Late-Start Group (N=424)		Hazard Ratio with Early Start (95% CI)	P Value
	No. of Events	No. of Events/ 100 Patient-Yr	No. of Events	No. of Events/ 100 Patient-Yr		
Primary outcome: death from any cause	152	10.2	155	9.8	1.04 (0.83–1.30)	0.75
Secondary outcomes						
Composite cardiovascular events	139	10.9	127	8.8	1.23 (0.97–1.56)	0.09
Cardiovascular death	63	4.2	71	4.5	0.94 (0.67–1.32)	0.70
Nonfatal myocardial infarction	47	3.4	37	2.4	1.39 (0.91–2.15)	0.13
Nonfatal stroke	33	2.3	29	1.9	1.21 (0.73–2.00)	0.45
Hospitalization with new-onset angina	42	3.0	39	2.6	1.15 (0.75–1.78)	0.52
Transient ischemic attack	9	0.6	4	0.3	2.36 (0.73–7.68)	0.15
Composite infectious events	148	12.4	174	14.3	0.87 (0.70–1.08)	0.20
Death from infection	39	2.6	28	1.8	1.46 (0.90–2.38)	0.12
Hospitalization for infection	135	11.3	170	13.9	0.81 (0.65–1.02)	0.07
Complications of dialysis						
Need for access revision	145	13.2	147	12.4	1.08 (0.85–1.35)	0.54
Access-site infection	47	3.4	50	3.5	0.99 (0.67–1.48)	0.97
Serious fluid or electrolyte disorder	146	13.2	175	15.0	0.88 (0.71–1.10)	0.26
Placement of temporary dialysis catheter	118	10.0	124	9.7	1.03 (0.80–1.32)	0.85
Death as a result of treatment withdrawal	24	1.6	22	1.4	1.17 (0.66–2.08)	0.60
Death from cancer	14	0.9	16	1.0	0.92 (0.45–1.89)	0.82
Death from another cause	12	0.8	18	1.1	0.72 (0.35–1.49)	0.37

Primary outcome: **Time-to-death**

37.6% (152/404) **early-starters (eGFR 10-14)**

36.6% (155/424) **late-starters (eGFR 5-7)**

(HR with early initiation 1.04; 95% CI, 0.83-1.30, *p=0.75*)

Secondary outcome:

No significant difference of adverse events

(cardiovascular, infections, complications of dialysis)

Is there evidence to guide us in the timing of dialysis initiation in children?

1. **Quality of Life (QoL)**
2. **Mortality**
3. **Morbidity**
   - **Infection & Inflammation**
   - **Growth**
   - **Anaemia**
   - **Metabolic disease**
4. **Economic considerations**

Quality of Life (QoL)

Quality of Life (QoL)

1. Chronic dialysis in children is associated with **lower QoL scores than any other chronic condition apart from cancer!**
2. Depression
3. Loss of schooling, less well with schoolwork
4. Family breakdown, difficulties maintaining employment
5. Restricted lifestyle, worse adherence
6. Feeling of ‘’being different”

Rees L, Assessment of dialysis adequacy: beyond urea kinetic measurements. Pediatr Nephrol 2019
Rees L et al, Chronic dialysis in children and adolescents: challenges and outcomes, Lancet Child Adolesc Health 2017
Clementi et al, Psychosocial considerations and recommendations for care of pediatric patients on dialysis. Pediatr Nephrol 2019
Neul et al, Health-related quality of life functioning over a 2-year period in children with end-stage renal disease. Pediatr Nephrol 2013

Mortality

Okuda et al, Estimated GFR at dialysis initiation and mortality in children and adolescents. Am J Kidney Dis 2019

Preka et al, Association between timing of dialysis initiation and clinical outcomes in the paediatric population: An ESPN-ERA-EDTA Registry study. Nephrol Dial Transplant 2019

Winnicki et al, Higher eGFR at dialysis initiation is not associated with a survival benefit in children. J Am Soc Nephrol 2019

US renal data system registry

Okuda et al, Am J Kidney Dis 2019

- **9,963** incident dialysis patients
- Age: **1-17 years old**

- **5 groups (eGFR)** :
  - <5 (late starters) HR 0.57 (95%CI 0.43-0.74)
  - 5-6.9
  - 7-8.9
  - 9-11.9
  - > 12 (early starters) HR 1.31 (95%CI 1.05-1.65)

↑Mortality risk across ↑ eGFRs

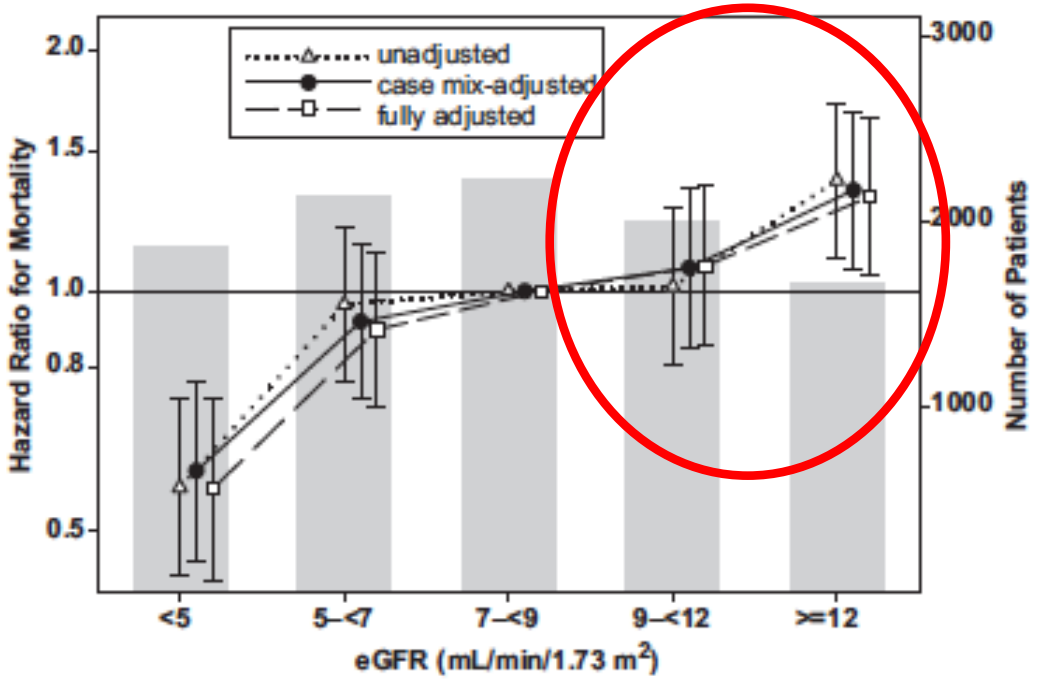
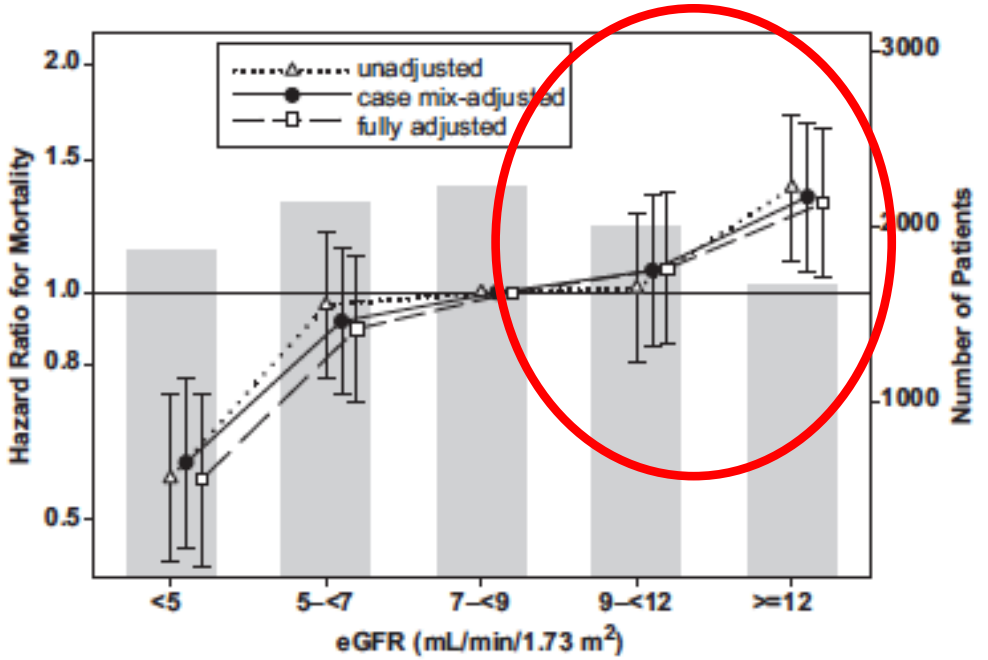


Figure 3. Hazard ratios for mortality across estimated glomerular filtration rates (eGFRs) at dialysis therapy initiation.

US renal data system registry

Okuda et al, Am J Kidney Dis 2019



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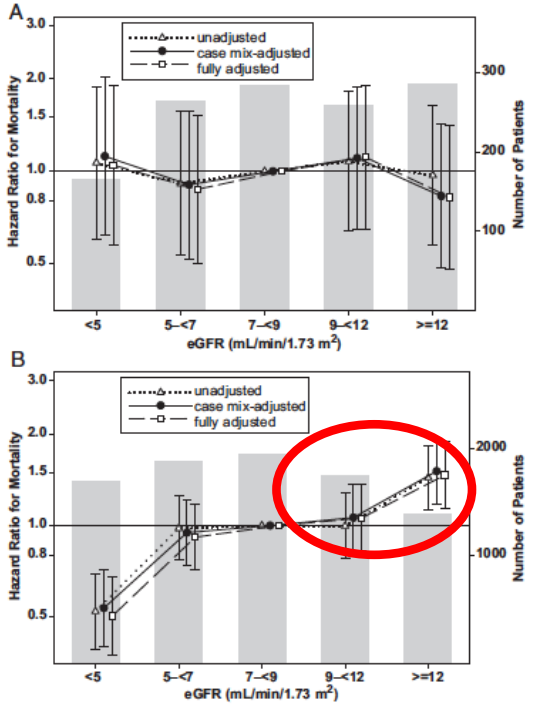


Figure 4. Hazard ratios for mortality in patients (A) younger than 6 years and (B) 6 years or older. Abbreviation: eGFR, estimated glomerular filtration rate.

Below 6 years old

Above 6 years old

US renal data system registry

Winnicki et al, JASN 2019

Table 2.

Adjusted hazards of death for the overall cohort and in analysis restricted to the year 2006–2015

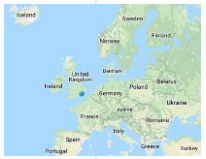
Characteristics	Adjusted HR (95% CI)	*P* Value
Years 1995–2015		
All patients (n=14,696)[a]	1.36 (1.24 to 1.50)	<0.001
Patients initiated on HD (n=8794)	1.56 (1.39 to 1.75)	<0.001
Patients initiated on PD (n=5902)	1.07 (0.91 to 1.25)	0.44
Years 2006–2015		
All patients (n=6757)[b]	1.34 (1.11 to 1.62)	0.002
Patients initiated on HD (n=4151)	1.68 (1.33 to 2.12)	<0.001
Patients initiated on PD (n=2606)	0.86 (0.62 to 1.20)	0.37

[a]A total of 474 persons missing from adjusted analysis due to missing covariate data.
[b]A total of 217 persons missing from adjusted analysis due to missing covariate data.

- **15,170** incident dialysis patients
- Age: **1 - 18 years old**

- **2 groups (eGFR)** :
- ≦ 10 ml/min/1.73m^2 → late starters
- > 10 ml/min/1.73m^2 → early starters

↑36% Mortality risk across ↑ eGFRs

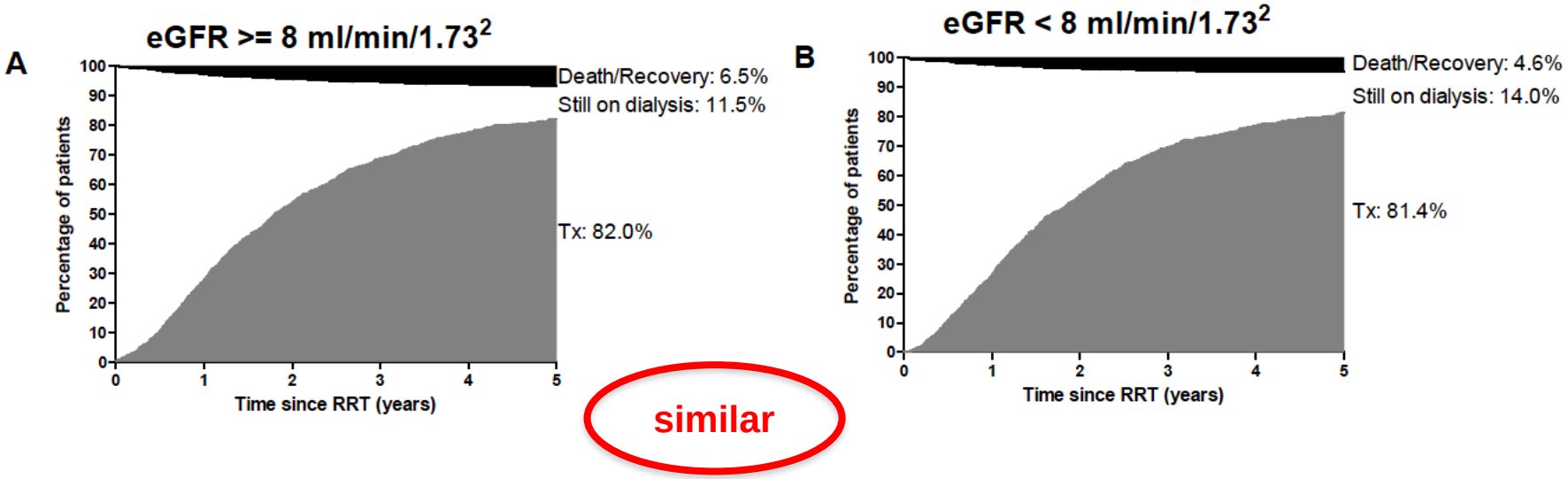


ESPN/ERA-EDTA registry data

Preka et al, Nephrol Dial Transplant 2019

- **2,963** incident dialysis patients
- Age: **< 18 years old**

- **2 groups (eGFR)** :
  - < 8 ml/min/1.73m^2 → late starters
  - ≥ 8 ml/min/1.73m^2 → early starters



Mortality risk : Late vs early initiation of dialysis:

- HR 1.00, 95% CI: 0.66-1.51
- aHR 0.82, 95% CI: 0.54-1.25

Likelihood to receive a Tx within 1,2 & 5 years after initiating dialysis:

1- year : 0.93, 95% CI 0.81-1.08 (aHR 1.00, 95% CI 0.86-1.16)

2- years: 0.98, 95% CI 0.88-1.10 (aHR 1.03, 95% CI 0.92-1.15)

5- years: 0.97, 95% CI 0.89-1.07 (aHR 1.02, 95% CI 0.93-1.12)

Is there evidence to guide us in the timing of initiation of dialysis in children?

1. Quality of Life (QoL)
2. Mortality
3. **Morbidity**
   - **Cardiovascular morbidity**
   - **Growth**
   - **Infection & Inflammation**
   - **Anaemia**
   - **Metabolic disease**
4. Economic considerations

Cardiovascular morbidity (HTN, LVH)

- IDEAL study (adults): no difference in LVEF, LVM, LVAV
- **Children**:

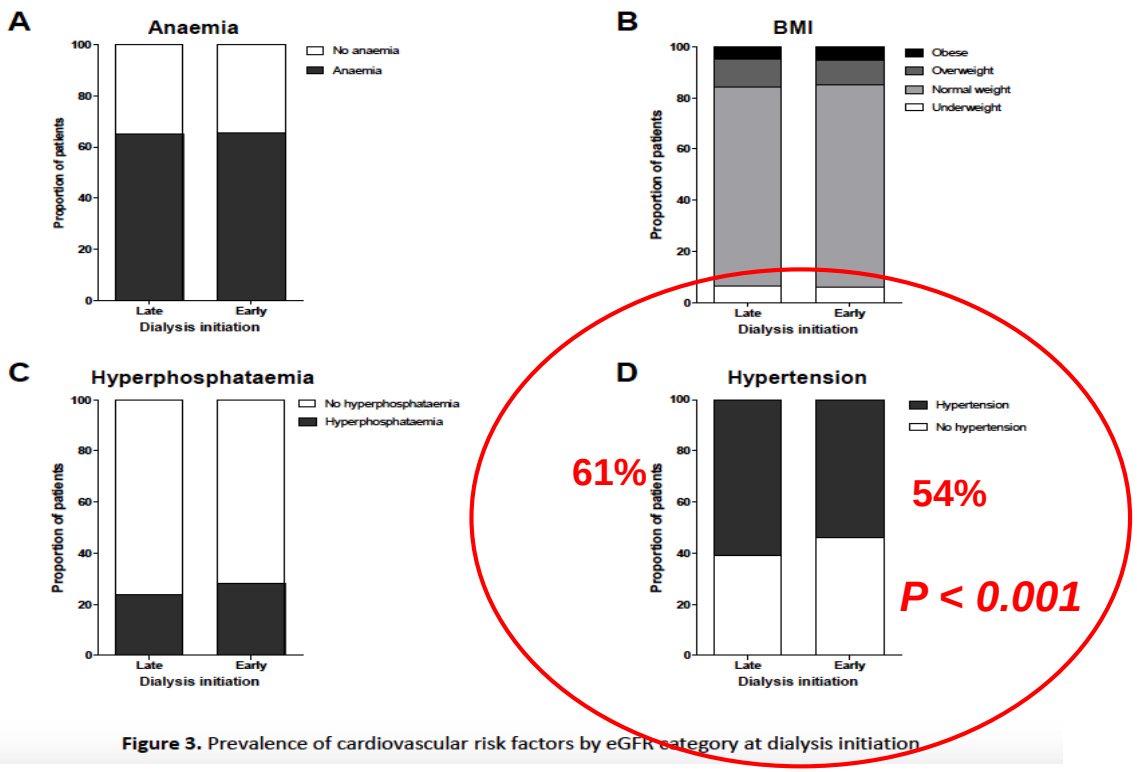


Figure 3. Prevalence of cardiovascular risk factors by eGFR category at dialysis initiation

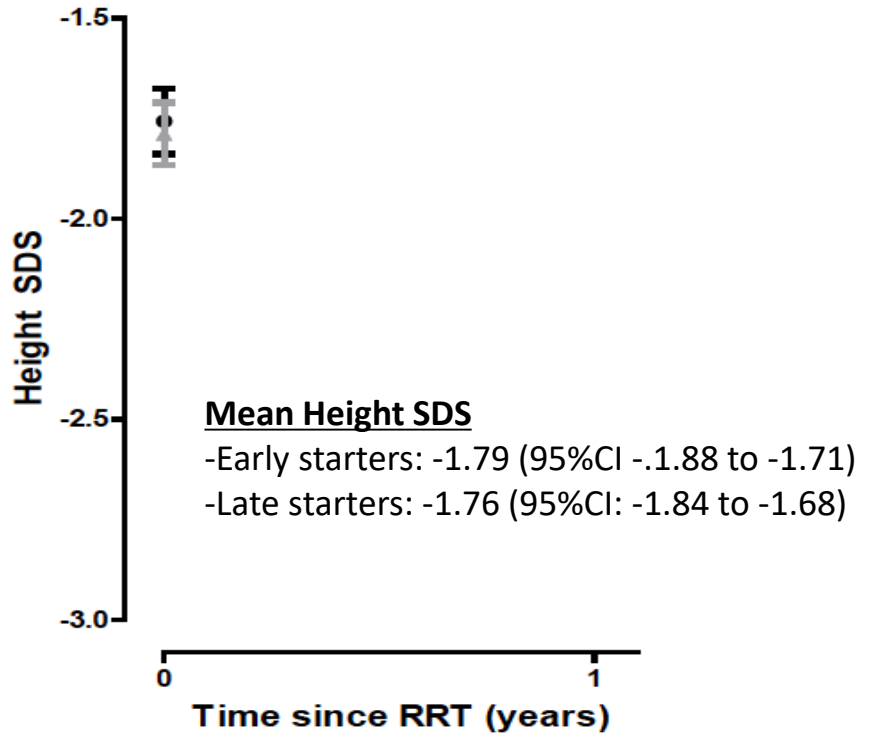
Preka et al NDT 2019

	Early-starters (> 10 ml/min/1.73m2)	**Late-starters** (<7 ml/min/1.73m2)	**P value**
LVMI (g/m^2)	53±28	**60±28**	NS
LVH	51%	**64%**	NS
Number of deaths	5	6	NS
Frequency of hospitalizations (episodes/person-year)	1.8	2.0	NS
CRP (mg/l) (N=0-6)	3.64±2.00	4.37±3.28	NS
Hemoglobin (g/dL)	10.5±2.1	10.3±1.9	NS

Bakkaloglu et al, Paediatr Nephrol 2017

Growth (Height, BMI)

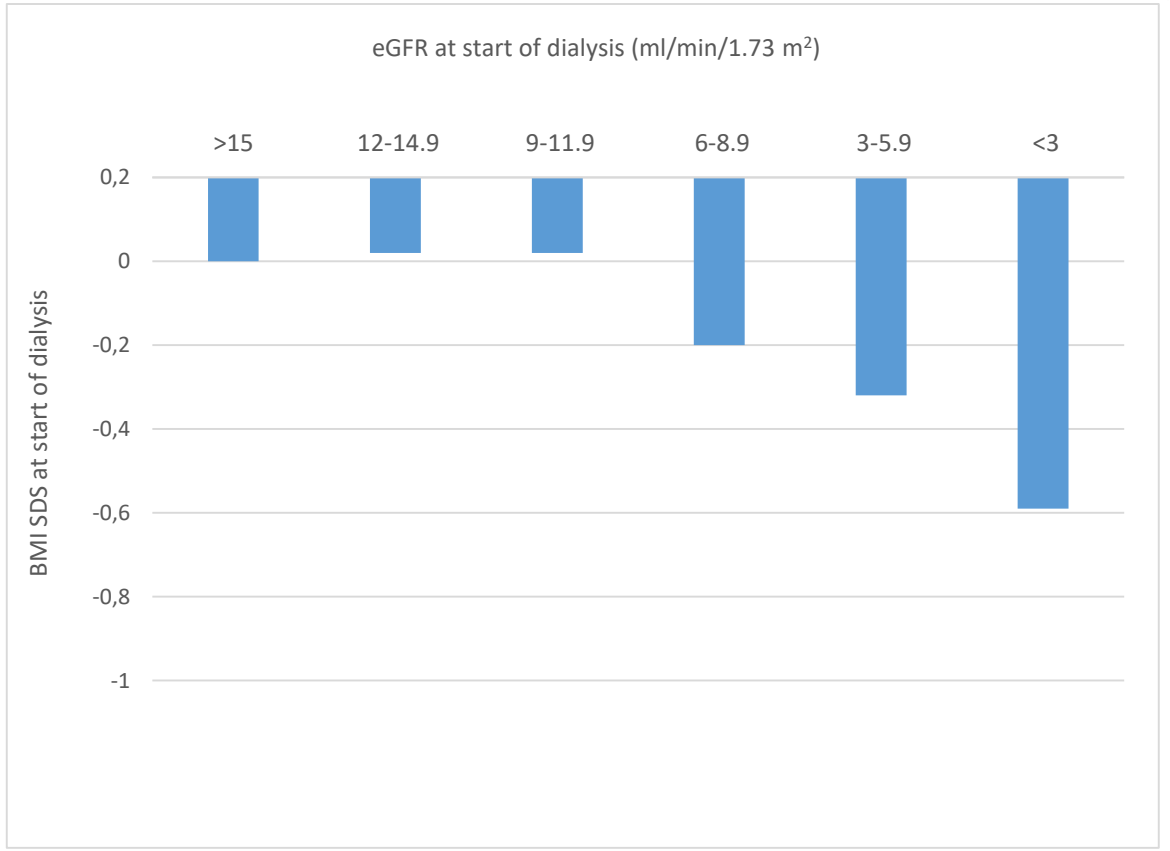
11% underweight with eGFR < 6
vs.
5.3% with eGFR 9-12 ml/min/1.73m2



Mean Height SDS
-Early starters: -1.79 (95%CI -.1.88 to -1.71)
-Late starters: -1.76 (95%CI: -1.84 to -1.68)

Figure 2. Modelled evolution of height standard deviations score (SDS) patients starting dialysis early (eGFR ≥ 8 ml/min/1.73 m2) (grey triangles), and patients starting dialysis late (eGFR < 8 ml/min/1.73 m2) (Black squares). Adjustments were made for age, sex, PRD, and treatment modality.

Preka et al NDT 2019



Mean BMI SDS at first observation according to eGFR at initiation of CPD

Schaefer et al, Sci Rep 2019

Further comorbidities:

1. **Infection & Inflammation** (IDEAL study, ESPN/ERA-EDTA registry data) – No difference

2. **Anaemia** [ESPN/ERA-EDTA Registry data showed slightly higher prevalence among late starters (aOR 1.14, 95%CI 0.99-1.32)]

3. **Metabolic disease** (ESPN/ERA-EDTA Registry data showed commoner hyperphosphatemia in early vs late starters (28% vs 24%)

Further comorbidities:

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Economic considerations:

- **IDEAL study**: higher dialysis-related costs associated with early start but similar resources costs (managing adverse events)
- **No data in children**

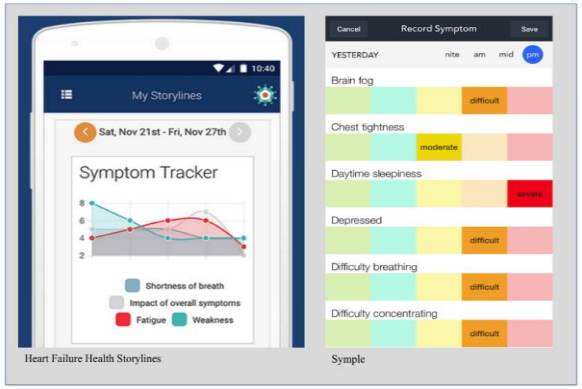
Poll Question (3): After all conservative treatment efforts have been tried, there is some evidence that early initiation of dialysis in children might improve:

a) Hypertension
b) Growth
c) Metabolic Bone Disease
d) Over-all-morbidity

Non eGFR-based approaches to determine timing of dialysis initiation

1. **Symptoms assessment -** smartphone-based mobile health apps
2. **Equations helping in estimating ESKD: Kidney Failure Risk Equation (KFRE) & CKD progression risk timelines**

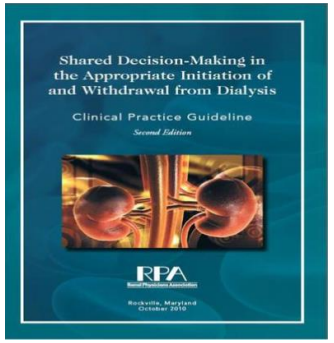
   Winnicki et al, JAMA Pediatr 2018
   Furth et al, Am J Kidney Dis 2018



3. **Novel markers of kidney function linked to kidney deterioration** (uremic retention solutes, proximal tubular secretion molecules) and the **impact of RRF** in outcome.

   Indoxyl sulfate
   P-crestyl sulfate
   Hippurate
   etc

4. Increased emphasis on the importance of **patient-provider-caregiver shared decision-making**



Conclusions

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1. **US renal data registry studies**: incremental and linear association between eGFRs at dialysis initiation and mortality, such that higher eGFRs at dialysis therapy initiation were associated with higher risk for mortality (except in patients < 6 years old)

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1. **US renal data registry studies**: incremental and linear association between eGFRs at dialysis initiation and mortality, such that higher eGFRs at dialysis therapy initiation were associated with higher risk for mortality (except in patients < 6 years old)

2. **ESPNA/ERA-EDTA data registry**: Not any association between timing of dialysis initiation and mortality, access to transplantation or growth. The only difference observed was with HTN, which was more prevalent in late starters → special attention for prevention of CVD should be considered when opting for conservative treatment

Recommendations

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3. A reasonable approach is to **defer initiation of dialysis in asymptomatic individuals** until the development of signs and symptoms consistent with uremic syndrome that may reasonably be expected to improve with dialysis treatment.

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4. **Deferred initiation does not, however means deferred preparation**, and early discussions regarding medical and psychosocial preparation for the initiation of dialysis should not be delayed (→ placement of dialysis access, dialysis modality selection, advance care planning, assistance with home therapies).

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4. **Deferred initiation does not, however means deferred preparation**, and early discussions regarding medical and psychosocial preparation for the initiation of dialysis should not be delayed (→ placement of dialysis access, dialysis modality selection, advance care planning, assistance with home therapies).
5. Critical need for the Nephrology research community to pursue work to better understand and define the components of the uremic syndrome.

International Committee of the Red Cross

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Mourad Mourad, aka the "doctor clown", entertains children in the kidney dialysis ward in a local hospital in Gaza.

Photo: Omar Al-Qatta

The optimal time for starting dialysis in children
should be discussed case by case and is definitely NOT merely dependent on the level of eGFR/Creat level

Thank you for your attention !

Happy to take questions/comments @ evgenia.preka@gmail.com

Extras (if needed for the discussion)

Limitations to acknowledge

Biases (survival, potential selection biases, lead-time biases…)

Nature of observational studies (although large)

Residual confounding factors (RRF? doses of GH? Feeding management?)

Change in methods for Screat calculation:

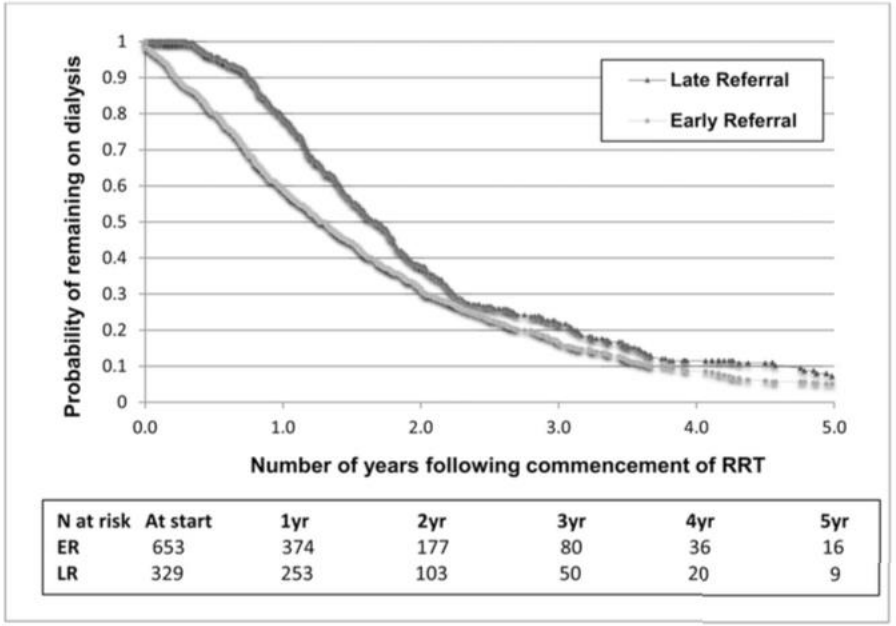
- before 2005 Jaffe method
- 2005-2009 transition period for most centers
- after 2009 Schwartz formula

UK registry data

Pruthi et al, cJASN 2016

- **1,603** incident dialysis patients
- Age: **3 months - 16 years old**

25% late referrals (LR > 3 months)
Median follow-up: 4.8 (2.9-7.6) years



N at risk	At start	1yr	2yr	3yr	4yr	5yr
ER	653	374	177	80	36	16
LR	329	253	103	50	20	9

No difference in **mortality** (HR 1.30; 95%CI, 0.7-2.3; p=0.40

Figure 2. | **Kaplan–Meier estimate of time to transplantation, by timing of referral in children with RRT.** Children that received pre-emptive transplants (all ER) and children aged <2 years at RRT start were excluded from this analysis. The log-rank test for the Kaplan–Meier analyses was $P<0.001$. ER, early referral; LR, late referral.

Transplantation (Tx) up to 1 year :

- 61% ER vs. 21% LR
- No difference in Tx after the 1st year

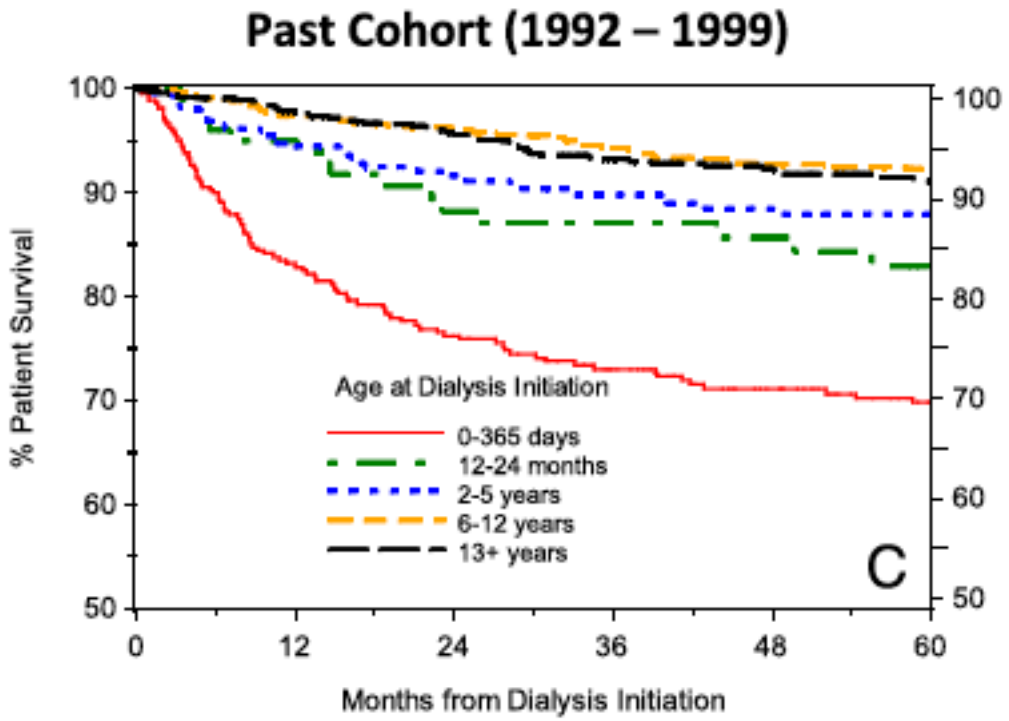
What is the optimal time/eGFR to start dialysis in children?

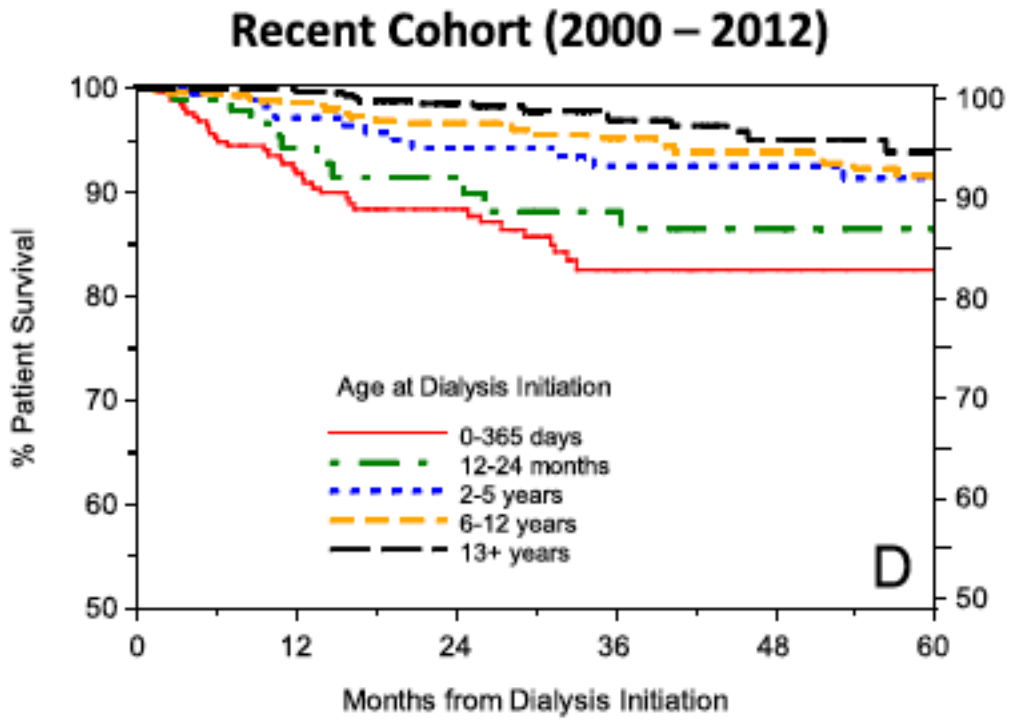
	Okuda et al, AJKD 03/2019	Preka et al, NDT 04/2019 in press
Study design	Retrospective cohort; USRDS Registry	Retrospective cohort; ESPN/ERA-EDTA Registry
Setting & Participants	9,963 incident dialysis patients ; aged 1-17 years old	2,963 incident dialysis patients; Aged < 18 years old
Primary outcome	1. **Time-to all-cause death**	**1. Patient's survival** **2. Access to Transplantation**
Secondary outcomes	**Predictors of dialysis initiation** (early vs. late)	**1. Growth** **2. Cardiovascular risk factors**
Groups divided (according to eGFR at start of dialysis)	5 groups: <5⇑ 5-6.9, 7-8.9, 9-11.9, >⇑12 Late starters Early starters	2 groups: - < 8 ml/min/1.73m² → late starters - ≥ 8 ml/min/1.73m² → early starters

↑Mortality risk across ↑ eGFRs

Patients with HTN should be carefully considered.

NAPRTCS Data: Overall survival according to age at which chronic PD was initiated for treatment of ESRD





Carey et al, Pediatrics 2015