Progression of CKD in children: How effective are therapeutic interventions?

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Introduction

- In the Kidney Disease Improving Global Outcome (KDIGO) CKD clinical practice guideline published in the year 2013, CKD is defined as:
  - Any abnormalities of kidney structure or function (kidney damage) with implications for health
  - Present for at least three consecutive months

Introduction

- End-stage kidney disease reduces life expectancy as exemplified by the 30–150 times higher mortality in children and teenagers receiving dialysis compared with same age healthy individuals.
- Early institution of supportive therapies and drug treatment aimed at reducing CKD progression and extrarenal complications is essential.

Kidney Function

Purpose of kidney function assessment

- To identify individuals with reduced level of kidney function who are at risk of accelerated renal function decline.
  - Serum creatinine
  - Serum cystatin c
  - eGFR estimating equations
  - Direct GFR measurements

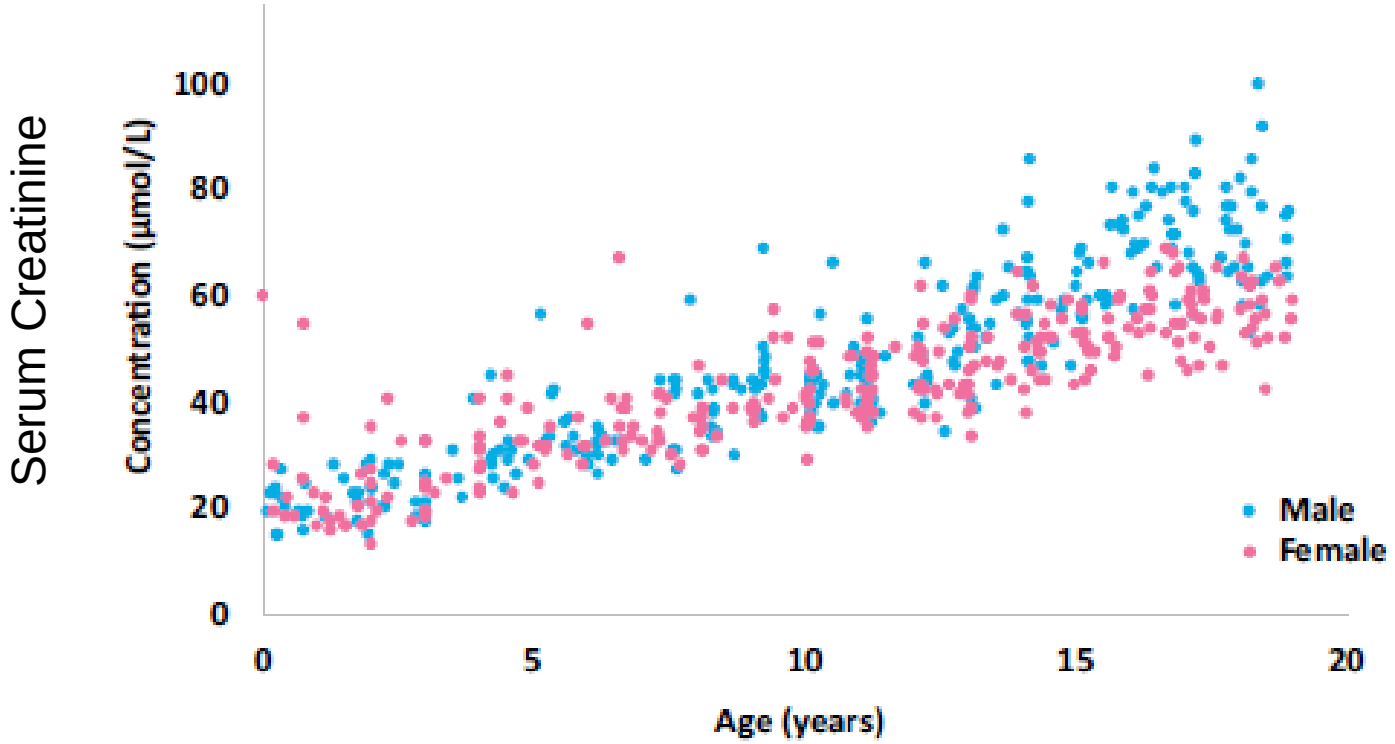
Clinica Chimica Acta 490 (2019) 88–97

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Pediatric reference intervals for clinical chemistry assays on Siemens ADVIA XPT/1800 and Dimension EXL in the CALIPER cohort of healthy children and adolescents



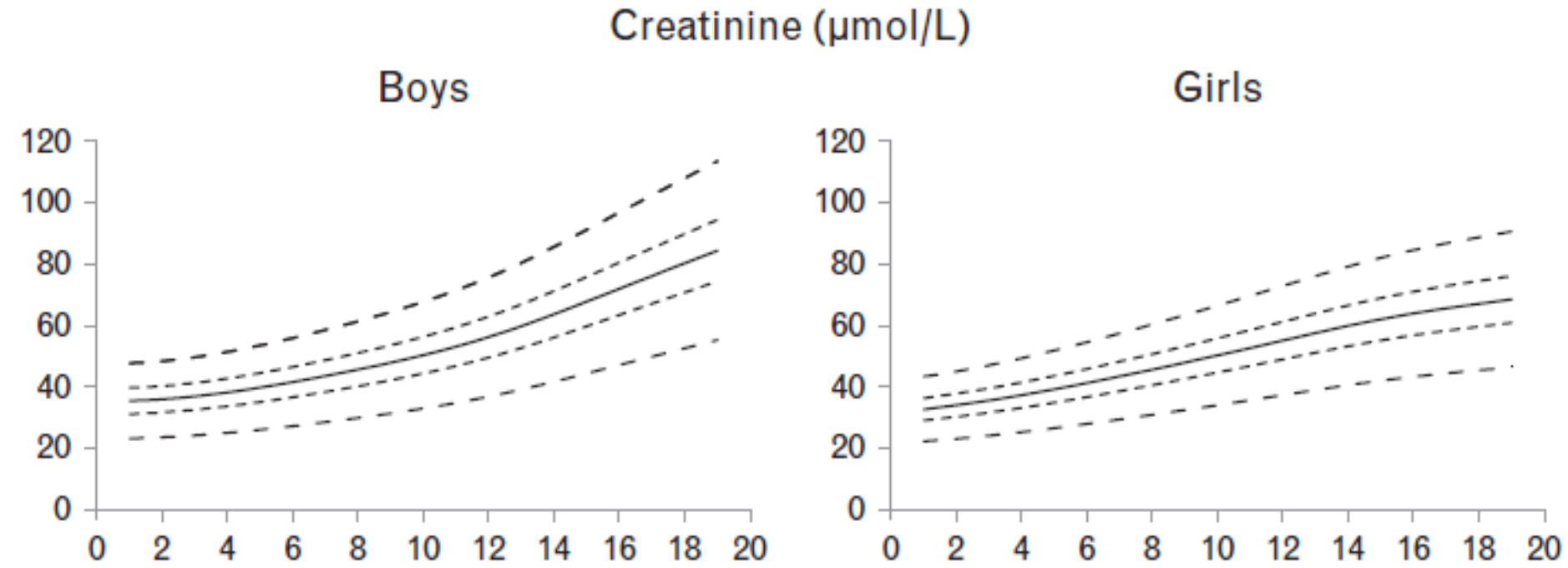
Pathology (August 2015) 47(5), pp. 452–461

CHEMICAL PATHOLOGY

Trends and physiology of common serum biochemistries in children aged 0–18 years

TZE PING LOH[1] AND MICHAEL PATRICK METZ[2,3]

[1]Department of Laboratory Medicine, National University Hospital, Singapore; [2]Division of Chemical Pathology, SA Pathology, Women's and Children's Hospital, and [3]School of Paediatrics and Reproductive Health, University of Adelaide, Adelaide, SA, Australia



Pediatr Nephrol (2010) 25:2107–2113
DOI 10.1007/s00467-010-1533-y

ORIGINAL ARTICLE

Reference values for serum creatinine in children younger than 1 year of age

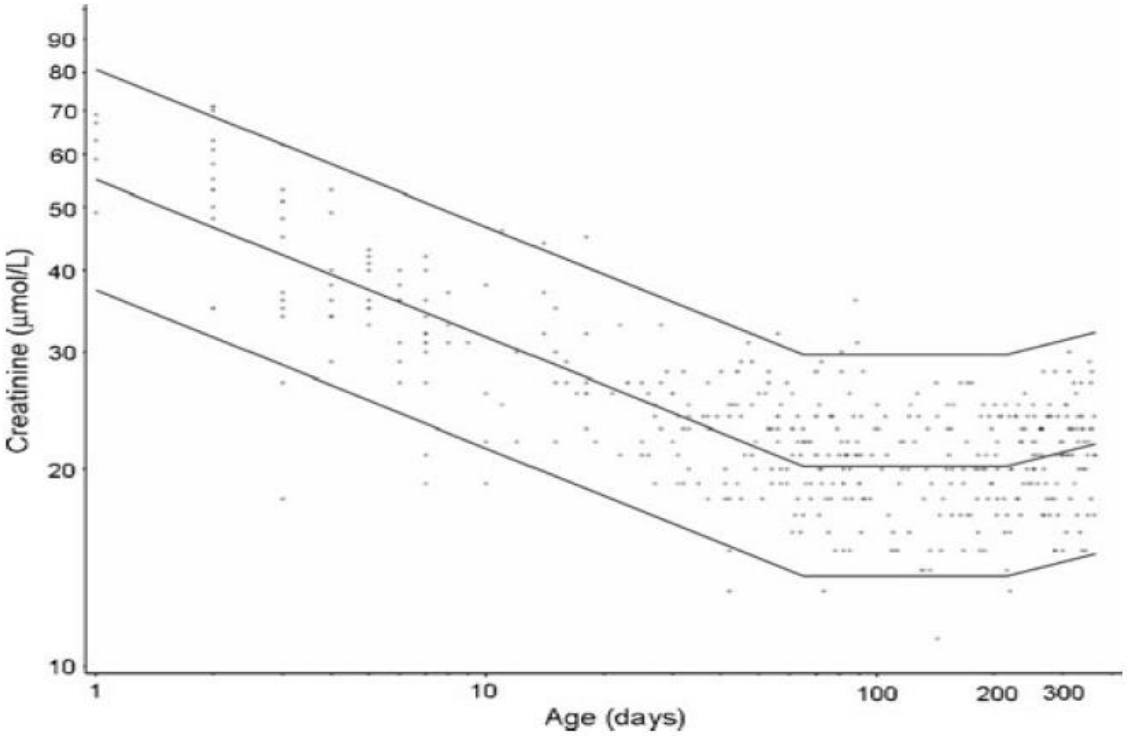


Fig. 1 Reference values of serum creatinine in children younger than 1 year of age. *Symbols* Individual serum creatinine value of each patient included in the study, *lines* geometric mean (*middle*) and the 2.5th (*lower*) and 97.5th (*upper*) percentiles

CLINICAL EPIDEMIOLOGY www.jasn.org

New Equations to Estimate GFR in Children with CKD

George J. Schwartz,* Alvaro Muñoz,† Michael F. Schneider,† Robert H. Mak,‡ Frederick Kaskel,§ Bradley A. Warady,‖ and Susan L. Furth†¶

*Department of Pediatrics, University of Rochester School of Medicine, Rochester, and §Department of Pediatrics, Albert Einstein College of Medicine, Bronx, New York; †Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health and ¶Department of Pediatrics, Johns Hopkins School of Medicine, Baltimore, Maryland; ‡Department of Pediatrics, Children's Hospital of San Diego, San Diego, California; ‖Department of Pediatrics, Children's Mercy Hospital, Kansas City, Missouri

eGFR = Ht (cm) x 36.5 mcmol/L)/SCr mcmol/L

www.kidney.org/professionals/kdoqi/gfr_calculatorPed

J Am Soc Nephrol 20: 629–637, 2009. doi: 10.1681/ASN.2008030287

Direct measurement of kidney function (GFR)

- Isotope-labeled markers such as
  - ^{51}Cr-EDTA, ^{99}mTc-DTPA, and ^{125}Iothalamate
  - and iohexol, a nonradioactive low-osmolar contrast agent widely used in clinical laboratories.
  - Unit: mL/min./1.73m^2

Definition and staging of CKD in children

Definition and staging of pediatric CKD

- The same criteria are used to define and stage CKD in children and adults.
- Definition of CKD
  - any abnormalities of kidney structure or function with implications for health
  - present for at least three consecutive months
- Staging of CKD
  - based on GFR, while the degree of proteinuria may predict individual patient outcome.

KDIGO CKD clinical practice guideline. Kidney Int Suppl (2013) 3 (1):1–150.

Prognosis of CKD by GFR and albuminuria category

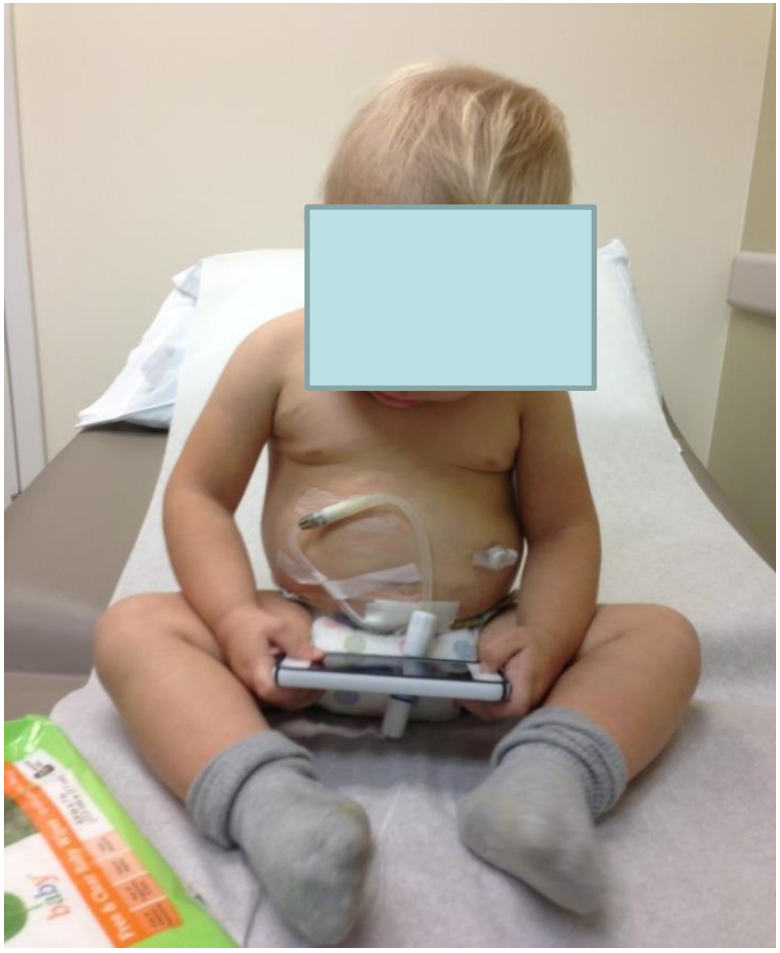
Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

Kidney Int Suppl (2013) 3 (1): 1–150.
doi:10.1038/kisup.2012.64

GFR categories (ml/min/ 1.73 m^2) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

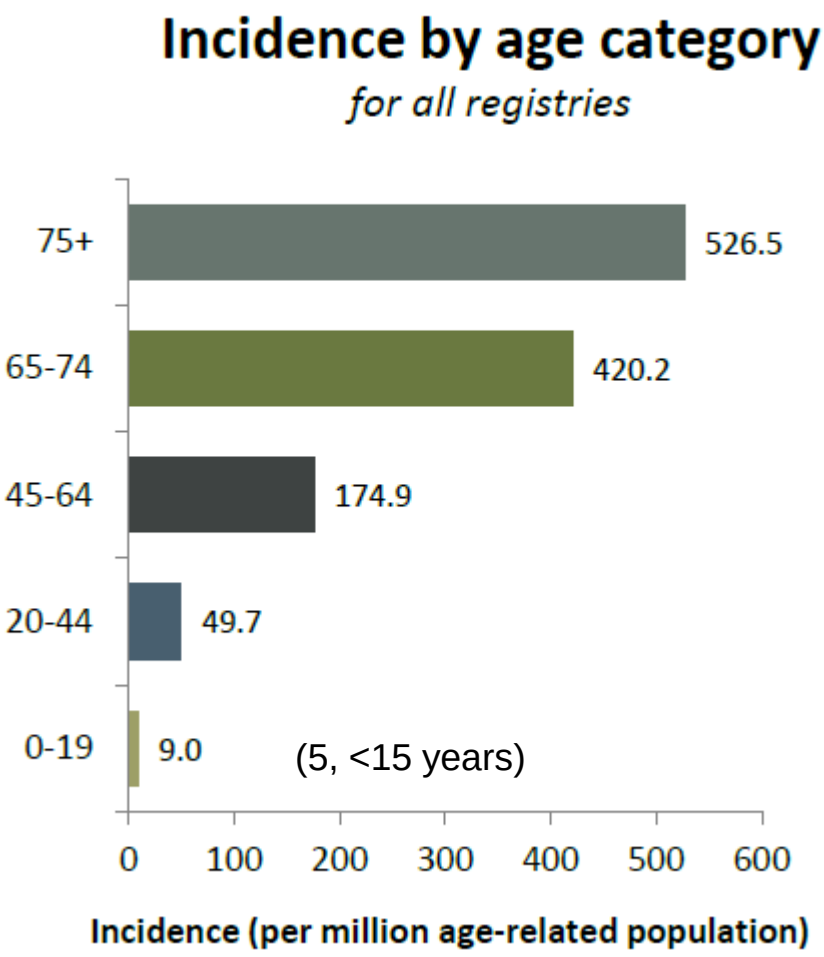
Epidemiology of childhood CKD

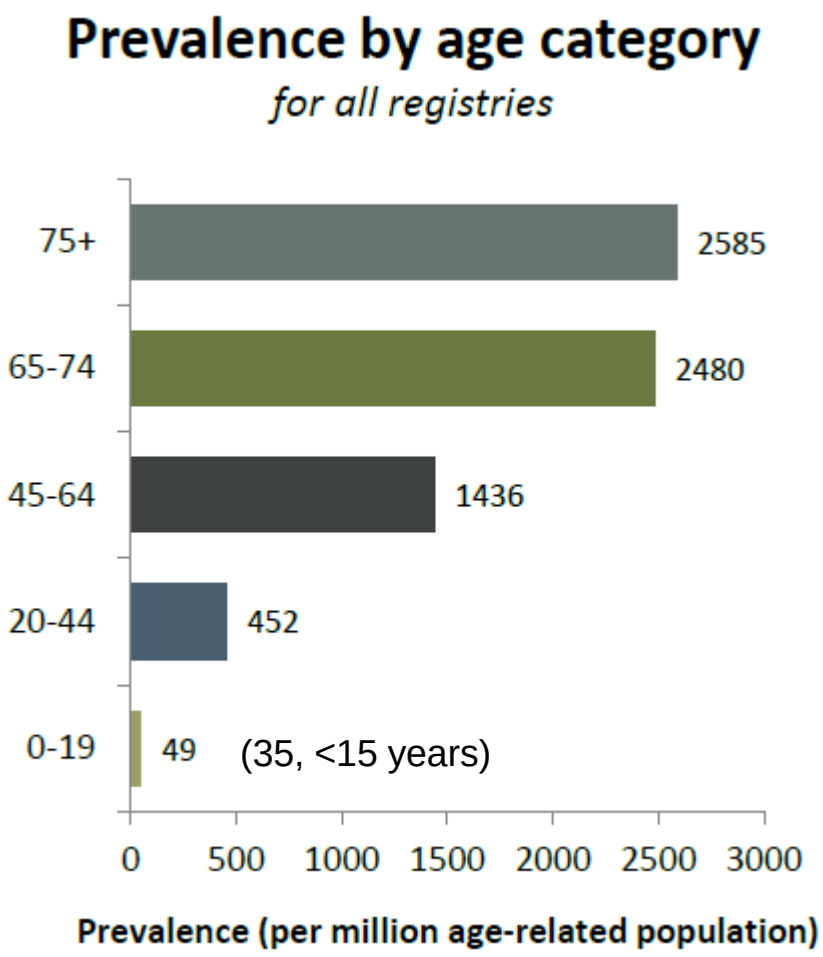


Europe/EDTA - Epidemiology

- Children 0–19 years of age who initiated KRT in the year 2013
- Incidence rate of 8.3 per million per year
- Point prevalence end of year 2013 was 55.3 pmarp.
- These numbers are 50% of the US numbers
  - Black race/non-White

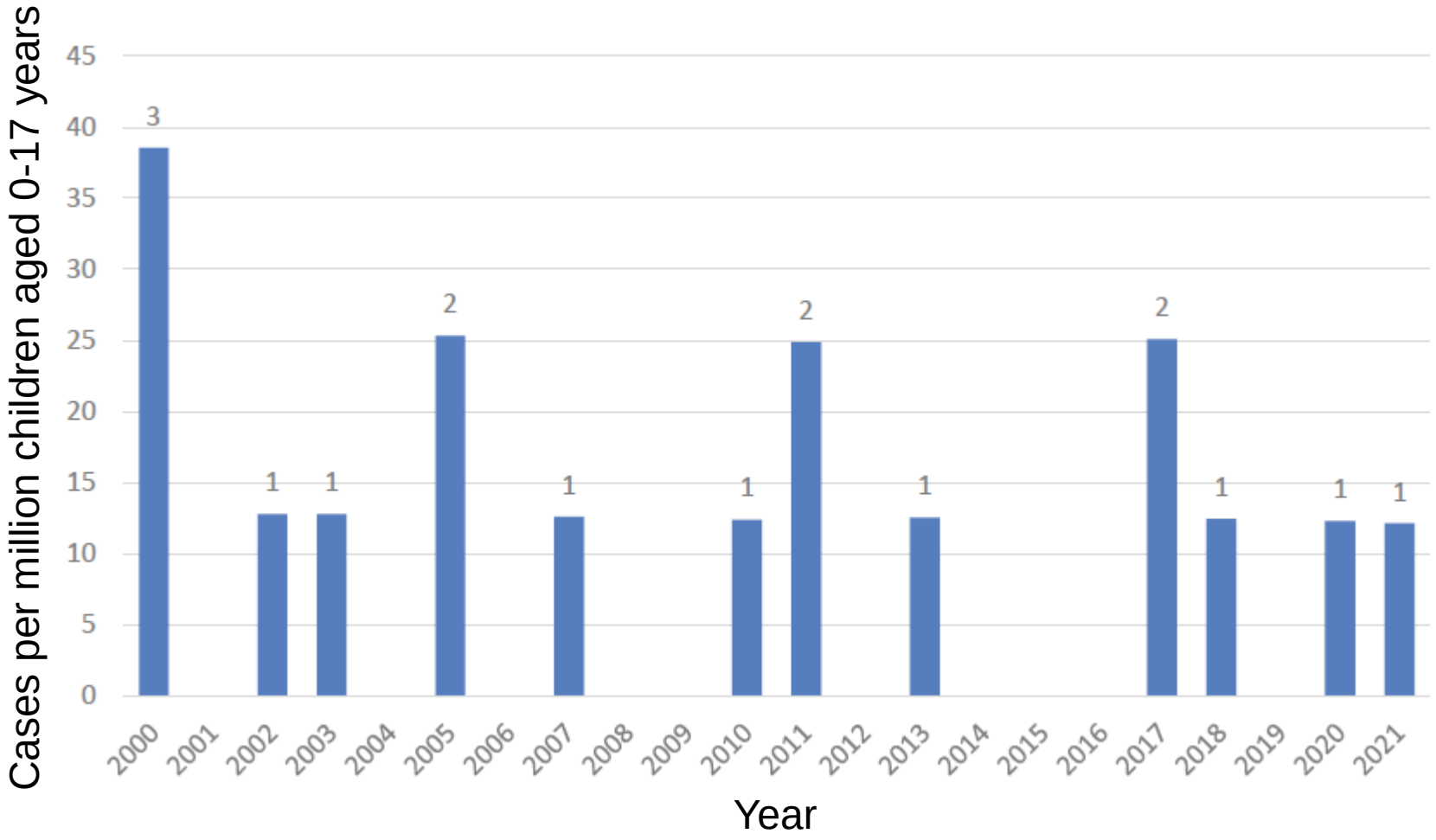
Europe-ERA/EDTA - 2021





Incidence of ESKD

The average annual incidence of ESKD was 9.7 cases per million children 0-17 years

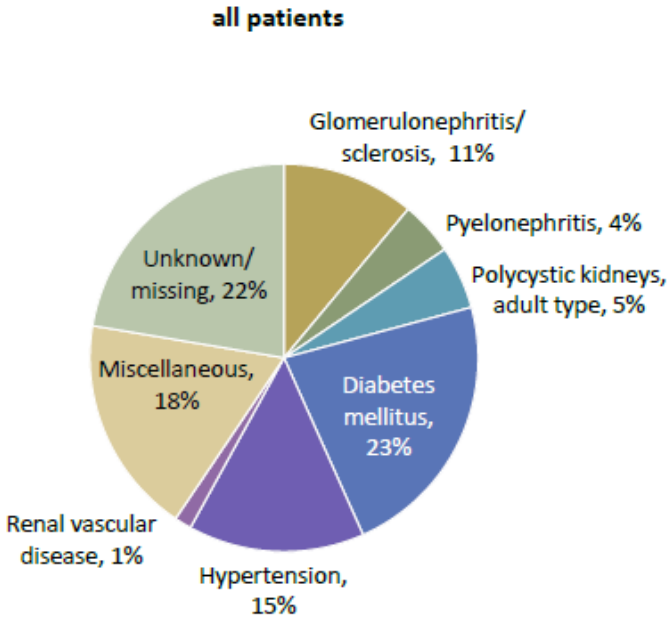


Aetiology of CKD in children

ERA/EDTA REGISTRY

Incidence by primary renal disease

patients from registries providing individual patient data only



2021 data

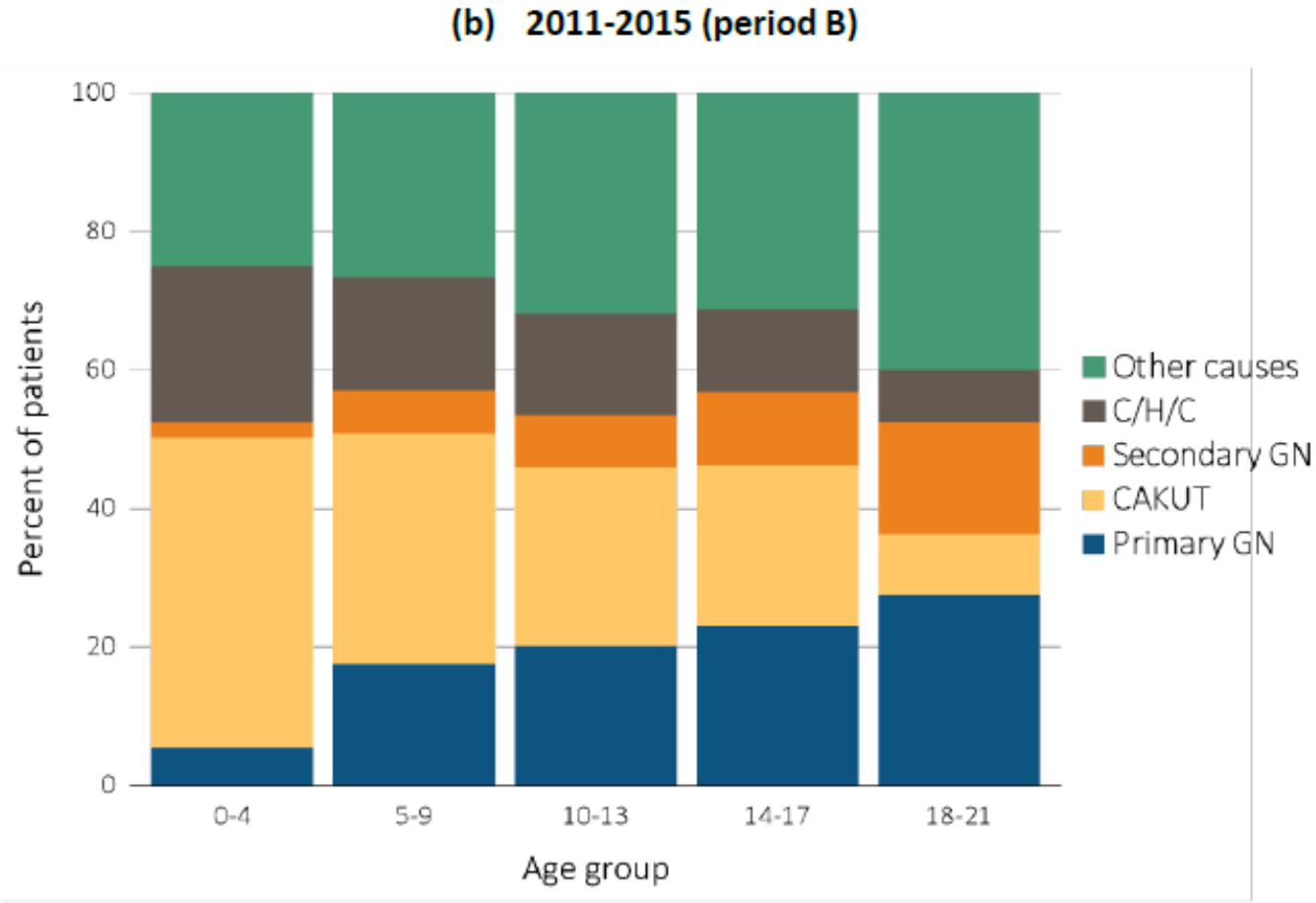
Table 3: PRD distribution at start of KRT in 2019

Cause of renal failure, among patients < 15 years of age, starting KRT in 2019 according to new and old PRD coding.

	N		Percent		Pmarp	
	New	Old	New	Old	New	Old
CAKUT	185	133	40.7	29.2	2.04	1.47
Glomerulonephritis	81	75	17.8	16.4	0.89	0.83
Cystic kidney disease	44	64	9.7	14.1	0.49	0.71
Hereditary nephropathy	-	28	-	6.1	-	0.31
Metabolic and tubulointerstitial disorders	16	10	3.5	2.2	0.18	0.11
Toxic/ischemic renal failure	5	3	1.1	0.7	0.06	0.03
HUS	16	16	3.5	3.5	0.18	0.18
Vascular	4	4	0.9	0.9	0.04	0.04
Miscellaneous	78	58	17.1	12.7	0.86	0.64
Unknown	26	64	5.7	14.1	0.29	0.71

2019 data

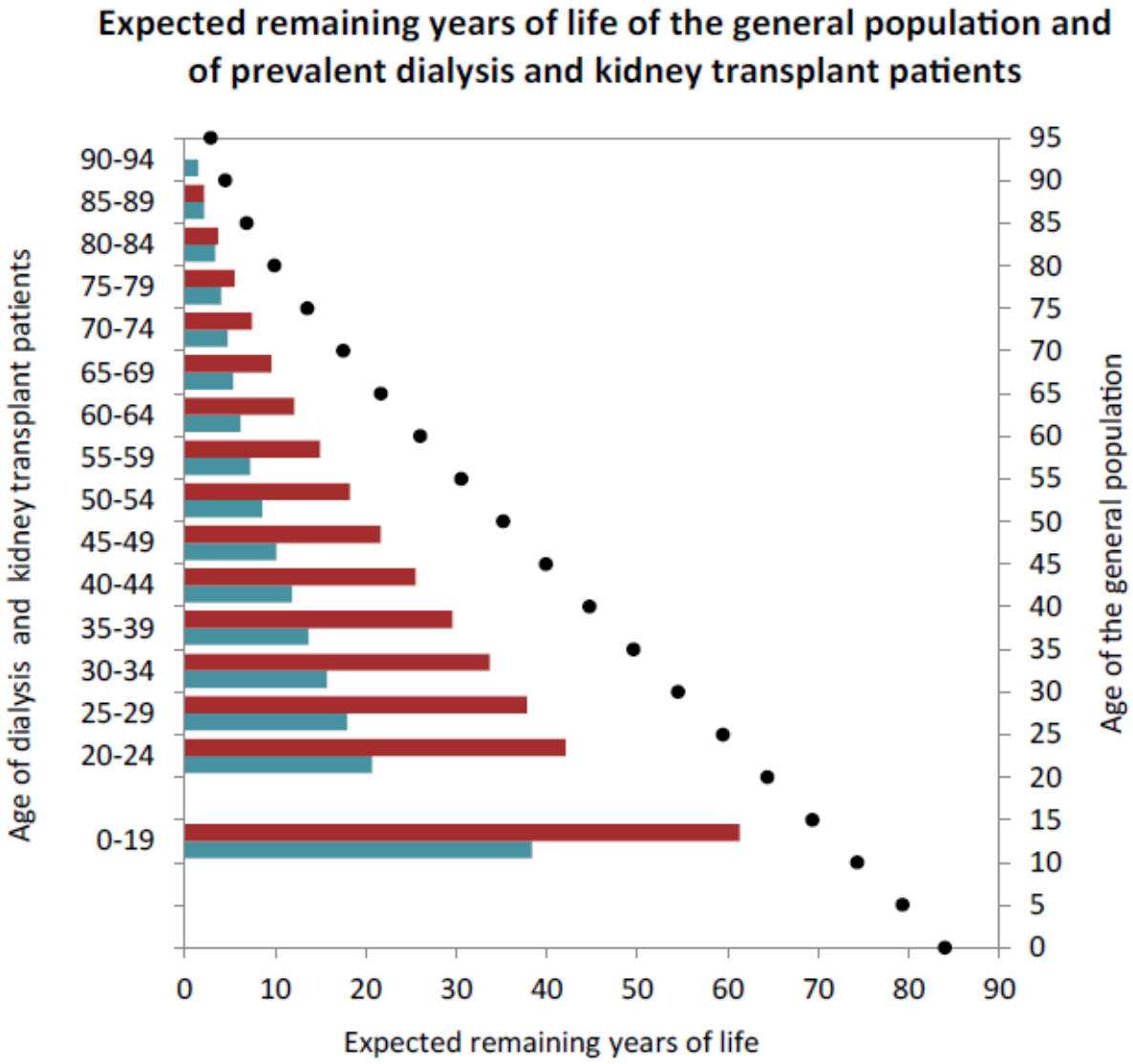
Etiology of ESKD Children



Data Source: Special analyses, USRDS ESRD Database. Abbreviations: CAKUT, congenital anomalies of the kidney and urinary tract; C/H/C, cystic/hereditary/congenital diseases; ESRD, end-stage renal disease; GN, glomerulonephritis

Outcomes of CKD in children

ERA/EDTA 2021 REGISTRY data



While the survival rate of children with ESKD has improved, it remains much lower than that of healthy kids.

Figure 1: Five-year patient survival

Incident KRT patients under the age of 15 starting KRT from 2007 onwards. Follow-up till 31st of December 2019.

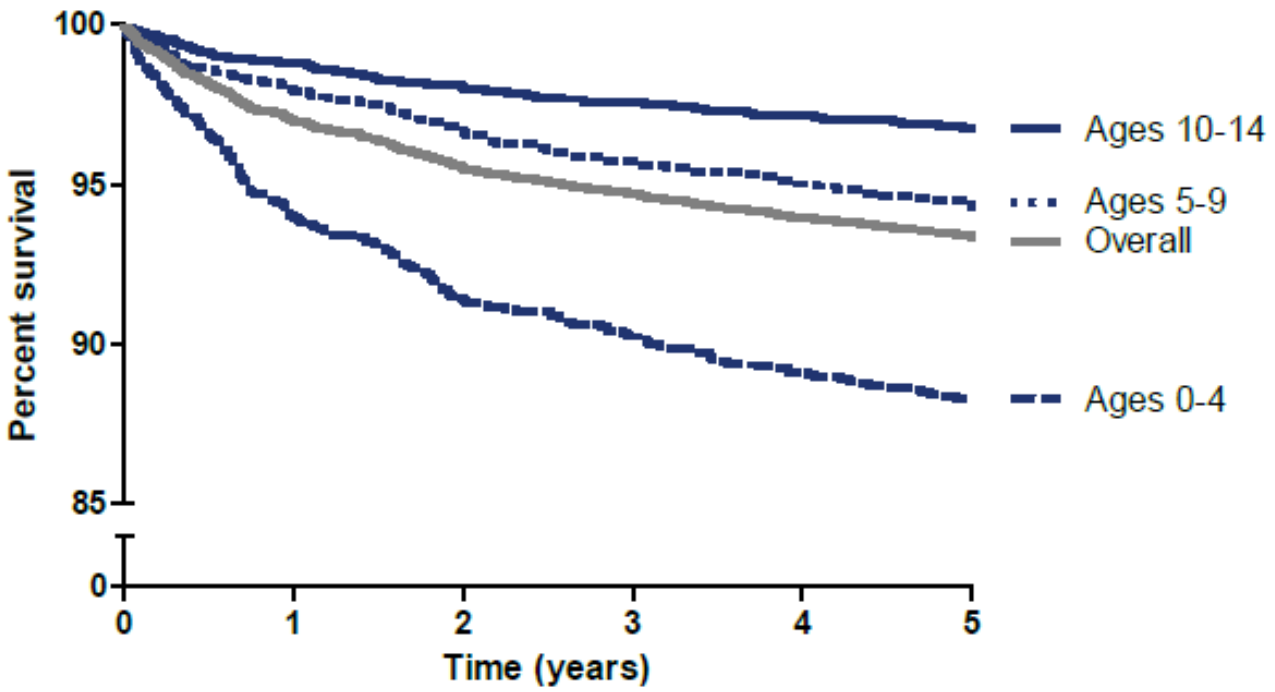


Table 7: Causes of Death

Causes of death according to the ERA coding list. Incident KRT patients under the age of 15 years starting KRT from 2007 onwards are included. Follow-up till 31st of December 2019.

Cause of death	Number of deaths	Percent
Myocardial ischemia and infarction	4	0.9
Cardiac failure	53	12.4
Cardiac arrest/sudden death other cause	62	14.5
Cerebro-vascular accident	36	8.4
Infection	116	27.1
Suicide/refusal or cessation of treatment	6	1.4
Treatment withdrawn	9	2.1
Malignant disease	2	0.5
Other identified cause of death	22	5.2
Cause of death uncertain/not determined	117	27.4

- These children now mainly die of cardiovascular causes and infection rather than from kidney failure.

Treatment of ESKD in Iceand 2000 - 2023

- 15 pediatric kidney transplants
  - Living donor, N=14
  - Deceased donor, N = 1
  - Median (range) age 9.4 (2-16) years
  - Incidence 7.5 cases per million children age 0-17 ára
- 4 underwent dialysis only (various reasons)
  - 3 died from serious underlying disease
  - One subsequently transplanted

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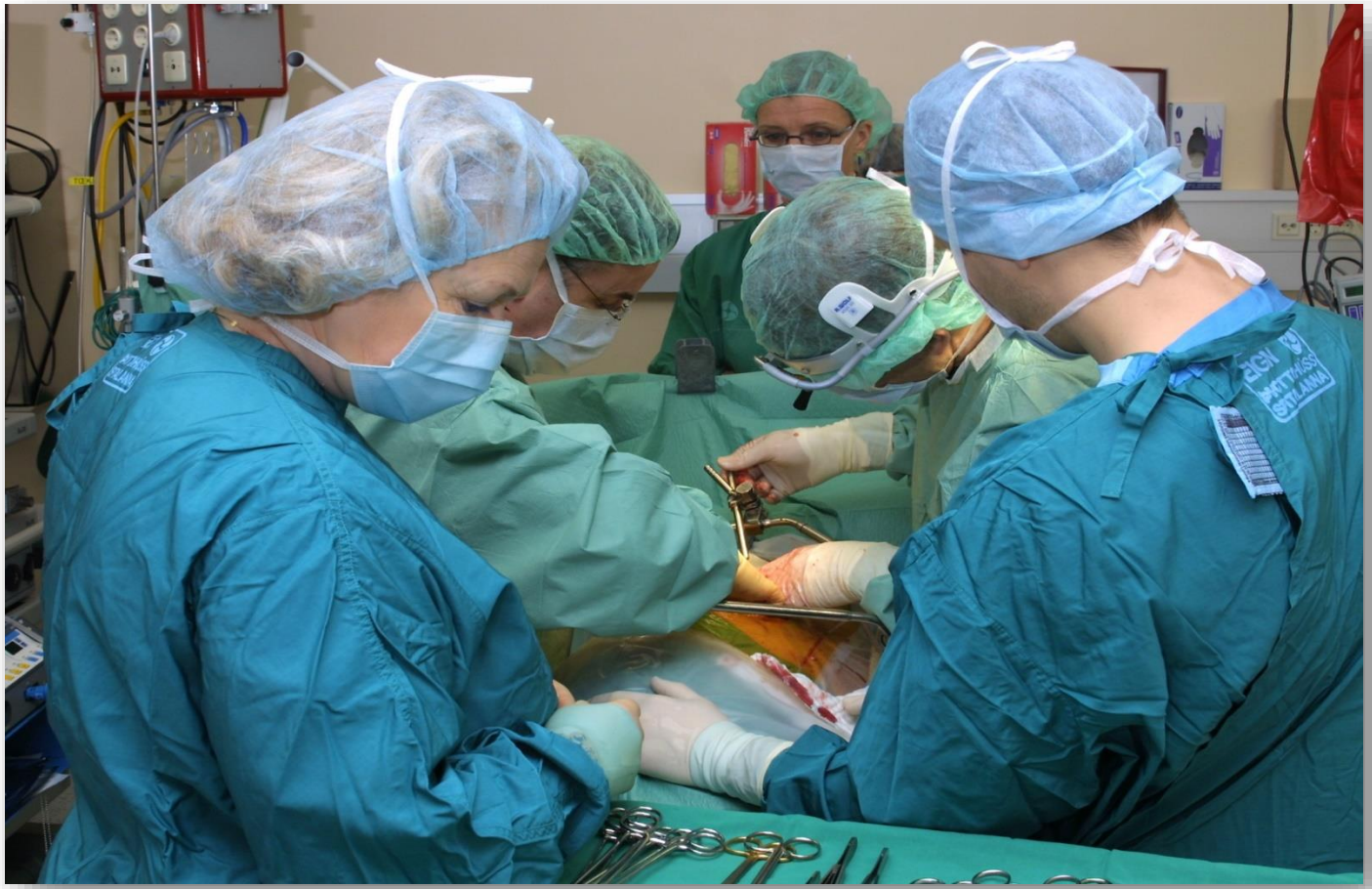

First kidney transplant in Iceland, December 2, 2003

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Clinical services - Kidney Transplantation

Total = 15 transplants in approximately 23 years – 2000 - 2023

- Iceland (8)
  - 31.05.2022 Living donor
  - 11.02.2020 Living donor
  - 05.06.2018 Living donor
  - 25.10.2017 Living donor
  - 29.05.2013 Living donor
  - 24.05.2011 Living donor
  - 20.10.2005 Living donor
  - 03.02.2004 Living donor
- Sweden (3)
  - 01.02.2023 Gothenburg - Living donor
  - 13.09.2022 Stokkholm - Living altruistic donor
  - 05.12.2012 Göteborg - Living altruistic donor
- Denmark/Copenhagen (2)
  - 05.12.2007 DD
  - 09.06.2000 Living donor
- USA (2)
  - 08.03.2002 Living donor
  - 30.10.2000 Living donor
- Tx candidates within the next 3-24 months
  - eGFR <25, N = 3
  - eGFR <30, N = 4

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Outcome of Childhood Kidney Transplantation in Iceland

- Patient survival was 100%
- Graft survival
  - 1 year 92.3%
  - 5 year 90.0%
  - 10 year 87.5%
- Three grafts were lost
  - At transplantation (renal venous thrombosis) and at 13 and 15 years following surgery.

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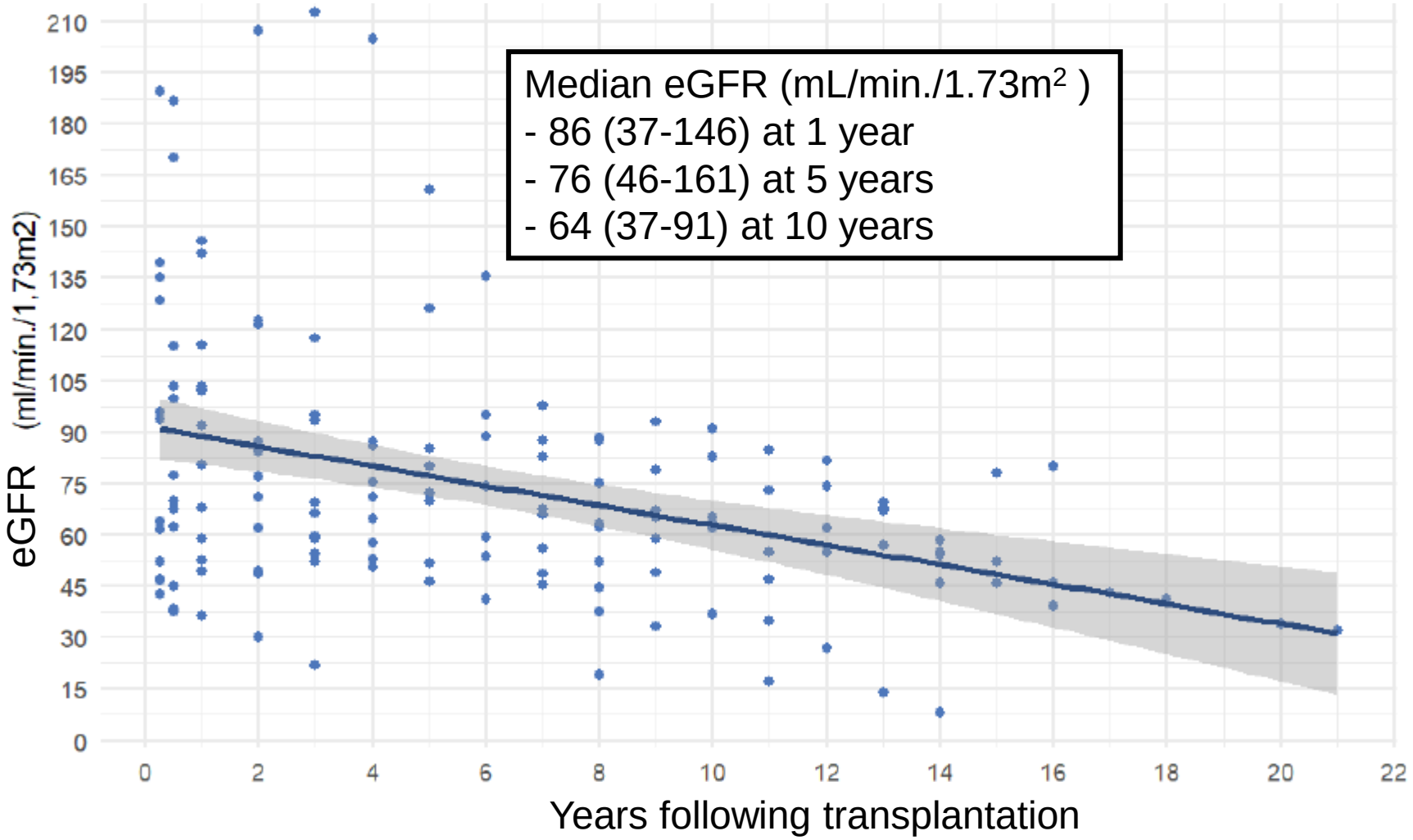
Graft function



Comorbidity in Children with CKD

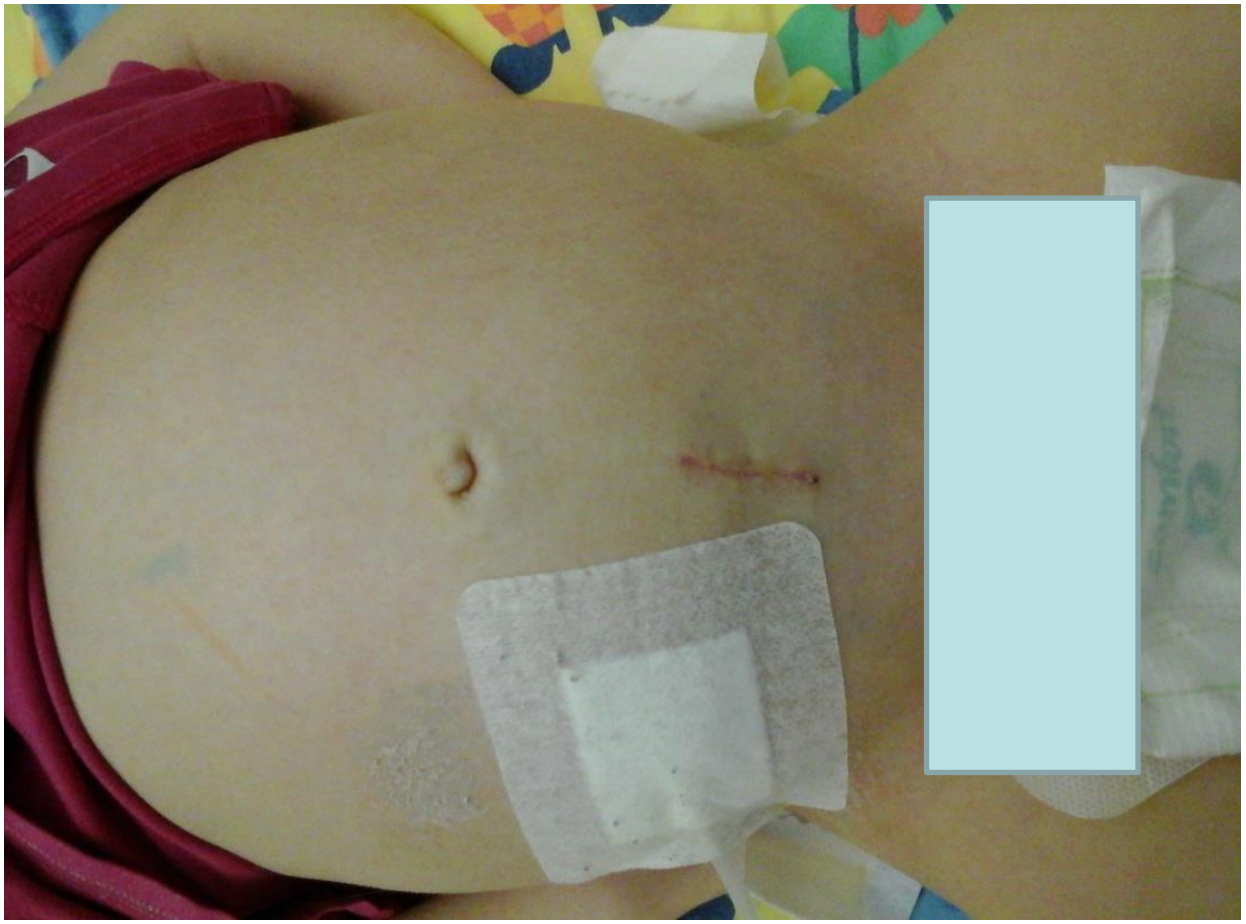
Comorbidity in children with CKD

- Hypertension
- Proteinuria
- Metabolic acidosis
- Anaemia
- CKD-MBD
- Poor linear growth
  - short stature
- Increased CV-risk and disease
- Dyslipidemia
- Neurocognitive problems

Factors associated with CKD progression

- Optimal management of all modifiable risk is likely needed to attain maximum slowing of renal function decline in affected children and delay the need for kidney Tx.
  - Hypertension
    - Intensified treatment significantly slows progression
  - Metabolic acidosis
    - Treatment significantly slows progression
  - Proteinuria
    - Treatment slows progression in the short run only
  - Anaemia
    - Treatment may slow disease progression

How fast does CKD progress in children?



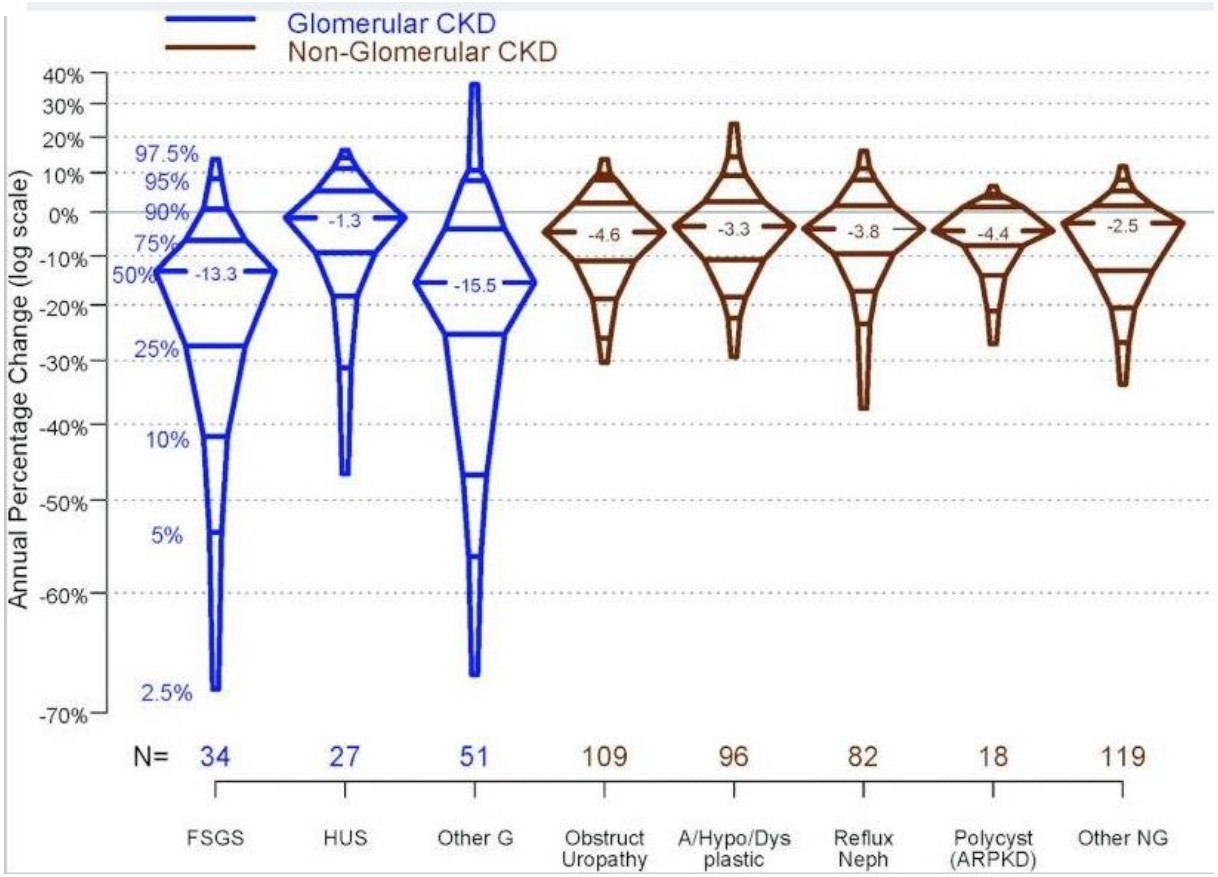
Rate of GFR decline among participants in the CKiD study

Metabolic Abnormalities, Cardiovascular Disease Risk Factors, and GFR Decline in Children with Chronic Kidney Disease

Susan L. Furth,[*†] Alison G. Abraham,[‡] Judith Jerry-Fluker,[‡] George J. Schwartz,[§] Mark Benfield,[‖] Frederick Kaskel,[¶] Craig Wong,[**] Robert H. Mak,[††] Marva Moxey-Mims,[‡‡] and Bradley A. Warady[§§]

Clin J Am Soc Nephrol. 2011 Sep; 6(9): 2132–2140

- CKiD study 586 children
- The median absolute annual declines in GFR
  a) −4.3 mL/min per 1.73 m^2 glomerular disease
  b) −1.5 mL/min per 1.73 m^2 nonglomerular disease



Annual percentage change in GFR across diagnosis categories

Original Investigation AJKD

Am J Kidney Dis. 2018 Jun;71(6):783-792

Estimating Time to ESRD in Children With CKD

Susan L. Furth, Chris Pierce,* Wun Fung Hui, Colin A. White, Craig S. Wong, Franz Schaefer, Elke Wühl, Alison G. Abraham,† and Bradley A. Warady,† on behalf of the Chronic Kidney Disease in Children (CKiD) and Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CRF in Pediatric Patients (ESCAPE) Study Investigators*

- Study population
  - 1,269 children aged 1 to 18 years enrolled in the observational CKiD study (70%) and in the European ESCAPE trial (30%).
- Outcome:
  - A composite event of renal replacement therapy, 50% reduction in eGFR, or eGFR < 15 mL/min/1.73 m^2.

Results:

- Lower eGFR and more severe proteinuria at study entry predicted faster the CKD progression
- Median times to event/ESKD
  - >10 years for eGFRs of 45 to 90 mL/min/1.73 m^2 and mild proteinuria
  - 0.8 years for eGFRs of 15 to 30 mL/min/1.73 m^2 and nephrotic-range proteinuria
- Children with glomerular disease were estimated to have a 43% shorter time to event than children with nonglomerular disease.

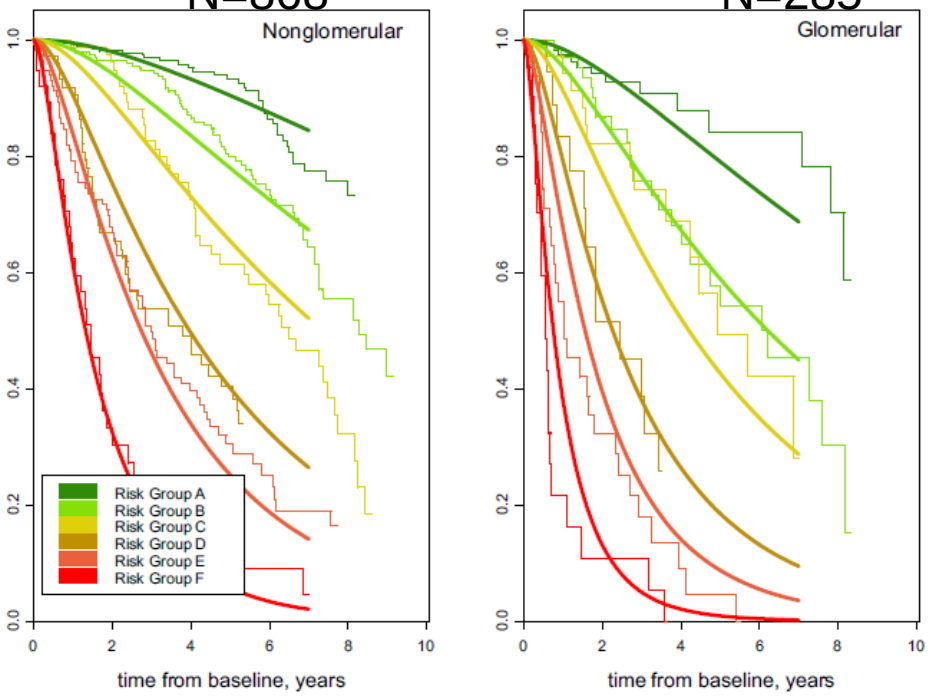
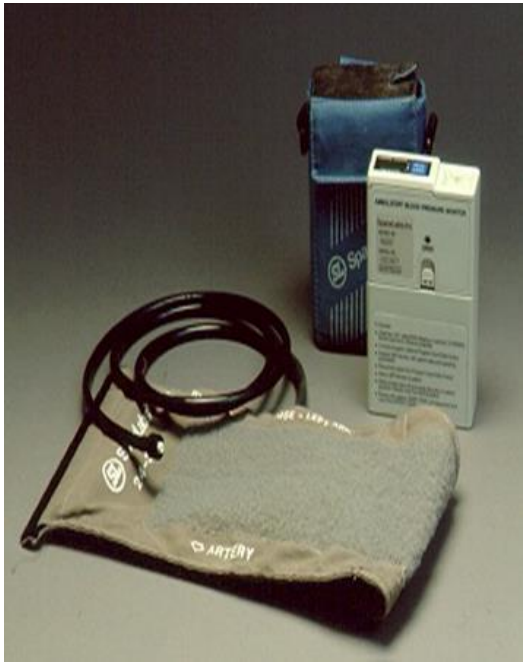


Figure 3. Parametric and nonparametric survival curves for the 6 risk stages (A-F) modeling time from study enrollment (baseline) t composite clinical event (50% glomerular filtration rate [GFR] decline, renal replacement therapy, or GFR < 15 mL/min/1.73 m² stratified by chronic kidney disease (CKD) diagnosis (n = 868 nonglomerular and n = 285 children with glomerular CKD). Parametri survival curves are generated from an accelerated failure time model using a conventional generalized gamma distribution with 7 bet indicator parameters: 6 risk stages (A-F) and glomerular CKD.

Can risk factors for CKD progression in children be modified?

Observational data

Blood pressure and CKD progression



Hypertension and Progression of Chronic Renal Insufficiency in Children: A Report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS)

- Hypertension is a highly significant and independent predictor for progression of CKD in children.
  - The study cohort consisted of 3834 patients aged 2 to 17 years with an estimated GFR (eGFR) <75 ml/min1.73 m^2.
  - End point: Time from enrollment to KRT.
  - Children with CKD and uncontrolled systolic hypertension (≥ 95th percentile) progressed more rapidly to kidney failure than children with BP < 95th percentile.
  - The prevalence of hypertension in children pre-dialysis was approximately 50%

Mitsnefes M, et al. (2003) J Am Soc Nephrol 14:2618–2622

AJKD
Original Investigation

Predictors of Rapid Progression of Glomerular and Nonglomerular Kidney Disease in Children and Adolescents: The Chronic Kidney Disease in Children (CKiD) Cohort

Bradley A. Warady, MD,[1] Alison G. Abraham, PhD,[2] George J. Schwartz, MD,[3] Craig S. Wong, MD,[4] Alvaro Muñoz, PhD,[2] Aisha Betoko, PhD,[2] Mark Mitsnefes, MD, MS,[5] Frederick Kaskel, MD, PhD,[6] Larry A. Greenbaum, MD, PhD,[7] Robert H. Mak, MD, PhD,[8] Joseph Flynn, MD,[9] Marva M. Moxey-Mims, MD,[10] and Susan Furth, MD, PhD[11]

Data from the CKiD study

– higher systolic BP was associated with accelerated GFR decline, especially in children with glomerular causes of CKD

Am J Kidney Dis. 2015 Jun; 65(6): 878–888.

Hypertension Volume 79, Issue 10, 2022; Pages 2288-2297

ORIGINAL ARTICLE

Nocturnal Hypertension in Children With Chronic Kidney Disease Is Common and Associated With Progression to Kidney Replacement Therapy

Monica L. Guzman-Limon, Shuai Jiang, Derek Ng, Joseph T. Flynn, Bradley Warady, Susan L. Furth, Joshua A. Samuels, for the Chronic Kidney Disease in Children study*

- CKD patients with isolated nocturnal hypertension had a significantly higher risk of progression to KRT compared with normotensive children.
- The risk was higher in those who had both daytime and nocturnal hypertension.

Hypertension in Children With Kidney Disease

Is Blood Pressure Improving in Children With Chronic Kidney Disease?

A Period Analysis

Gina-Marie Barletta, Christopher Pierce, Mark Mitsnefes, Joshua Samuels, Bradley A. Warady, Susan Furth, Joseph Flynn

- Despite publication of hypertension recommendations and guidelines for BP control in pediatric patients with CKD, this CKiD study suggests that hypertension remains under-recognized and undertreated in children with CKD.
- Room for improvement

Hypertension. 2018 Mar; 71(3): 444–450.

Proteinuria and CKD progression

Normal urinary protein excretion

- Normal urinary protein excretion is <240 mg/m^2/day in children <6 months of age and <150 mg/m^2/day in older children
  - Uromodulin secreted by the renal tubules makes up close to 50% of renal protein excretion
  - Approximately 30–40% is albumin
  - Filtered low molecular weight (LMW) plasma proteins, such as beta-2-microglobulin and retinol-binding protein, account for the remaining 10–20%.

Physiological proteinuria

- Orthostatic proteinuria
- Febrile proteinuria
- Exercise proteinuria
  - In all these situations, proteinuria is transient and absent when tested in a first morning urine sample collected directly after getting up, after recovery from the febrile condition, or after recovery from strenuous exercise, respectively.

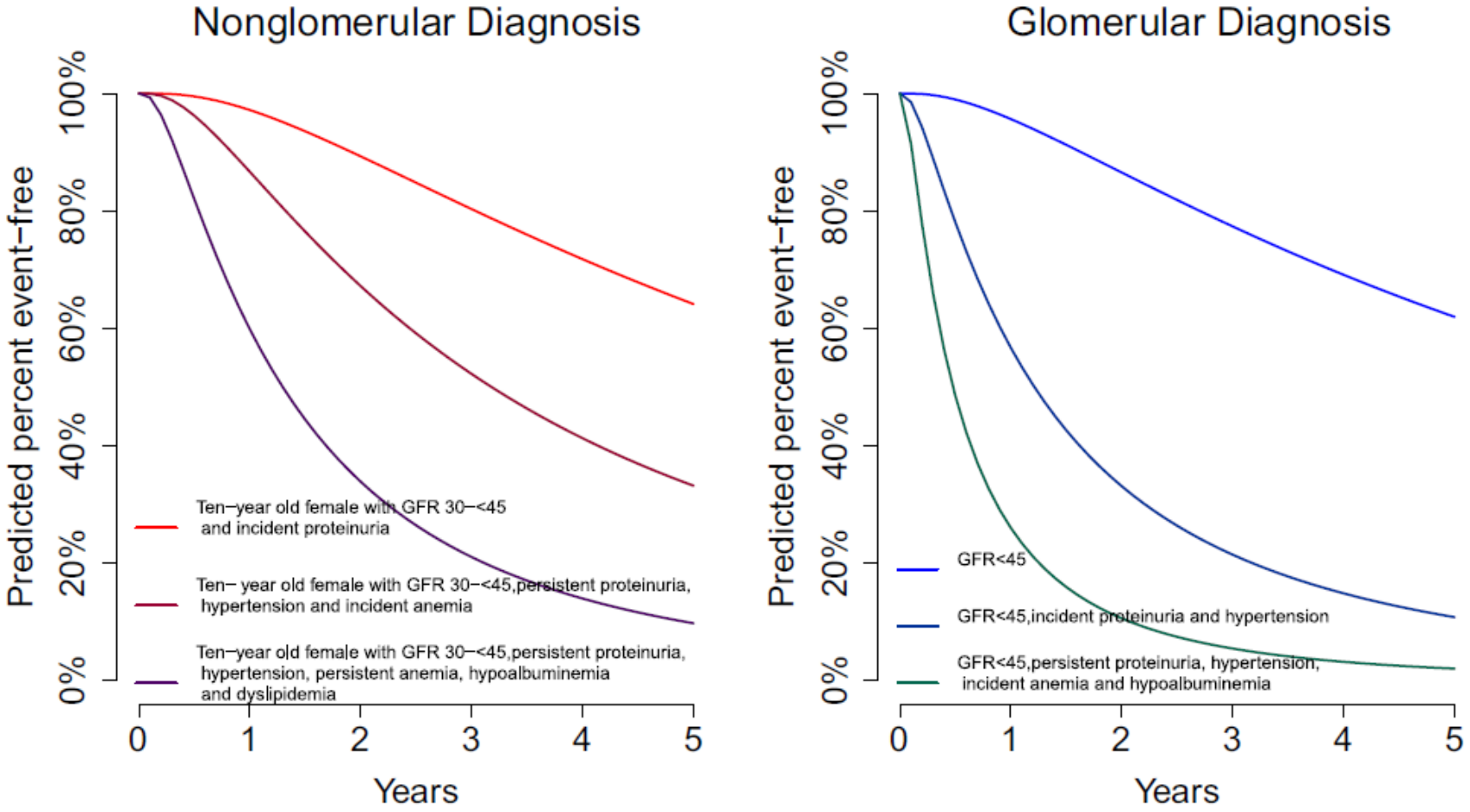
Pathologic/abnormal proteinuria

- Increased glomerular membrane permeability (glomerular proteinuria)
  - albuminuria
- Reduced tubular reabsorption of LMW weight proteins (tubular proteinuria)
- Increased filtered LMW protein load exceeding the tubular reabsorptive capacity (overflow proteinuria)

Predictors of Rapid Progression of Glomerular and Nonglomerular Kidney Disease in Children and Adolescents: The CKiD Cohort

Bradley A. Warady et al. Am J Kidney Dis. 2015 June ; 65(6): 878–888

Prospective 5-year follow-up of 496 children with CKD enrolled in the CKiD study.

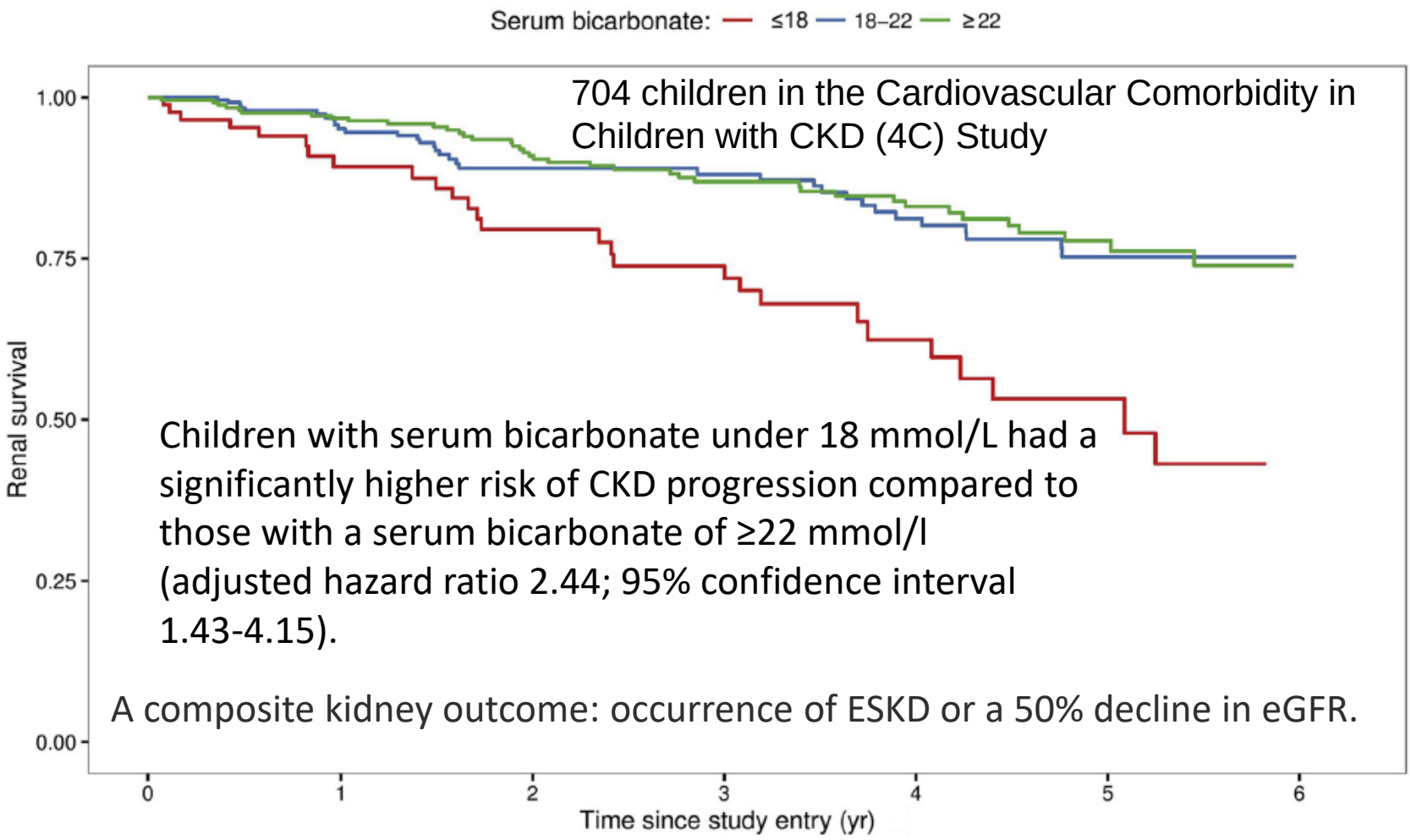


Estimates of survival curves for the composite event (50% glomerular filtration rate [GFR] decline or renal replacement therapy) based on log-normal models of participants with different constellations of clinical variables for glomerular and nonglomerular participants. Values of variables in the models not listed in the figure are considered not present (ie, zero).

Metabolic acidosis and CKD progression

Metabolic acidosis is common and associates with disease progression in children with chronic kidney disease

J. Harambat. Kidney International (2017) 92, 1507–1514;



Anemia and CKD progression

The CKiD study

In pediatric patients with CKD, hemoglobin declines as an iohexol-determined glomerular filtration rate decreases below 43 ml/min per 1.73 m^2.

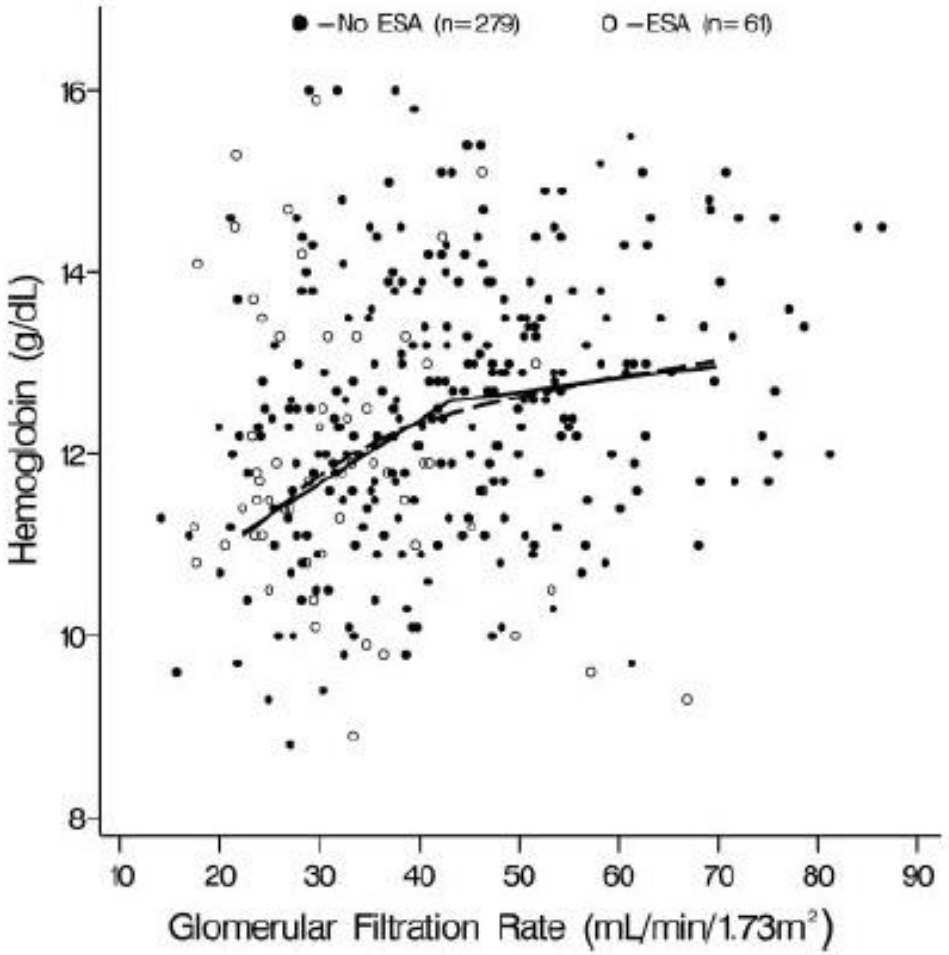


Figure 1. Hemoglobin *versus* GFR in children with chronic kidney disease (CKD): Linear threshold model (solid line) and nonparametric smoothing model (dashed line) describing relationship of hemoglobin concentration and GFR in 340 pediatric patients with CKD.

Fadrowski JJ, et al (2008) Clin J Am Soc Nephrol 3 (2):457–462

Progression of kidney disease and anemia

- Anemia leads to kidney tissue hypoxia that may contribute to the progression to ESKD.
- The correction of anemia may lead to increased oxygen delivery to tubular cells, decrease tubular damage and protect against nephron loss induced by tubular injury.

Susan M Koshy, Denis F Geary. Pediatr Nephrol (2008) 23:209–219

Factors associated with CAKUT and CKD progression

CKD and CAKUT

- Important to avoid UTIs and to optimize bladder drainage to maintain kidney function.
- Assure adequate water intake, appropriate voiding habits, and avoid constipation.

Other factors and CKD progression

Obesity in childhood and adolescence is associated with CKD later in life and may accelerate CKD progression

CEP Clin Exp Pediatr Vol. 64, No. 10, 511-518, 2021
https://doi.org/10.3345/cep.2021.00108
Review article

Obesity and chronic kidney disease: prevalence, mechanism, and management

Hyung Eun Yim, MD, PhD[1], Kee Hwan Yoo, MD, PhD[2]
[1]Department of Pediatrics, Korea University Ansan Hospital, Korea University Hospital, Korea University College of Medicine, Seoul, Korea

Very high serum total cholesterol is a significant risk factor for CKD progression in children.

Pediatric Nephrology
https://doi.org/10.1007/s00467-023-06033-6
ORIGINAL ARTICLE

Association between serum total cholesterol and chronic kidney disease progression in children: results from the KNOW-PedCKD

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Fibroblast Growth Factor 23 and Risk of CKD Progression in Children

Anthony A. Portale,* Myles S. Wolf,† Shari Messinger,‡ Farzana
Susan L. Furth,¶ and Isidro B. Salusky**

Higher baseline FGF23 levels were independently associated with CKD progression in CKiD study subjects.

Longitudinal Changes in Uric Acid Concentration and Their Relationship with CKD Progression in Children and Adolescents

Graphical Abstract

HYPOTHESES: Elevated serum uric acid and increases in serum uric acid are risk factors for CKD progression in children

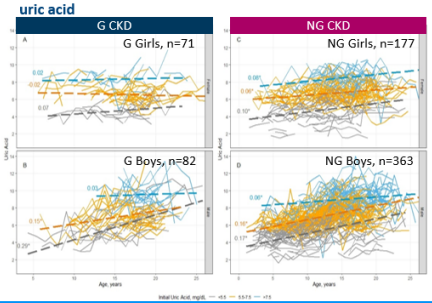
DESIGN & OUTCOMES: Multicenter prospective cohort study with percentage change in eGFR as the primary outcome

CKiD Chronic Kidney Disease in Children

n=153 with glomerular CKD

n=540 with non-glomerular CKD

Serum uric acid by age stratified by CKD etiology, sex, initial uric acid



Percentage change in eGFR (95% CI)		
G CKD	**Per year**	**Per +1 mg/dL uric acid**
Initial uric acid		
<5.5 mg/dL	-1.4 % (-3.6%, +0.8%)	-5.7% (-8.4%, -3.0%
5.5-7.5 mg/dL	-7.7% (-10.1%, -5.3%)	-4.3% (-6.8%, -1.6%)
>7.5 mg/dL	-14.7% (-18.9%,-10.2%)	-1.6% (-4.0%, +0.9%)
NG CKD		
Initial uric acid		
<5.5 mg/dL	-1.4% (-2.3%, -0.5%)	-5.1% (-6.3%, -4.0%)
5.5-7.5 mg/dL	-4.1% (-4.9%, -3.2%)	-3.3% (-4.1%, -2.6%)
>7.5 mg/dL	-8.6% (-10.3%, -6.8%)	-0.8% (-1.8%, +0.2%)

CONCLUSION: Higher uric acid levels are risk factors for more severe progression of CKD in children and adolescents; increases in uric acid are associated with CKD progression in those with initial uric acid <7.5 mg/dL

Schwartz et al. 2022

Pediatric Nephrology
Journal of the International Pediatric Nephrology Association
IPNA

George J Schwartz et al. Pediatr Nephrol(2023) 38:489–497

Can risk factors for CKD progression in children be modified?

Interventional studies

- The “Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CKD in Pediatric Patients (ESCAPE) trial”

Blood pressure control and CKD progression

- The ESCAPE-trial
  - Prospective, multicenter, randomized clinical trial
  - 385 European children with CKD, age 3-18 years
  - eGFR 15-80 mL/min/1.73m^2 at trial onset
    - ramipril 6 mg/m^2/day, and other antihypertensives not targeting the renin–angiotensin system to attain BP goal
    - Patients randomly assigned to two groups
      - intensified blood-pressure control
        - » target 24-hour mean arterial pressure below the 50th percentile
      - conventional blood-pressure control
        - » target mean arterial ABP pressure in the 50th to 95th percentile
    - Primary composite end point
      - time to a 50% drop in glomerular filtration rate or progression to end-stage kidney disease.

Wuhl E, et al. N Engl J Med 361:1639–1650

Blood pressure control and progression of renal disease

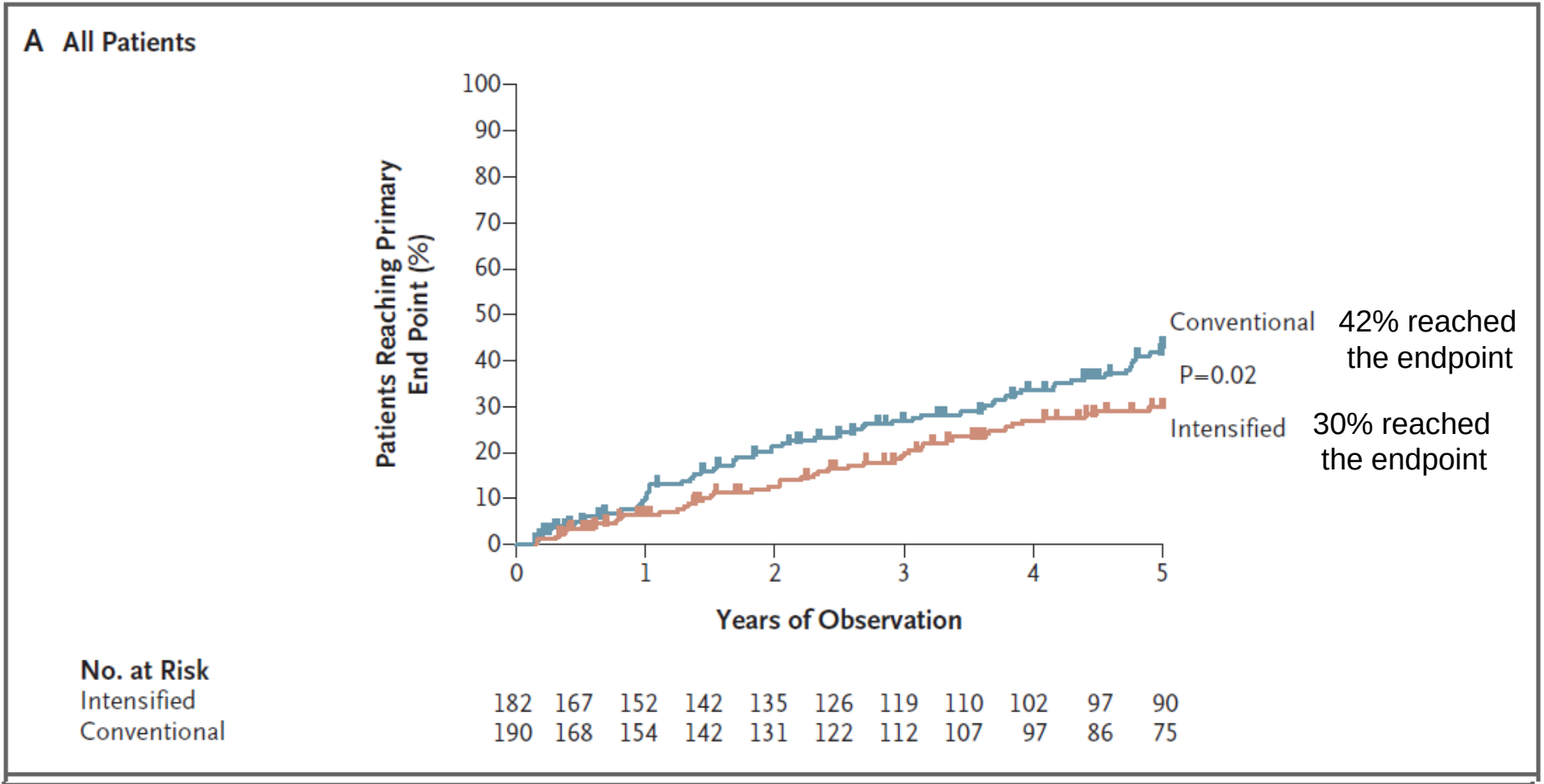


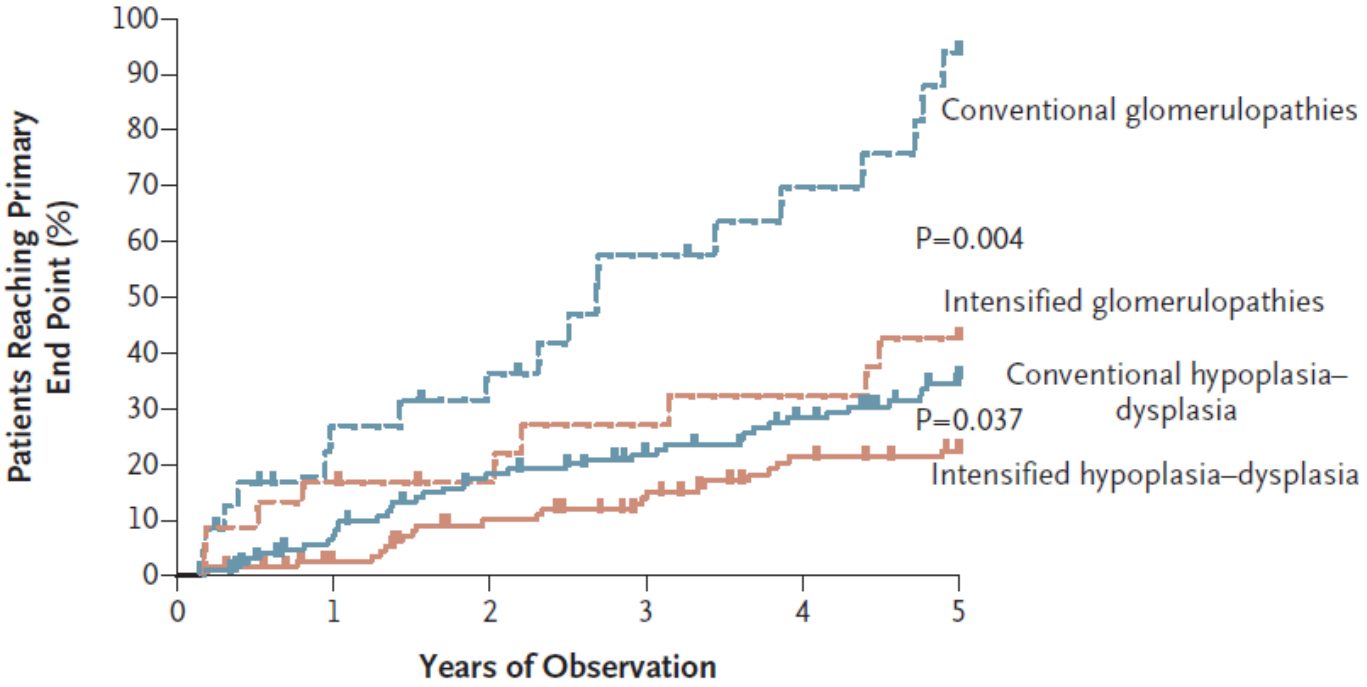
Figure 2. Progression of Renal Disease, According to Blood-Pressure–Control Group.

The cumulative probability of reaching the primary composite end point of a 50% decline in the glomerular filtration rate or progression to end-stage renal disease is shown for all patients (Panel A) and for patients with renal hypoplasia–dysplasia or glomerulopathies (Panel B).

Wuhl E et al. N Engl J Med, 2009

Blood pressure control and progression of renal disease

B Glomerulopathies or Hypoplasia–Dysplasia



No. at Risk

Intensified glomerulopathies	28	21	19	18	17	15	15	14	14	12	12
Conventional glomerulopathies	24	20	16	15	13	11	8	6	5	4	1
Intensified hypoplasia–dysplasia	125	118	112	102	97	93	88	81	76	74	71
Conventional hypoplasia–dysplasia	139	127	116	108	101	98	91	88	78	70	63

Figure 2. Progression of Renal Disease, According to Blood-Pressure–Control Group.

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Wuhl E et al. N Engl J Med, 2009

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The ESCAPE-trial

In contrast to the persistently excellent blood pressure control, proteinuria gradually increased again over time, resulting in a level of proteinuria after 36 months that did not differ significantly from baseline

The early antiproteinuric response was, however, predictive of long-term benefit with respect to kidney function

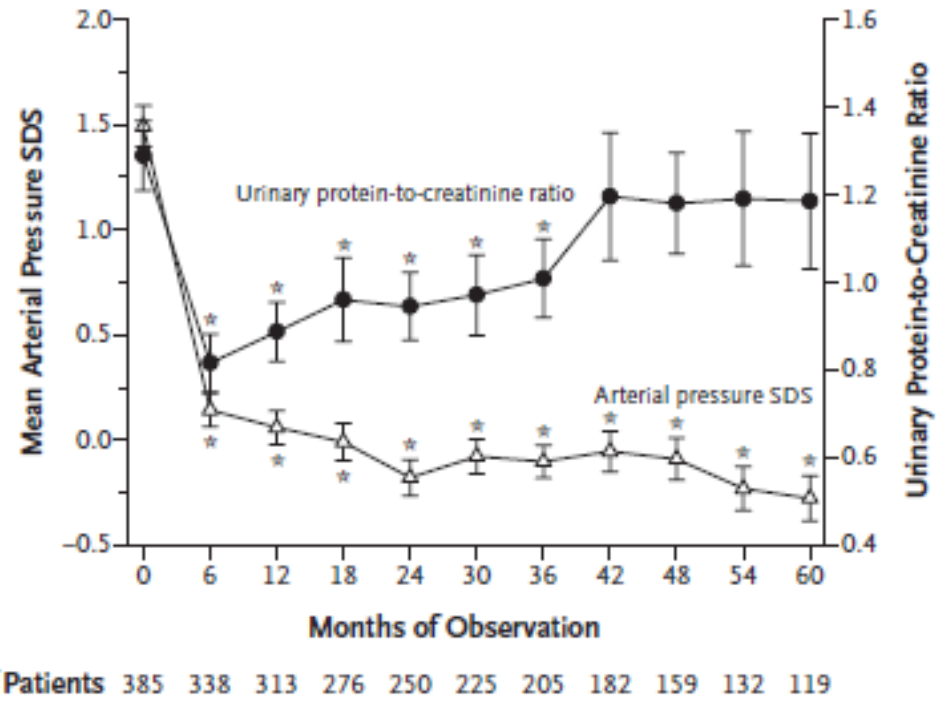
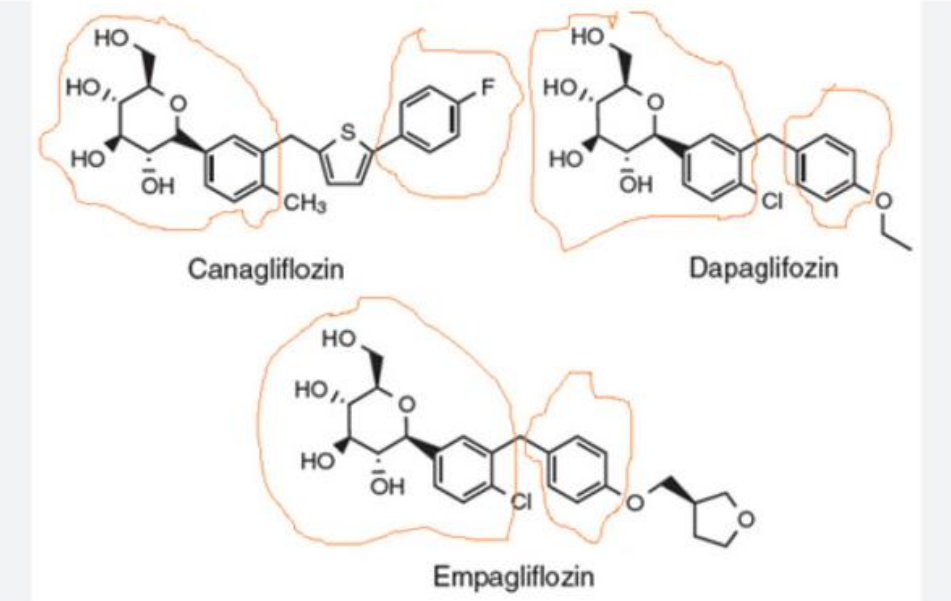


Figure 4. Course of Normalized 24-Hour Mean Arterial Pressure and Urinary Protein Excretion (Ratio of Protein to Creatinine) in the Total Study Cohort.

Data are means ±SE. Urinary protein excretion was expressed as the ratio of protein (in milligrams) to creatinine (in milligrams). Asterisks indicate significant differences from baseline values ($P<0.05$). SDS denotes standard-deviation score.

Novel therapeutic agents reducing CKD progression



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D., for the DAPA-CKD Trial Committees and Investigators*

- Recently, sodium-glucose cotransporter 2 inhibitors (SGLT2i) have demonstrated benefits in reducing proteinuria and improving kidney outcomes in patients with proteinuric CKD with and without type 2 diabetes in adults.

N Engl J Med. 2020;383:1436–1446

- Dapaglifozin and empagliflozin FDA approved for treatment of type 2 diabetes in children over 10 years of age

Sodium-glucose transporter 2 inhibitors (SGLT2i)

- Have in clinical trials, in the adult population with and without T2DM, reduced:
  - Albuminuria or proteinuria by 30–50%
  - The risk of CKD progression and kidney replacement therapy
  - Death due to kidney- or cardiovascular disease

N Engl J Med. 2020;383:1436–1446

2021 Dec 21;7(3):638-641
KI REPORTS
KIReports.org
2021 Dec 21;7(3):638-641
RESEARCH LETTER

Efficacy and Safety of Dapagliflozin in Children With Inherited Proteinuric Kidney Disease: A Pilot Study

Jiaojiao Liu[1,3], Jingyi Cui[1,3], Xiaoyan Fang[1], Jing Chen[1], Weili Yan[2], Qian Shen[1] and Hong Xu[1]

- Dapaglifozin
  - 8 patients were prescribed dapagliflozin 5 mg per day (body weight <30 kg) or 10 mg per day (body weight >30 kg) for 12 weeks.
  - 5 had Alport syndrome
  - A small pilot study with of dapagliflozin
    - 4 had AS
    - 1 Dent disease
    - 3 other hereditary proteinuric nephropathies
- 22% reduction in proteinuria after 12 weeks of treatment

Other drug treatments under investigation

- Finerenone
  - mineralocorticoid receptor antagonist
- Vitamin D receptor activators
- Selective endothelin receptor antagonists
- Bardoxolone
  - a novel drug that is a robust inducer of the Nrf2 pathway, which inhibits NF-κB, leading to antioxidant and anti-inflammatory effects

Summary

Summary - I

- So, how effective are therapeutic interventions?
  - Currently available treatments significantly reduce the rate of CKD progression in children
- However, developing better strategies to address CKD progression in children still is an important unmet medical need.

Summary -II

- Hypertension and proteinuria are the most important independent risk factors for CKD progression in both children and adults
- In pediatric CKD patients, strict/intensified BP control is crucial to the preservation of kidney function and cardiovascular health.
- RAAS antagonists are the drug class of first choice.

Summary - III

- Optimal management of all modifiable risk is likely needed to attain maximum slowing of renal function decline in affected children.
  - Metabolic acidosis
  - Anaemia
  - Obesity
  - Hyperuricemia?
  - Dyslipidemia
  - CKD-MBD/FGF23 levels

Summary IV

- The potential role for glifozines and other novel interventions that slow CKD progression in children with CKD needs to be studied.