What do we know about kidney measures and their value for detecting CKD and Discriminating stage and prognosis

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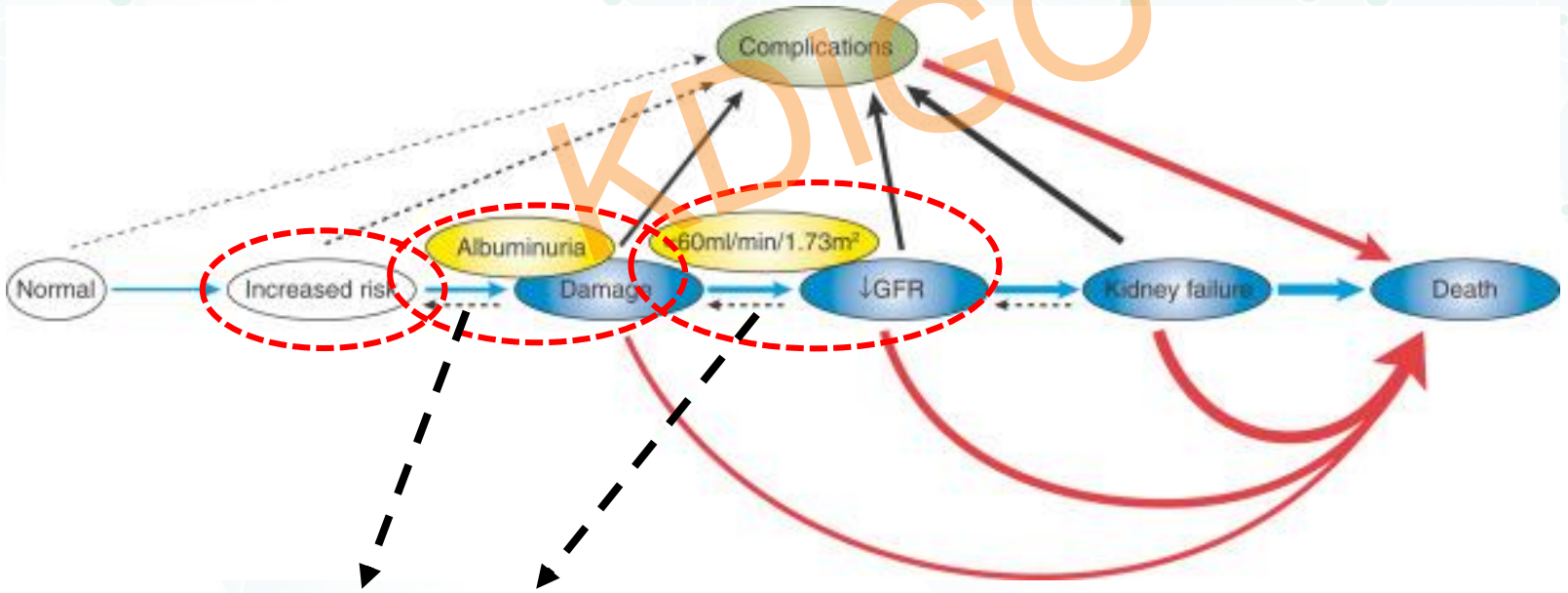
DISCLOSURES

- I have nothing to declare

OVERVIEW

- How should we judge the value of current tests?
  - By prognosis or stage re-classification?
  - Use the CKD-PC model that prognosis is the primary factor.
- Relative value of GFR markers beyond creatinine on prognosis
- Albuminuria as a prognostic marker, beyond GFR estimates
- Differences by populations, e.g. impact of race/age on GFR estimation?

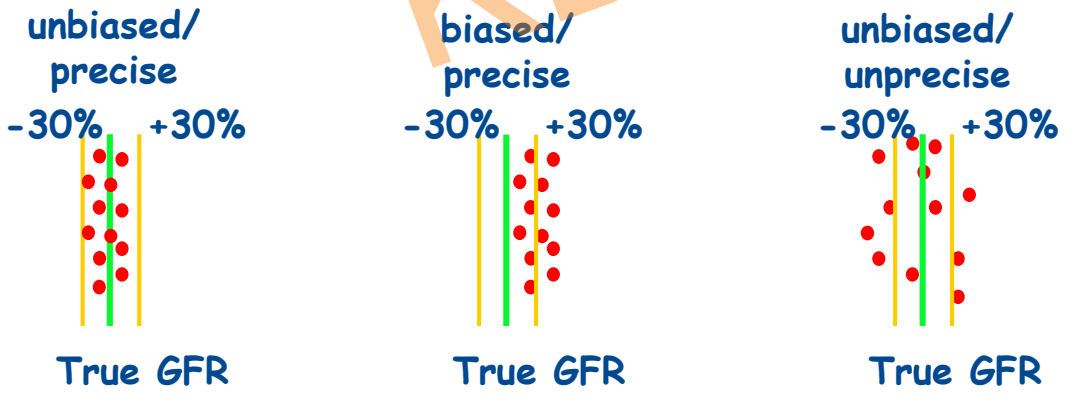
CONCEPTUAL MODEL OF THE COURSE AND OUTCOMES OF CHRONIC KIDNEY DISEASE (CKD)



National Kidney Foundation. K/DOQI Clinical Practice Guidelines for CDD. Am J Kidney Dis 2002

1. Value of current GFR assessment methods?

- **Bias:** Difference between mGFR and eGFR
- **Precision:** SD around the bias = random error; variance (R^2)
- **Accuracy:** Estimated GFR values within 30% (15% or 10%) of the measured GFR value



1. VALUE OF CURRENT GFR ASSESSMENT METHODS?

- **Biological Variability:** day-to-day variability of GFR between **4 and 10% in healthy subjects**, and **5 and 15% in CKD patients**, depending on GFR assessment method.

Brochner-Mortensenet al., Scand J Clin Lab Invest 1976
Delanaye P et al., NDT 2008
Gaspari et al., JASN 1998

- **Accuracy of eGFR** (for correct CKD classification):

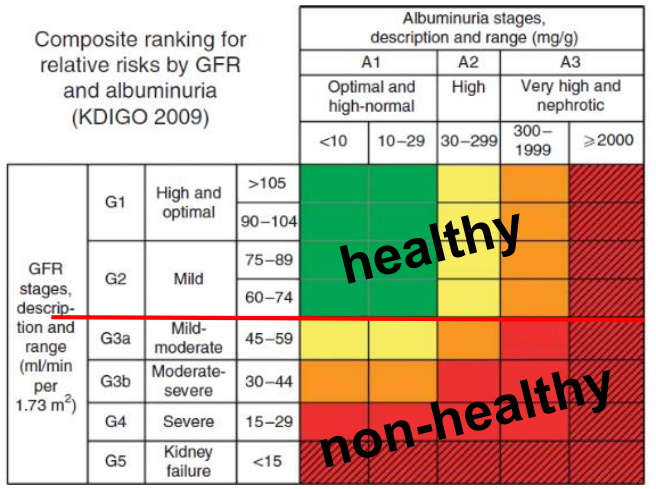
➢ P30: percentage of estimated values within 30% of measured GFR value.

Example: mGFR = 60 ml/min/1.73m²
30% of 60 = 18 ml/min
>> **P30 ranges between 42 and 78 ml/min/1.73m² (includes three CKD stages!)**
MDRD with P30 of 81% means that **19% lies outside** this range.

➢ P30 of 81%: includes Stage IIIa and IIIb (42-78 ml/min)

➢ mGFR = 60 with **P15: (±9): 51-69 ml/min/1.73m²**

>> **More reliable for CKD stage discrimination**!



1. VALUE OF CURRENT GFR ASSESSMENT METHODS?

- Equations give only a rough GFR estimate!
  - **Large variation in children, adolescents, older adults, different races and ethnicities!**
- GFR equations are always population-specific:
  - equation developed in CKD patients underestimates GFR in individuals with normal kidney function (e.g. kidney donors)
  - equation developed in healthy individuals (e.g. kidney donors) overestimates GFR in CKD patients.
- Automated GFR reporting in most Western countries (either MDRD or CKD-EPI)
- Drug dosing recommendations based on Cockcroft-Gault (Clcr) > low awareness!
- KDIGO recommendation for eGFR equations' performance metric: P30 ≥ 90%
- Accuracy of eGFR equations lower in high GFR range (above 60 ml/min/1.73m²)

1.1 Renal Biomarker beyond Creatinine?

Cystatin C: Low molecular weight protein produced in all nucleated body cells

- Cystatin C **most prominent nontraditional renal biomarker for GFR prediction**
- Cystatin C is **less influenced** by variations in **muscle mass, age, and sex**
- Cystatin C is included in CKD diagnostic criteria for KDIGO guidelines: confirmatory test for stage 3a
- Non-GFR determinants of Cystatin C not fully understood
- Lab analysis with **standardized assays**
- Cystatin C is more strongly associated with adverse non-renal outcomes (e.g. CV-events and death) compared to serum creatinine
- Still more expensive than serum creatinine

1.2 Cystatin C versus Creatinine : Non-GFR determinants

Non-GFR Determinants	Creatinine	Cystatin C
Age	decrease / increase	no change/increase (?)
Female gender	decrease	no change
Race	African Am.: increase	no change (?)
	Hispanics: decrease	no change (?)
<u>Body habitus</u>		
-**muscular**	increase	hardly any change
-sarcopenia	decrease	no change/increase
-obesity	no change	increase

adapted from Stevens & Levey JASN 2009

1.2 Cystatin C versus Creatinine : Non-GFR determinants

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Age	decrease / increase	no change/increase (?)
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Body habitus		
-**muscular**	increase	hardly any change
-sarcopenia	decrease	no change/increase
-obesity	no change	increase
Chronic or acute illness		
-malnutrition, inflammation	decrease	increase
-diabetes	rather decrease	increase
-malignancy	no change	increase/no change (?)
-HIV	No change	increase
Medication	increase under cimetidine, antibiotics	increase under high cell turnover, higher doses of steroids (?)
Diet		
-vegetarian	decrease	no change
-cooked meat	Increase	no change
Smoking	no change	Increase

adapted from Stevens & Levey JASN 2009

1.3 The Influence of Age on GFR Assessment

Current KDIGO guidelines in **Children, Adolescents and Adults:**

- for children (age 0-18): creatinine-based Chronic Kidney Disease in Children **($CKid_{SCr}$)**
- for adults (age 18+): creatinine-based **CKD-EPI**

- Cross-sectional dataset, 5,764 subjects (age 10-30 yrs)

- **Results:** Implausible eGFR changes when transitioning from child- to adulthood
- Positive bias of 21 ml/min/1.73m² with **CKD-EPIcr** at age 18-20 yrs
- Negative bias of -2.7 ml/min/1.73m² with **$CKid_{SCr}$** equation in children at 16-18 yrs of
- Mean change of eGFR: 23 ml/min/1.73m² at transition to adult care

clinical investigation

Kidney International, (2019)

Estimating glomerular filtration rate at the transition from pediatric to adult care

Hans Pottel[1,13], Jonas Björk[2,3,13], Arend Bökenkamp[4,13], Ulla Berg[5], Kajsa Åsling-Monemi[5], Luciano Selistre[6], Laurence Dubourg[7,13], Magnus Hansson[8], Karin Littmann[8], Ian Jones[9], Per Sjöström[9], Ulf Nyman[10,12,13] and Pierre Delanaye[11,12,13]

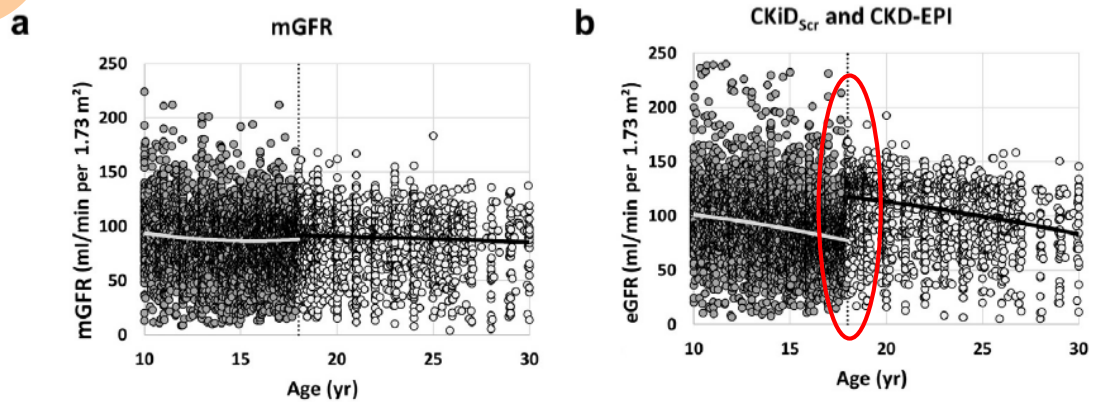
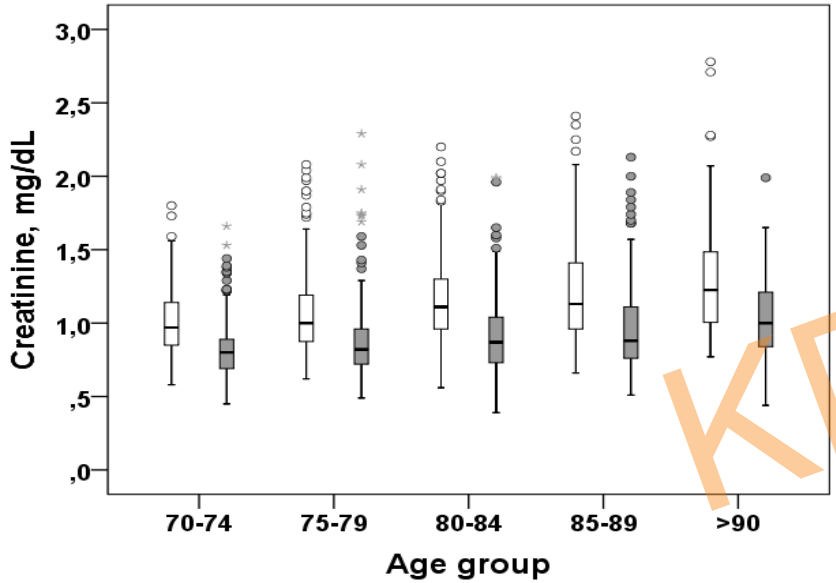
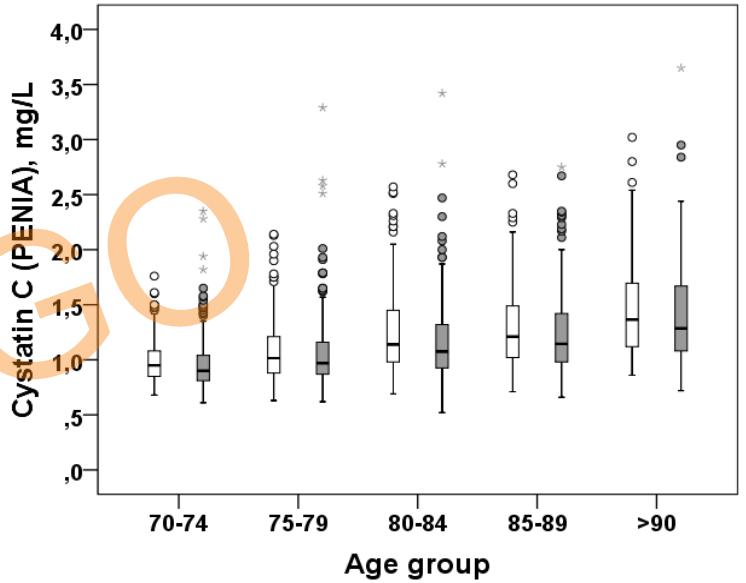


Figure 1 | Measured GFR (mGFR) (a) or estimated GFR (eGFR)—(b) creatinine-based Chronic Kidney Disease in Children ($CKiD_{Scr}$) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), (c) Full Age Spectrum (FAS)–Age, (d) FAS-Height (FAS-Ht), (e) Lund-Malmö-Revised equation (LMR)—for 3946 children (age <18 years) and for 1818 young adults (18 ≤ age ≤ 30 years). The solid lines are the median quantiles calculated on mGFR or eGFR versus age separately for both age groups.

1.3 The Influence of Age on GFR Assessment

Creatinine and Cystatin C increases with Age (cross-sectional BIS Data)





Age Strata	Median (mg/dL)	N
70-74	.86	573
75-79	.90	475
80-84	.99	429
85-89	1.01	385
>90	1.16	206
Total	.94	**2,068**

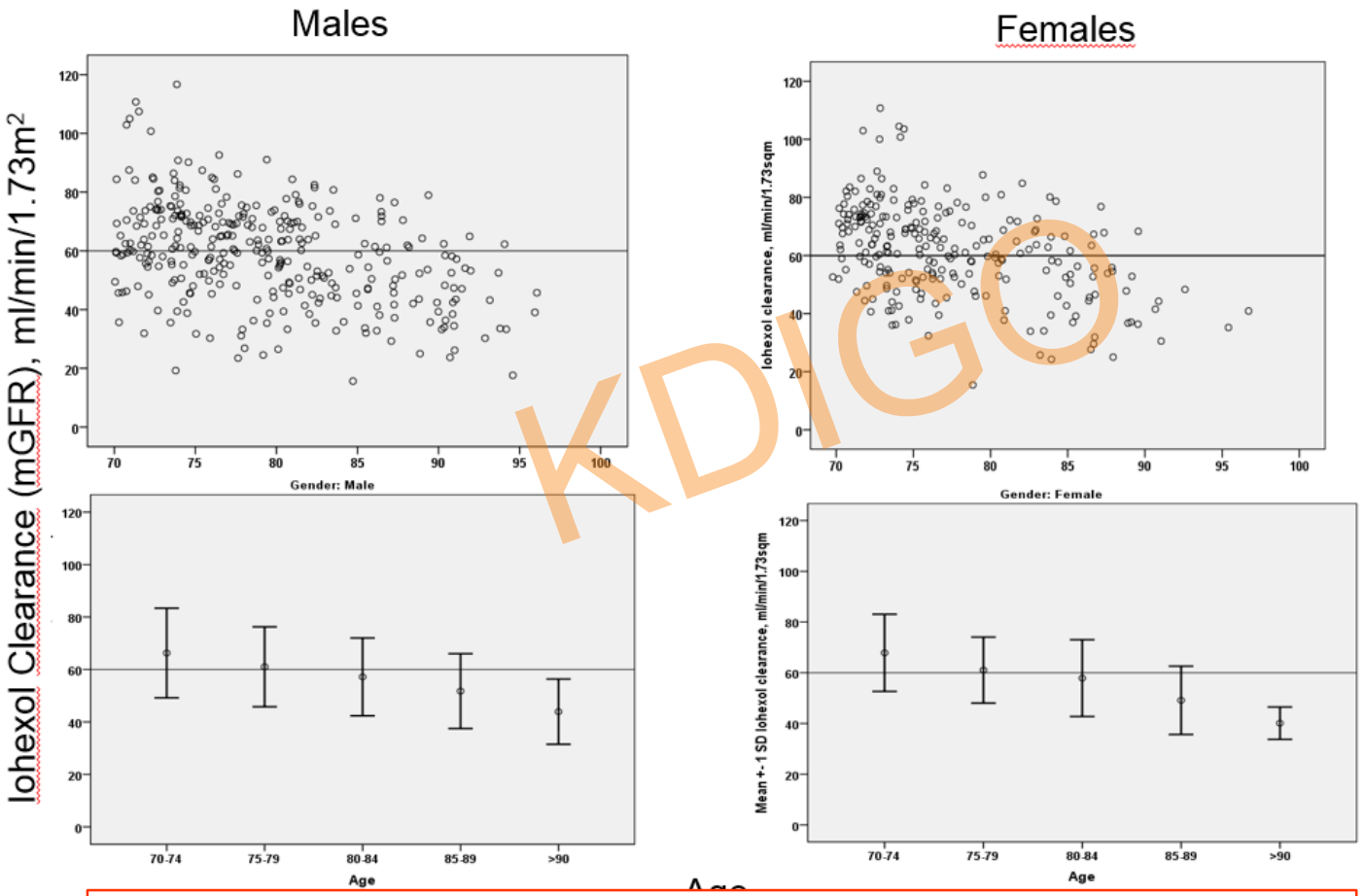
Age Strata	Median (mg/L)	N
70-74	.99	573
75-79	1.08	475
80-84	1.20	429
85-89	1.29	385
>90	1.42	206
Total	1.12	**2,068**

BIS Berliner Initiative Studie

Ebert et al., NDT 2016

1.3 The Influence of Age on GFR Assessment

Measured GFR across the age strata (cross-sectional BIS Data)



Measured GFR decreases with increasing Age

BIS Berliner Initiative Studie

Ebert et al., NDT 2016

1.3 The Influence of Age on GFR Assessment

Loesment-Wendelmuth *et al. BMC Nephrology* (2017) 18:87
DOI 10.1186/s12882-017-0508-7

CASE REPORT

Two elderly patients with normal and elevated cystatin C – a case

Amina Loesment-Wendelmuth[1], Elke Schaeffner[2] and Natalie Ebert[2*]

Case presentation: Patient 1, a 102-year-old woman, presented with a Scr of 0.45 mg/dl, while her Scys was elevated (1.55 mg/l). Depending on which of the five GFR estimating equations was used, the patient could be classified into four different CKD-Stages (2, 3a, 3b and 4). The largest difference between the eGFR-results was 94 ml/min/1.73 m^2 (Δ-eGFR).
Patient 2, an 88-year-old man, also had normal Scr (0.93 mg/dl) but elevated Scys (1.55 mg/l). An iohexol clearance measurement yielded a measured GFR (mGFR) of 44 ml/min/1.73 m^2. Four out of five GFR equations would have overestimated the patient's kidney function.

Fig. 1 Estimated GFR results depending on different equations in patient 1 and 2

BIS study participant:
-Female
-102 years
-Crea: 0.45 mg/dl
-Cyst. C: 1.55 mg/l
-BMI: 17.26

1.4 The influence of Race on GFR assessment

- Muscle mass and creatinine tubular secretion may differ by race/ethnicity
- MDRD study equation first to include race coefficient for African American
- The coefficient for African American has shown not to be accurate in other black populations (Africa, Europe, Caribbean & Indigenous Australians).
- Estimated GFR with race coefficient results in lower prevalence of CKD in African Americans than Whites, despite the considerably higher risk of ESRD in African Americans.
- Asian populations: variety of proposed race coefficients (MDRD & CKD-EPI equations) but lack of white reference group
- In HIV+ Blacks burden of CKD is underestimated when using current eGFR equations. However, accurate GFR assessment critical as they have at least a 3-fold incidence of ESKD compared to HIV+ Whites
- Measured GFR can improve understanding of non-GFR determinants in different races/ethnicities

Coresh J et al., Am J Kidney Dis 1998
Perrone RD et al., Clin Chem 1992
Peralta CA et al, Nephrol Dial Transplant 2010
Delanaye P et al., Clin J Am Soc Nephrol 2011
Maple-Brown LJ et al., Am J Kidney Dis 2012
Anker et al., Ethnicity and Disease 2016
Bukabau JB et al., PLoS One 2018.

PROGRESSION OF CKD AND CV RISK/MORTALITY PREDICTION

2. GFR and Albuminuria for Prediction of CV Risk

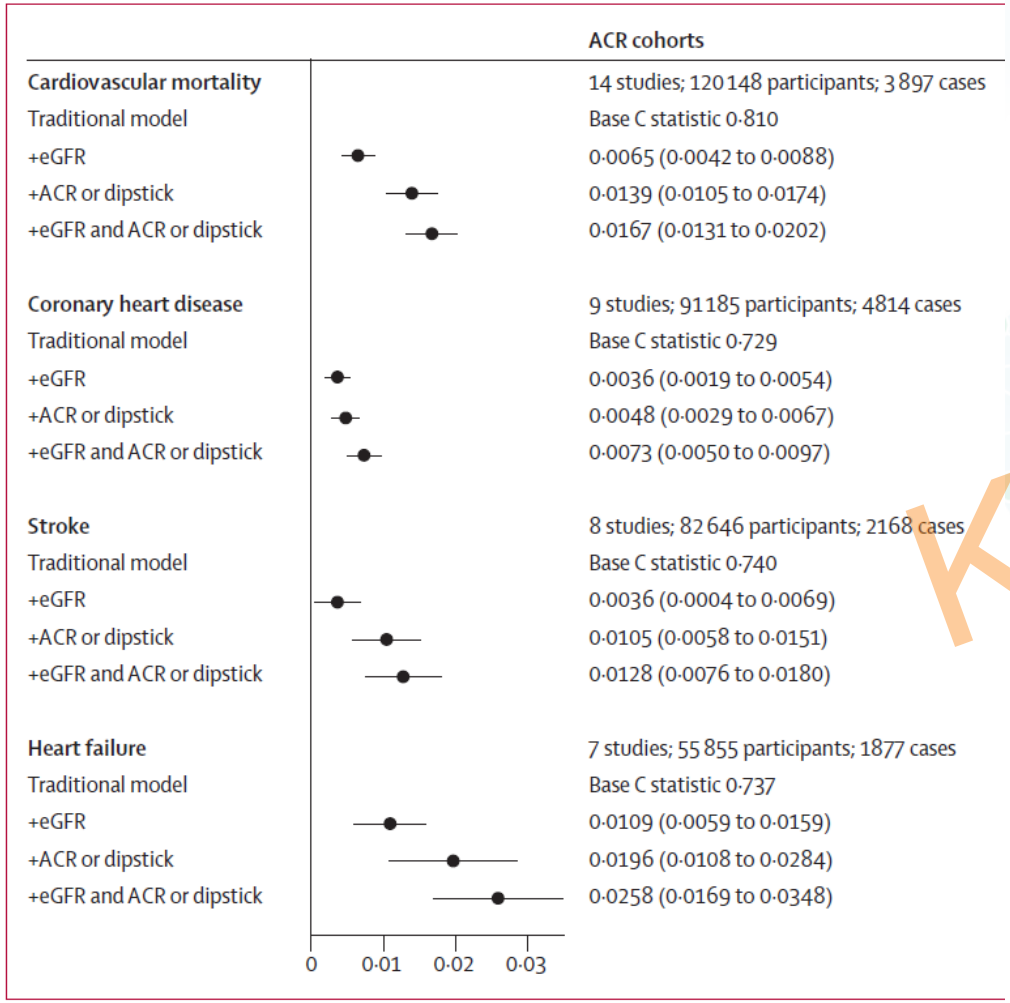


Figure 2: Cardiovascular outcomes in the general population and high-risk cohorts, with addition of kidney measures in ACR cohorts and dipstick cohorts
Figure shows difference in C statistics and 95% CIs for cardiovascular outcomes after addition of kidney measures to traditional models in the combined general-population and high-risk cohorts. There was only one study with dipstick proteinuria and heart failure, and thus meta-analysis was not done for this category. eGFR=estimated glomerular filtration rate. ACR=urine albumin-to-creatinine ratio.

Meta-analysis (CKD-Prognosis Consortium) from 24 cohorts (637,315 participants w/o PH of CV disease). Evaluated risk prediction improvement by Creatinine-based eGFR and albuminuria (ACR)

Outcomes: CV mortality, coronary disease, stroke, and heart failure.

Summary:

- eGFRcr & albuminuria **independently** improved prediction of CV events, particularly for **CV mortality and heart failure**.
- **ACR outperformed** eGFR and most of modifiable traditional risk factors for both outcomes and **stroke**.
- For individuals with **CKD, diabetes, or hypertension**, creatinine-based eGFR and albuminuria are especially useful for prediction of CV risk.

Matsushita et al., Lancet Diab Endocrinol 2015

2. GFR and Albuminuria for Prediction of CV Risk

Cystatin C-based GFR for determining CV risk based on kidney function

- eGFR based on creatinine and cystatin C best estimate of measured GFR
- However **cystatin C-based eGFR predicts clinical outcomes better than the combination of creatinine and cystatin C**
- The contribution of non-GFR determinants (less dependent on age, sex, and race) of cystatin C to CVD prediction may account for this observation.

Shlipak et al., NEJM 2013
Waheed et al., Am J Kidney Dis 2012

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cystatin C versus Creatinine in Determining Risk Based on Kidney Function

Michael G. Shlipak, M.D., M.P.H., Kunihiro Matsushita, M.D., Ph.D., Johan Ärnlöv, M.D., Ph.D., Lesley A. Inker, M.D., Ronit Katz, D.Phil., Kevan R. Polkinghorne, F.R.A.C.P., M.Clin.Epi., Ph.D., Dietrich Rothenbacher, M.D., M.P.H., Mark J. Sarnak, M.D., Brad C. Astor, Ph.D., M.P.H., Josef Coresh, M.D., Ph.D., Andrew S. Levey, M.D., and Ron T. Gansevoort, M.D., Ph.D., for the CKD Prognosis Consortium*

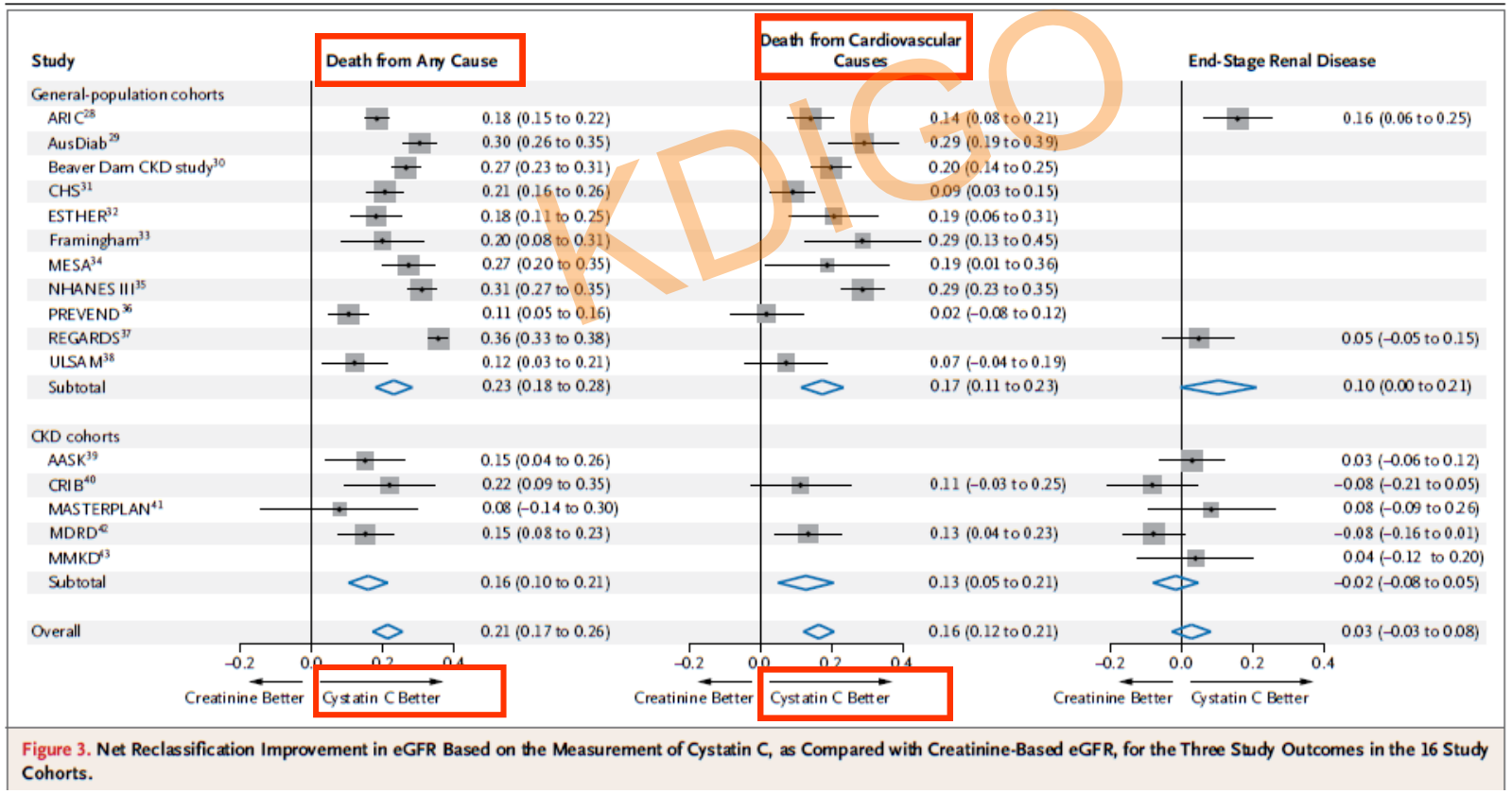


Figure 3. Net Reclassification Improvement in eGFR Based on the Measurement of Cystatin C, as Compared with Creatinine-Based eGFR, for the Three Study Outcomes in the 16 Study Cohorts.

2.1 GFR & ALBUMINURIA FOR IDENTIFICATION OF CKD-ASSOCIATED RISK

ORIGINAL CONTRIBUTION

ONLINE FIRST

Detection of Chronic Kidney Disease With Creatinine, Cystatin C, and Urine Albumin-to-Creatinine Ratio and Association With Progression to End-Stage Renal Disease and Mortality

Carmen A. Peralta, MD, MAS
Michael G. Shlipak, MD, MPH
Suzanne Judd, PhD
Mary Cushman, MD
William McClellan, MD, MPH

Context A triple-marker approach for chronic kidney disease (CKD) evaluation has not been well studied.

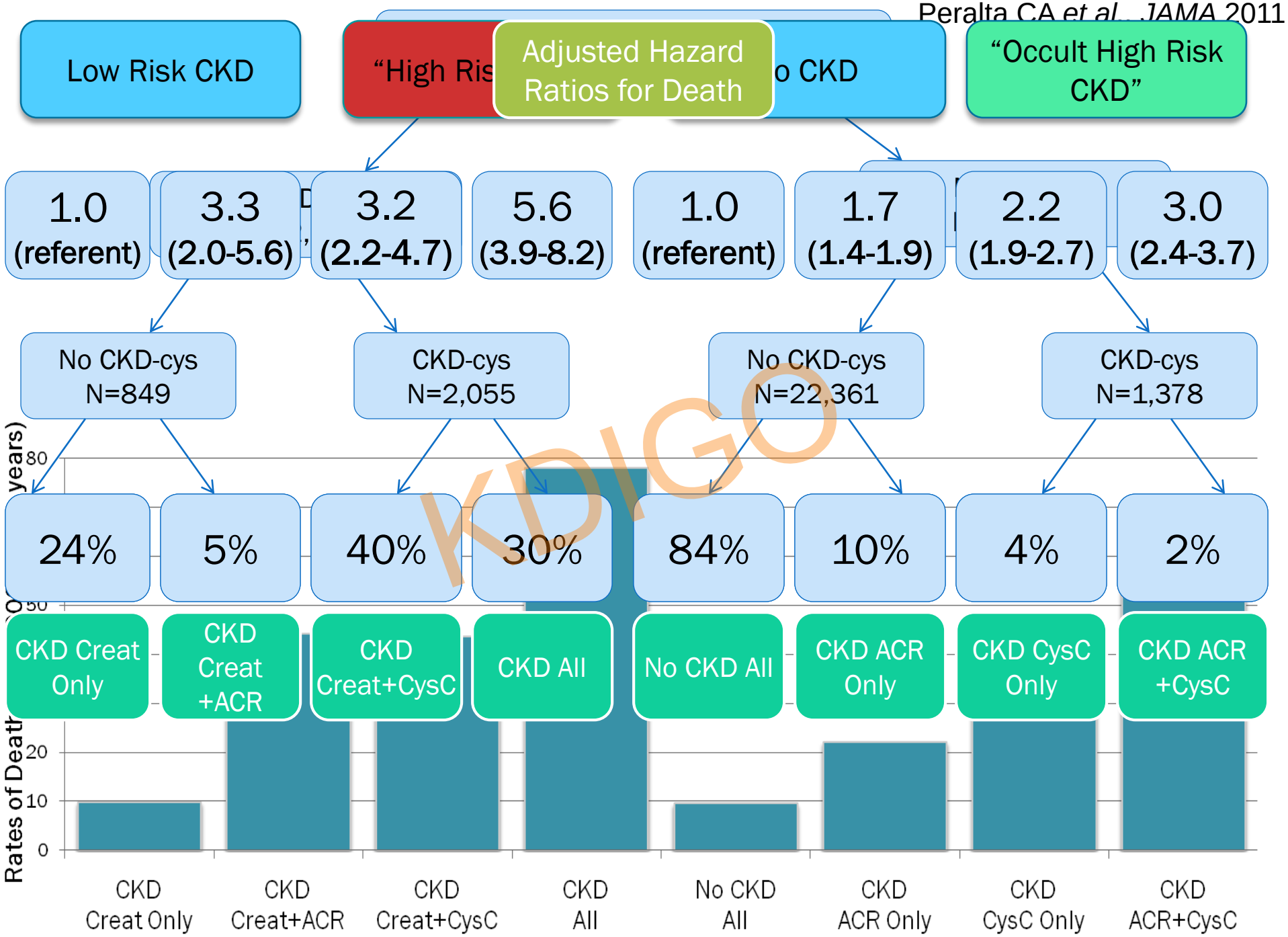
Objective To evaluate whether combining creatinine, cystatin C, and urine albumin-to-creatinine ratio (ACR) would improve identification of risks associated with CKD compared with creatinine alone.

Design, Setting, and Participants Prospective cohort study involving 26 643 US adults

Prospective cohort study involving 26,643 US adults (REGARDS) between 2003 -2010.
Main outcome measure: **All-cause mortality and incident ESKD (median follow up 4.6 yrs)**
Mean age 65 years, 40% Black, and 54% women. N=1940 died and 177 developed end-stage kidney disease.

Peralta et al., JAMA 2011

Peralta CA *et al*., *JAMA* 2011



Thank you to Mike, Carmen and Erica!

2.2 Clinical utility and Cost of Cystatin C in Primary Care I

PLOS | MEDICINE

RESEARCH ARTICLE

The clinical utility and cost impact of cystatin C measurement in the diagnosis and management of chronic kidney disease: A primary care cohort study

Adam Shardlow[1,2]*, Natasha J. McIntyre[2], Simon D. S. Fraser[3], Paul Roderick[3], James Raftery[3], Richard J. Fluck[1], Christopher W. McIntyre[4], Maarten W. Taal[1,2]

1 Renal Unit, Royal Derby Hospital, Derby, United Kingdom, **2** Centre for Kidney Research and Innovation, Division of Medical Sciences and Graduate Entry Medicine, School of Medicine, University of Nottingham, Royal Derby Hospital, Derby, United Kingdom, **3** Academic Unit of Primary Care and Population Sciences, Faculty of Medicine, University of Southampton, Southampton, United Kingdom, **4** Division of Nephrology, Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario, Canada

* adam.shardlow@nhs.net

PLOS Medicine | https://doi.org/10.1371/journal.pmed.1002400 October 10, 2017

GFR was estimated from serum creatinine and cystatin C in a cohort of 1,741 individuals with a mean age of 73 years diagnosed with chronic kidney disease in **primary care**.

2.2 Clinical utility and Cost of Cystatin C in Primary Care II

Use of cystatin C to confirm diagnosis of CKD in primary care:

- **7.7%** of people were reclassified as **not having CKD**
- **59%** were reclassified as having **more advanced disease**

- Cystatin C as recommended in current guidelines would result in increased healthcare costs.
- Data do not support use of cystatin C to confirm a diagnosis of CKD in primary care.
- Cystatin C may be useful in settings where creatinine is known to be unreliable, for example in people with extremes of body habitus.

2.3 Beta-trace Protein (BTP) and Beta2-Microglobulin (B2M)

	Production	Glomerulus	prox.Tubulus	Extrarenal Elimination
Ideal marker	at constant rate	freely filtered	neither secreted nor reabsorbed	no
BTP	PGD-synthase; produced in CNS; serum origin unknown	unlikely to be freely filtered	secretion unknown; partial reabsorption	unknown
B2M	component of class I MHC molecules	freely filtered	completely reabsorbed & metabolized at tubulus	unknown

Assay: nephelometric or ELISA, **no standardization.**
B2M: Data from ARIC and CRIC show that B2M-based eGFR was associated with CVD events (MI, heart failure, and stroke) beyond traditional risk factors.
B2M as prognostic factor in multiple myeloma.

Foster et al. Am J Kidney Dis 2016
Matsushita et al., Arteriosler Throm Vasc Biol 2014
White et al., Kidney Intern 2009

2.3 Beta-trace Protein (BTP) and Beta2-Microglobulin (B2M)

Little data / uncertainty:

- regarding production and metabolism
- regarding lab. assays
- regarding its non-GFR determinants:
  - Age & sex: likely
  - Race: unknown
  - Muscle mass: possibly
  - Inflammation: possibly
  - Cardiovascular disease / pregnancy / genetic factors: yes
  - Liver disease: unknown

Foster et al. Am J Kidney Dis 2016
Matsushita et al., Arteriosler Throm Vasc Biol 2014
White et al., Kidney Intern 2009

2.4 Panel of Filtration Markers - Metabolomics

- „Panel eGFR“: several filtration marker through one single blood test
- More markers may minimize impact of non-GFR determinants of each marker → may increase accuracy of eGFR using a panel
- Two groups of novel filtration markers are identified: **low- molecular-weight proteins** (LMW: cystatin C, β2-microglobulin and β- trace protein) and **metabolites** (pseudouridine, acetylthreonine, myoinositol, phenylacetylglutamine and tryptophan).

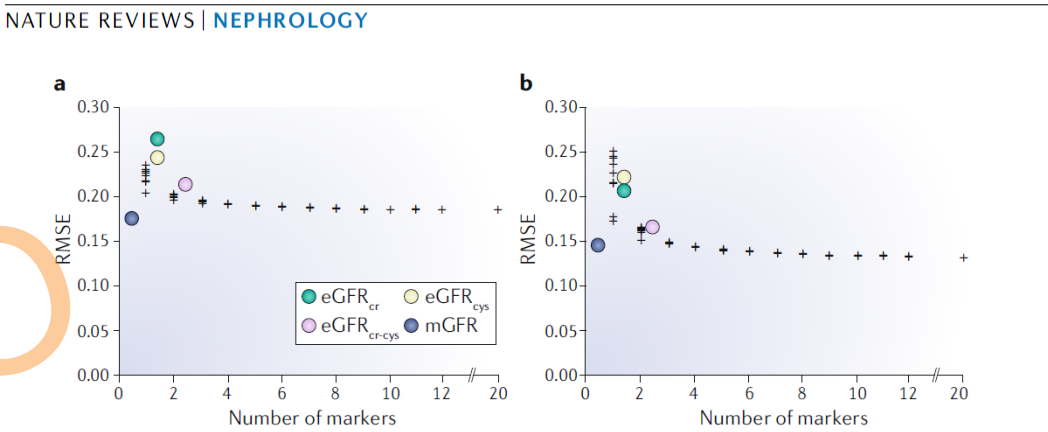


Fig. 3 | **Estimated performance of eGFR using a panel of filtration markers.** A comparison of the performance of estimated glomerular filtration rates (eGFRs) using subsets of 20 metabolites most negatively correlated with simultaneously measured GFR Published online: 16 September 2019 American Study of Kidney Diseases[93]. **a** | Data are from 714 of the 1,043 participants at the initial screening visit. **b** | Data are from 188 of the 829 participants who demonstrated a <25% difference between mGFRs at 42, 48 and 52 months of follow-up. The root mean squared error (RMSE) is shown for the top 10 eGFR models for any given number of markers (selected from the 20 metabolites) without demographic characteristics. Most of the eGFR models using ≥3 markers have a very similar RMSE, indicating that different models can achieve similar precision. For comparison, RMSE is shown for CKD-EPI equations for eGFR based on creatinine (eGFR$_{cr}$), cystatin C (eGFR$_{cys}$) and both creatinine and cystatin C (eGFR$_{cr\text{-}cys}$) at the same visit and for mGFR at an adjacent visit (second screening visit

- No standardized assay, variability/reproducibility ?
- Non-GFR determinants are not clear
- Additional benefit for CV-risk prediction?
- Additional clinical benefit is not clear
- Cost-effectiveness?

2.5 Other Markers for Predicting CV Risk in CKD Patients ?

Coronary artery calcium (CAC)

- Study from CKD-PC compared 3 measures of subclinical atherosclerosis: 1. CAC, 2. ankle brachial index, and 3. carotid intima-media thickness, for improving CVD risk prediction beyond traditional risk factors in pts. with and without CKD.
- Data showed **usefulness of CAC** over other measures **for predicting CVD events** in pts. with CKD.
- However, concerns about clinical implications of CAC in CKD patients due to their unique calcium-phosphate metabolism.

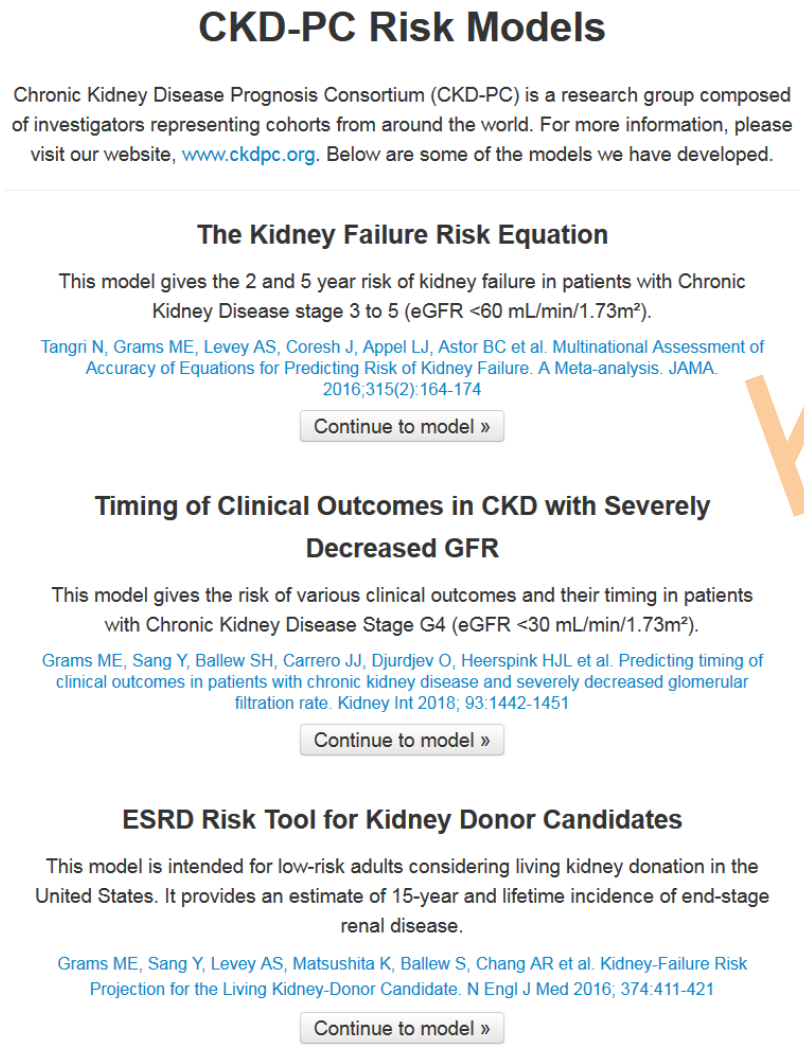
High-sensitivity cardiac troponin T levels and natriuretic peptides

- Several studies have demonstrated: cardiac troponin T and natriuretic peptides improve prediction of CVD events particularly **heart failure**, beyond traditional risk factors even in the CKD population.
- Concerns about interpretation of these biomarker in CKD pts., as they may be elevated due to reduced kidney function not cardiac damage or overload.

Matsushita et al., Curr Opin Nephrol Hypertens 2016
Matsushita et al., J Am Soc Nephrol 2015
Matsushita et al., Arterioscler Thromb Vasc Biol 2014

3. GFR AND PROGNOSIS: DIFFERENT RISK MODEL EQUATIONS

Current risk models from CKD-PC
http://www.ckdpcrisk.org/



CKD-PC Risk Models

Chronic Kidney Disease Prognosis Consortium (CKD-PC) is a research group composed of investigators representing cohorts from around the world. For more information, please visit our website, www.ckdpc.org. Below are some of the models we have developed.

The Kidney Failure Risk Equation

This model gives the 2 and 5 year risk of kidney failure in patients with Chronic Kidney Disease stage 3 to 5 (eGFR <60 mL/min/1.73m²).

Tangri N, Grams ME, Levey AS, Coresh J, Appel LJ, Astor BC et al. Multinational Assessment of Accuracy of Equations for Predicting Risk of Kidney Failure. A Meta-analysis. JAMA. 2016;315(2):164-174

Continue to model »

Timing of Clinical Outcomes in CKD with Severely Decreased GFR

This model gives the risk of various clinical outcomes and their timing in patients with Chronic Kidney Disease Stage G4 (eGFR <30 mL/min/1.73m²).

Grams ME, Sang Y, Ballew SH, Carrero JJ, Djurdjev O, Heerspink HJL et al. Predicting timing of clinical outcomes in patients with chronic kidney disease and severely decreased glomerular filtration rate. Kidney Int 2018; 93:1442-1451

Continue to model »

ESRD Risk Tool for Kidney Donor Candidates

This model is intended for low-risk adults considering living kidney donation in the United States. It provides an estimate of 15-year and lifetime incidence of end-stage renal disease.

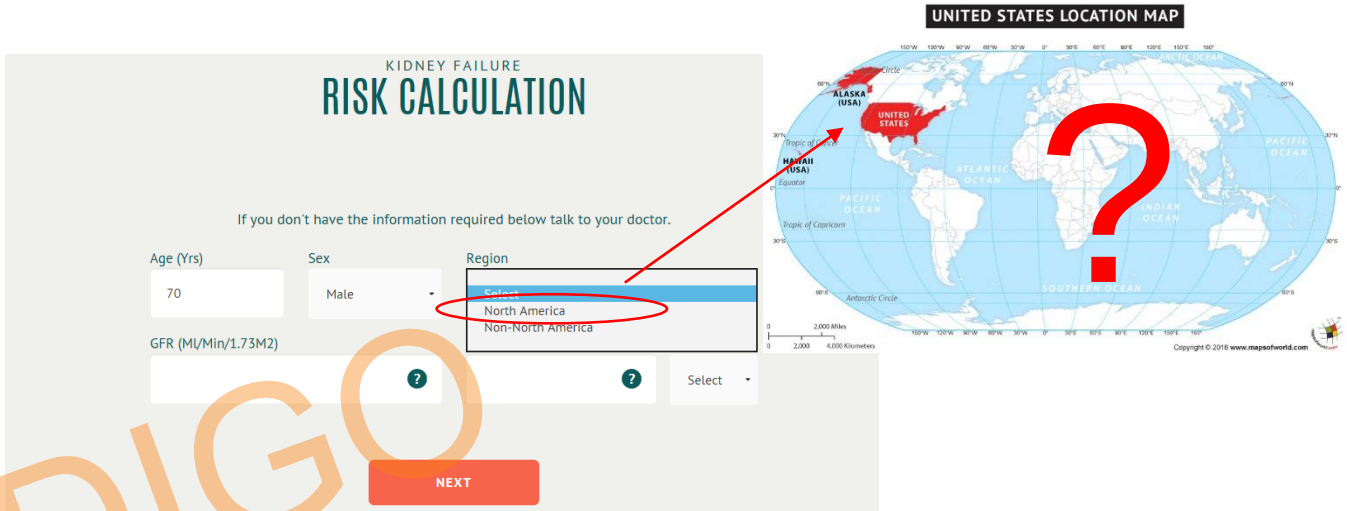
Grams ME, Sang Y, Levey AS, Matsushita K, Ballew S, Chang AR et al. Kidney-Failure Risk Projection for the Living Kidney-Donor Candidate. N Engl J Med 2016; 374:411-421

Continue to model »

- Importance of 'risk discussion' between patients and physicians for **shared decision-making** (The AHA/ACC Guideline on the Assessment of Cardiovascular Risk).
- Such discussions would **include the patient's predicted risk for CVD,** potential benefits/harms of treatments, and patient preferences of preventive therapies.
- Use of risk prediction scores in clinical practice are rare, particularly in primary care!
- **How to communicate risk to the patient??**

3. GFR and Prognosis: Different Risk Model Equations

- Generalizability of Risk calculators



- External Validation in different populations?!

3. GFR and Prognosis: Different Risk Model Equations

- SCORE/SCORE-OP Validation in BIS Data

Performance of risk prediction scores for cardiovascular mortality in people 70 years or older: External validation and implications

Marco Piccininni & **Jessica L Rohmann**, Dörte Huscher, Nina Mielke, Natalie Ebert, Giancarlo Logroscino, Elke Schäffner & Tobias Kurth *(& indicates equal contribution)*

RESULTS

Risk score	Actual number of fatal CV events	Predicted number of fatal CV events	Difference between actual & predicted fatal CV events (%)	Nam-D'Agostino chi-square	C-index
SCORE-H	382	372	-2.6%	29.7	0.72
SCORE-L	384	258	-32.8%	117.6	0.72
SCORE OP High	399	677	+69.7%	327.9	0.79
SCORE OP Low	397	519	+30.7%	76.3	0.80

- SCORE showed better calibration
  - High-risk region version, only slight underestimation of risk
- SCORE OP showed better discrimination

DISCUSSION

- SCORE OP consistently overestimated fatal CV event risk
  - Interesting because was developed to correct for suspected overestimation of SCORE in elderly!
  - Could lead to potential treatment at feasible, hypothetical treatment thresholds (see side panel)
  - Age group 65-68, SCORE-L has higher risk estimates than SCORE OP-L for medium and high-risk profiles, but not true for any of the risk profiles in individuals aged ≥70 (see side panel)
- Low transportability of SCORE OP observed
  - Further external validation needed before use in routine clinical practice

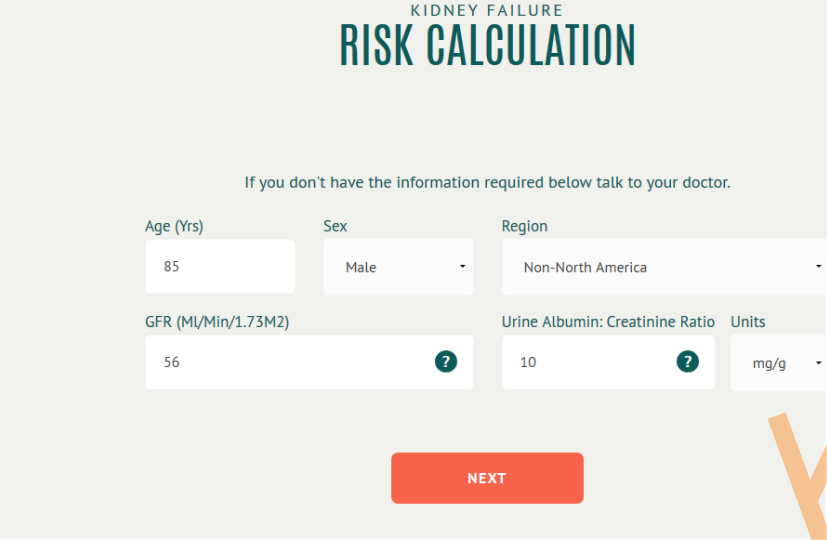
Poster Presentation

Society for Epidemiologic Research

KDIGO Kidney Disease Improving Global Outcomes

3. GFR and Prognosis: Different Risk Model Equations

- Non-uniform recommendations of Risk calculators



2018 ESC/ESH Guidelines for the management of arterial hypertension FREE

Bryan Williams ✉, Giuseppe Mancia ✉, Wilko Spiering, Enrico Agabiti Rosei, Michel Azizi, Michel Burnier, Denis L Clement, Antonio Coca, Giovanni de Simone, Anna Dominiczak ...
Show more
Author Notes

European Heart Journal, Volume 39, Issue 33, 01 September 2018, Pages 3021–3104, https://doi.org/10.1093/eurheartj/ehy339
Published: 25 August 2018

Table 23

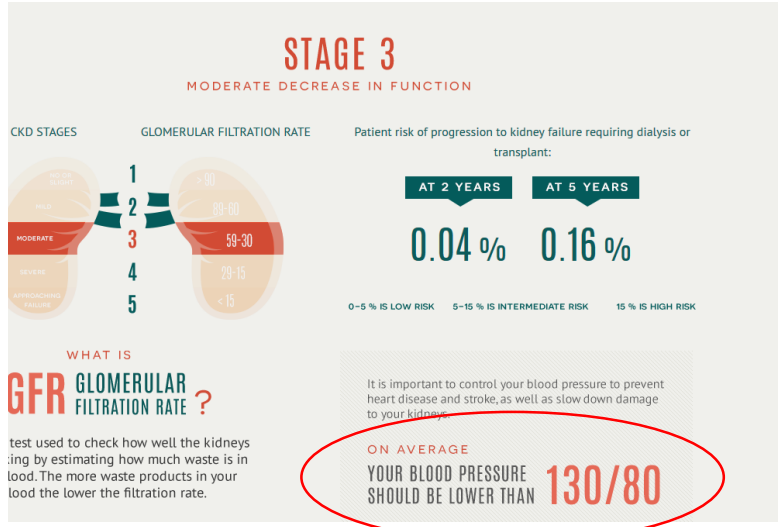
Office blood pressure treatment target range

Age group	Office SBP treatment target ranges (mmHg)					Office DBP treatment target range (mmHg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke[a]/TIA	
18 – 65 years	**Target to 130***or lower if tolerated* Not <120	**Target to 130***or lower if tolerated* Not <120	**Target to <140 to 130***if tolerated*	**Target to 130***or lower if tolerated* Not <120	**Target to 130***or lower if tolerated* Not <120	70–79
65 – 79 years[b]	**Target to 130-139***if tolerated*	**Target to 130-139***if tolerated*	**Target to 130-139***if tolerated*	**Target to 130-139***if tolerated*	**Target to 130-139***if tolerated*	70–79
≥80 years[b]	**Target to 130-139***if tolerated*	**Target to 130-139***if tolerated*	**Target to 130-139***if tolerated*	**Target to 130-139***if tolerated*	**Target to 130-139***if tolerated*	70–79
Office DBP treatment target range (mmHg)	70–79	70–79	70–79	70–79	70–79	

CAD = coronary artery disease; CKD = chronic kidney disease (includes diabetic and non-diabetic CKD); DBP = diastolic blood pressure; SBP = systolic blood pressure; TIA = transient ischaemic attack.

a Refers to patients with previous stroke and does not refer to blood pressure targets immediately after acute stroke.

b Treatment decisions and blood pressure targets may need to be modified in older patients who are frail and independent.



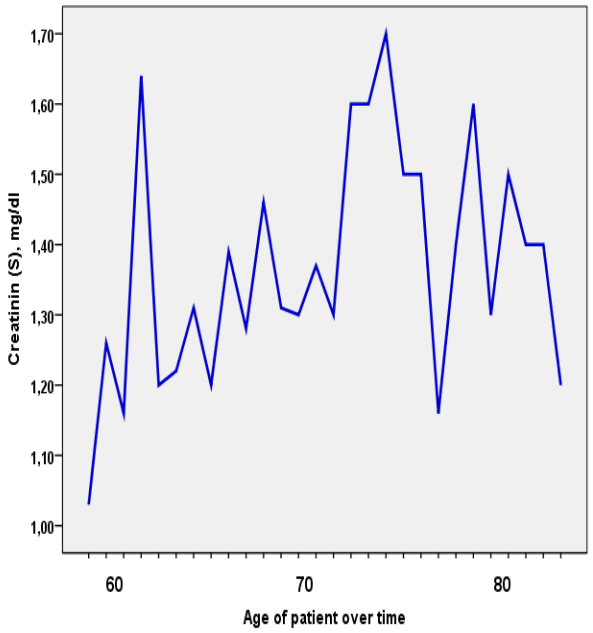
3.1 Case Report: 87 y old Male with CKD in 2015

- Male patient, 87 yrs
- Comorbidities: **Art. Hypertension**, **Type II DM**, **Hyperlipoproteinemia**, **Hyperuricemia**
- **Medication**: Metformin, Simvastatin, Candesartan, Amlodipin, Allopurinol
- PMH: **No CV-events**, no coronary artery disease
- Physical activity: 45 min, daily
- No history of **smoking** within the last 50 yrs
- Moderate alcohol consumption

3.1 Case Report: Creatinine, BUN and Hb slopes over time

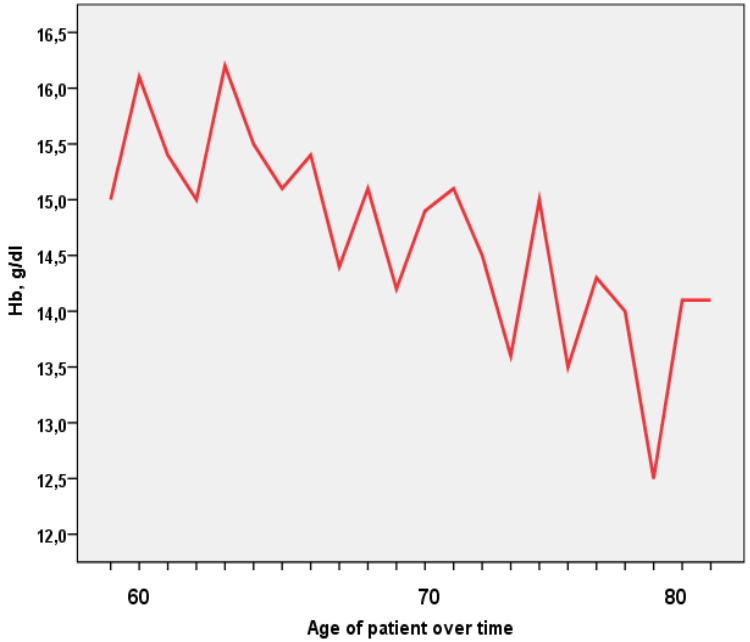
Parameter

Creatinine



BUN

Hemoglobin



eGFR since 1988: between 79 and 37 ml/min/1.73m^2,
last value in 2015: **54 ml/min/1.73m^2**

Considering creatinine/eGFR slopes for risk assessment?

4. GFR-Slope & Change in Albuminuria as Surrogate endpoint for CKD Progression – Data from The CKD-PC

Evaluating Glomerular Filtration Rate Slope as a Surrogate End Point for ESKD in Clinical Trials: An Individual Participant Meta-Analysis of Observational Data

Received January 4, 2019. Accepted April 17, 2019.

Morgan E. Grams,[1] Yingying Sang,[1] Shoshana H. Ballew,[1] Kunihiro Matsushita,[1] Brad C. Astor,[2,3] Juan Jesus Carrero,[4] Alex R. Chang,[5] Lesley A. Inker,[6] Timothy Kenealy,[7,8] Csaba P. Kovesdy,[9,10] Brian J. Lee,[11] Adeera Levin,[12] David Naimark,[13] Michelle J. Pena,[14] Jesse D. Schold,[15,16] Varda Shalev,[17]

Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies

Lancet Diabetes Endocrinol 2019; 7: 115–27

Josef Coresh, Hiddo J L Heerspink, Yingying Sang, Kunihiro Matsushita, Johan Arnlov, Brad C Astor, Corri Black, Nigel J Brunskill, Juan-Jesus Carrero, Harold I Feldman, Caroline S Fox, Lesley A Inker, Areef Ishani, Sadayoshi Ito, Simerjot Jassal, Tsuneo Konta, Kevan Polkinghorne, Solfrid Romundstad, Marit D Solbu, Nikita Stempniewicz, Benedicte Stengel, Marcello Tonelli, Mitsumasa Umesawa, Sushrut S Waikar, Chi-Pang Wen, Jack F M Wetzels, Mark Woodward, Morgan E Grams, Csaba P Kovesdy, Andrew S Levey, Ron T Gansevoort, for the Chronic Kidney Disease Prognosis Consortium and Chronic Kidney Disease Epidemiology Collaboration*

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Special Report AJKD

Change in Albuminuria and GFR as End Points for Clinical Trials in Early Stages of CKD: A Scientific Workshop Sponsored by the National Kidney Foundation in Collaboration With the US Food and Drug Administration and European Medicines Agency

Andrew S. Levey, Ron T. Gansevoort, Josef Coresh, Lesley A. Inker, Hiddo L. Heerspink, Morgan E. Grams, Tom Greene, Hocine Tighiouart, Kunihiro Matsushita, Shoshana H. Ballew, Yingying Sang, Edward Vonesh, Jian Ying, Tom Manley, Dick de Zeeuw, Kai-Uwe Eckardt, Adeera Levin, Vlado Perkovic, Luxia Zhang, and Kerry Willis

- Slower **decline in eGFR** was associated with lower **risk of subsequent ESKD**, even in participants with eGFR ≥60 ml/min per 1.73 m².
- **Change in albuminuria** associated with subsequent **risk of end-stage kidney disease** → as surrogate endpoint for end-stage kidney disease in clinical trials of **progression of chronic kidney disease.**
- **Change in albuminuria** and **GFR slope** as surrogate end points in clinical trials for **chronic kidney disease progression** with **stronger support for change in GFR** than albuminuria.

WRAP - UP

- Keep in mind: estimated GFR is a **rough estimate** with relatively large variation in different populations (children, adolescents, older adults, Blacks, Asians, Indigenous…).
- Combination of creatinine and cystatin C provides the **most accurate GFR estimates**, particularly in older adults (and children).
- Two key CKD measures, eGFR and albuminuria, improve CVD risk prediction beyond traditional risk factors.
- Adding cystatin C to creatinine and ACR for risk **prediction** (CVD and mortality) can more accurately distinguish prognostic differences – Primary care ?
- Albuminuria is independently **associated** with risk of mortality, MI and progression to ESRD.
- Other biomarkers reflecting pathophysiological process of CVD, such as CAC, hsTropT & natriuretic peptides, may further improve CV-risk **prediction** in CKD pts.
- External validation of risk **prediction** scores in diverse populations is lacking.
- eGFR slope & change in albuminuria (chronicity) as surrogate endpoint for CKD-progression.

THANK YOU FOR YOUR ATTENTION!

QUESTIONS?