Universitair Ziekenhuis Gent

ERBP

UNIVERSITEIT GENT

WHEN TO START DIALYSIS?

R Vanholder,
University Hospital,
Gent, Belgium

- **EUROPEAN BEST PRACTICE GUIDLINES 2002** ←→
- **EUROPEAN RENAL BEST PRACTICE 2011**

- **EUROPEAN BEST PRACTICE GUIDLINES 2002** ←→ **EUROPEAN RENAL BEST PRACTICE 2011**

When to start dialysis: updated guidance following publication of the Initiating Dialysis Early and Late (IDEAL) study

James Tattersall[1], Friedo Dekker[2], Olof Heimbürger[3], Kitty J. Jager[4], Norbert Lameire[5], Elizabeth Lindley[1], Wim Van Biesen[5], Raymond Vanholder[5], Carmine Zoccali[6] and on behalf of the ERBP Advisory board

– Author Affiliations

[1]Leeds Teaching Hospitals Trust, Leeds, UK
[2]Leiden University Medical Center, Leiden, The Netherlands
[3]Karolinska Institutet, Huddinge University Hospital, Stockholm, Sweden
[4]Academic Medical Center University of Amsterdam, The Netherlands
[5]University Hospital, Ghent, Belgium
[6]Ospedali Riuniti, Reggio Calabria, Italy

EBPG 2002

- **Start with GFR < 15 mL/min in case of uremic symptoms**
- **Start before 6 mL/min, aim at 8-10 mL/min**
- **High risk patients (e.g. diabetics) may start earlier**
- **Estimation renal function not with blood urea or creatinine or Cockcroft & Gault**
- **GFR estimation with 24 hr collection, MDRD or decay method (EDTA, …)**

RELEVANT STUDIES

STUDY/YEAR	RCT/OBS	FAVORS H/L
CANUSA 1996	OBS	H
Fink et al 1999	OBS	L
NECOSAD 2001	OBS	H
Traynor 2002	OBS	L
Kazmi 2005	OBS	L
Stel 2009	OBS	L
Wright 2010	OBS	L
Huang 2010	OBS	L
Lasalle 2010	OBS	L
IDEAL 2010	RCT	N
Clark 2011	OBS	L
Evans 2011	OBS	L

RCT: Randomized controlled trial; OBS: observational; Favors H: start at high GFR = early start; Favors L: start at low GFR = late start ; N: favors none

OBSERVATIONAL TRIALS BASED ON eGFR

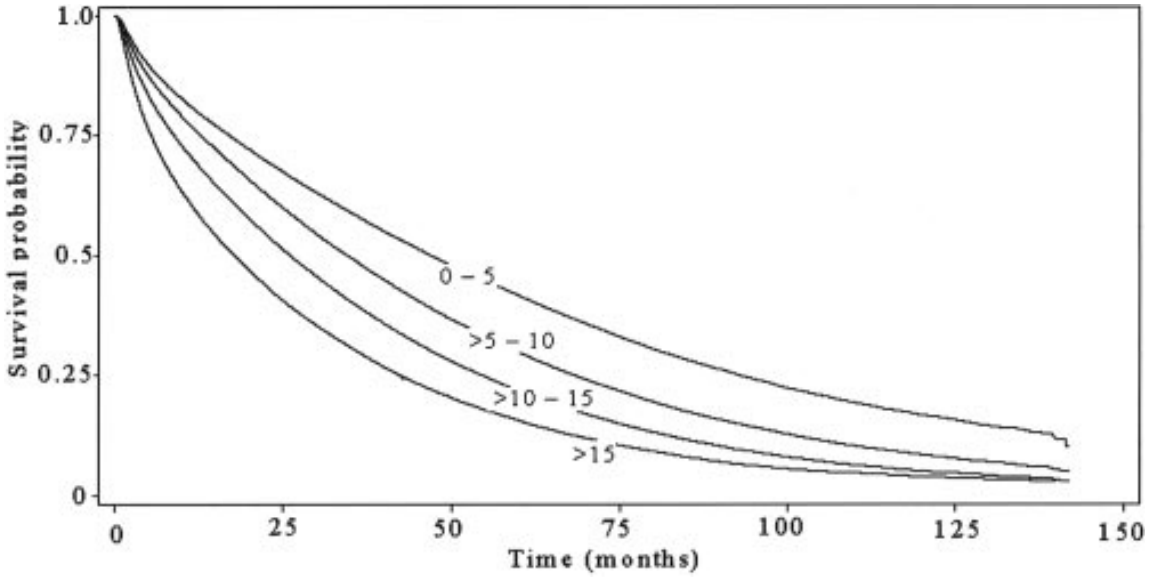

Figure 1. Kaplan-Meier survival curves (survival versus time after dialysis initiation) for categories of patients divided by the residual renal function (eGFR, ml/min per 1.73 m2) at the initiation of dialysis.

Wright et al, cJASN, 5: 1828-1835; 2010

Kazmi et al, AJKD, 46: 887-896; 2005
Hwang et al, NDT, 25: 2616-2624; 2010
Stel et al, NDT, 24: 3175-3182; 2009
Lassalle et al, KI, 77: 700-707; 2010
Clark et al, CMAJ, 183: 47-53; 2011
Fink et al, AJKD, 34: 694-701; 1999

BIAS

- **In favor of low GFR (late start)**
  - **Only the fittest surviving long enough to start dialysis were included. Thoses tarting late were thus in better condition (survival bias)**
  - **Patients with more symptoms and comorbidity will be started earlier**
  - **Patients with low muscle mass and volume overload will have lower Screa and higher eGFR**
- **In favor of high GFR (early start)**
  - **In late starters the period before enrolment when they can also develop problems is not included (lead time bias)**

SWEDISH STUDY

- **Prospective enrollment all patients at eGFR < 16 mL/min**
- **No lead time or survival bias**
- **All other bias (eGFR based on Screa and earlier start in worse patients) remains**

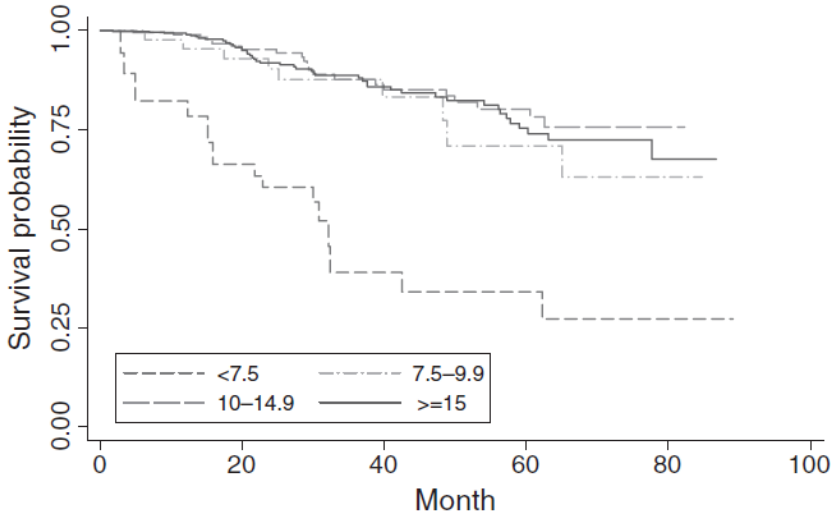

Figure 1. Kaplan–Meier survival curves by level of estimated glomerular filtration rate (eGFR, mL min^{-1} per 1.73 m^2) for 901 patients with stage 4/5 chronic kidney disease and not yet subjected to renal replacement therapy (RRT). Patients who moved from one eGFR stratum to another were censored in the old stratum and restarted from time 0 in the new stratum. Censoring also occurred at initiation of RRT.

Evans et al, J Int Med, 269: 289-298; 2011

SYNTHESIS

- **All these studies discourage an early start but all are also prone to bias that could explain the result**
- **There is no indication for a lower limit of eGFR at which one should absolutely start, although there must be such a limit (otherwise, one would never have to start)**
- **Renal function parameters based on Screa are probably misleading as a guide to start dialysis**

NECOSAD: BASED ON Mgfr (TIMED URINE COLLECTIONS)

	Late starters (n=94)	Timely starters (n=159)
Demography		
Mean (SD) age in years	56 (16)	57 (16)
Male/female	61 (65%)/33 (35%)	96 (60%)/63 (40%)
Primary kidney disease		
Diabetes mellitus	21 (22%)	21 (13%)
Glomerulonephritis	14 (15%)	22 (14%)
Renal vascular disease	9 (10%)	23 (14%)
Other	50 (53%)	93 (58%)
Khan score		
Low	40 (43%)	84 (53%)
Medium	34 (36%)	47 (30%)
High	20 (21%)	28 (18%)
Mean (SD) renal function variables		
GFR (mL/min per 1·73 m^2)	4·9 (1·7)	7·1 (2·4)*
Renal Kt/V_{urea} (per week)	1·0 (0·4)	1·5 (0·6)*
nPNA (g/kg daily)	0·7 (0·2)	1·1 (0·3)*
Body-mass index (kg/m^2)	25·4 (5·0)	24·6 (3·2)
Serum albumin (g/L)	36·4 (10·9)	38·2 (6·2)
Number on haemodialysis†	38 (40%)	61 (38%)

Data are number of patients (%) unless otherwise stated. GFR=glomerular filtration rate; nPNA=normalised protein equivalent of nitrogen appearance. *p<0·05 late *vs* timely starters. †Rest of patients were on peritoneal dialysis.

Korevaar et al, Lancet, 358: 1046-1050; 2001

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ADVANTAGE FOR EARLY START DISAPPEARS AFTER CORRECTION FOR LEAD TIME BIAS

Korevaar et al, Lancet, 358: 1046-1050; 2001

CANUSA: BASED ON m GFR (TIMED URINE COLLECTIONS)

Variable	Relative Mortality Risk	95 % Confidence interval
Age (per year)	1.03	1.01 – 1.05
IDDM	1.49	0.92 – 2.42
CVD	2.12	1.35 – 3.34
Country (USA)	1.95	1.14 – 3.31
Serum albumin (↑ 1 g/L)	0.94	0.90 – 0.97
CCr (↑ 5 L/wk/1.73 m²)	**0.93**	**0.88 – 0.98**
SGA (↑ 1 unit)	0.75	0.66 – 0.85

Churchill et al, JASN, 7: 198-207; 1996

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*

Cooper et al, NEJM: 363:609-19; 2010

EARLY VS. LATE START DIALYSIS

METHODS

We randomly assigned patients 18 years of age or older with progressive chronic kidney disease and an estimated glomerular filtration rate (GFR) between 10.0 and 15.0 ml per minute per 1.73 m^2 of body-surface area (calculated with the use of the Cockcroft–Gault equation) to planned initiation of dialysis when the estimated GFR was 10.0 to 14.0 ml per minute (early start) or when the estimated GFR was 5.0 to 7.0 ml per minute (late start). The primary outcome was death from any cause.

Cooper et al, NEJM, 363:609-19; 2010

IDEAL STUDY - MORTALITY

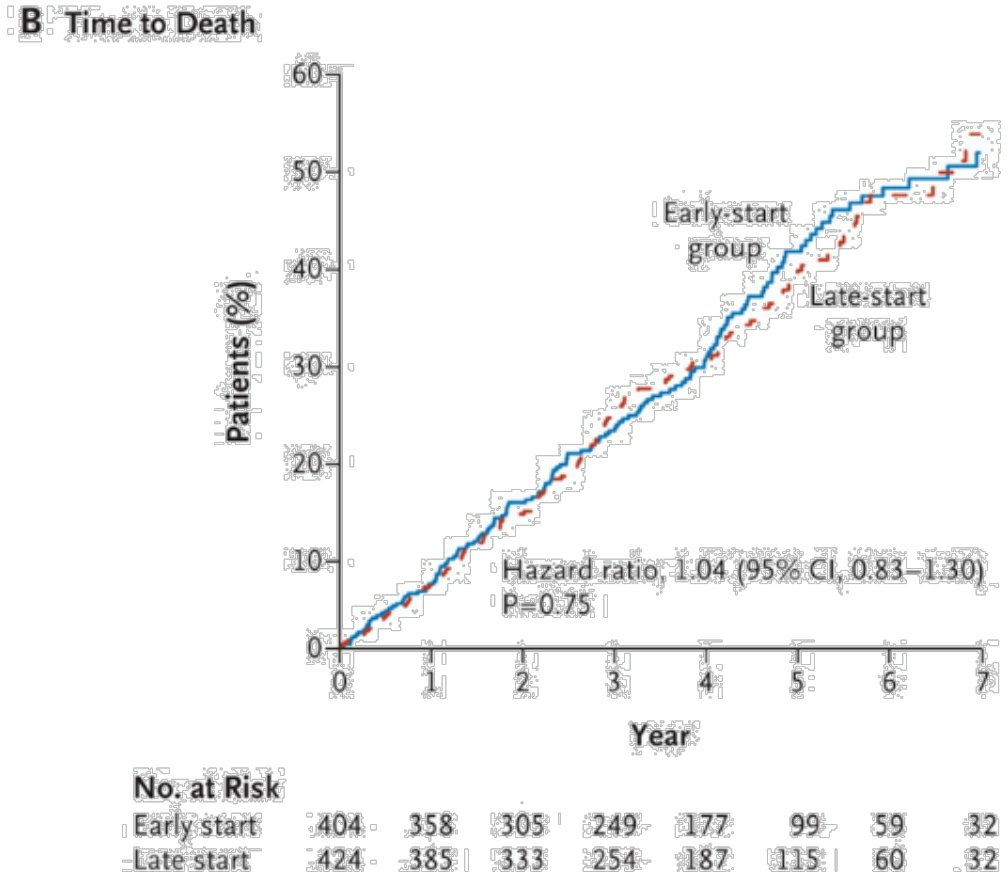

Figure 2. Kaplan–Meier Curves for Time to the Initiation of Dialysis and for Time to Death

The data for time to the initiation of dialysis (Panel A) were censored at the time of death, transplantation, or withdrawal of consent or at the time a patient transferred to a nonparticipating hospital, emigrated, or could not be contacted. The curves for time to death (Panel B) are truncated at 7 years of follow-up and a cumulative hazard of 60%.

Cooper et al, NEJM, 363:609-619; 2010

EARLY VS. LATE START DIALYSIS

RESULTS

Between July 2000 and November 2008, a total of 828 adults (mean age, 60.4 years; 542 men and 286 women; 355 with diabetes) underwent randomization, with a median time to the initiation of dialysis of 1.80 months (95% confidence interval [CI], 1.60 to 2.23) in the early-start group and 7.40 months (95% CI, 6.23 to 8.27) in the late-start group. A total of 75.9% of the patients in the late-start group initiated dialysis when the estimated GFR was above the target of 7.0 ml per minute, owing to the development of symptoms. During a median follow-up period of 3.59 years, 152 of 404 patients in the early-start group (37.6%) and 155 of 424 in the late-start group (36.6%) died (hazard ratio with early initiation, 1.04; 95% CI, 0.83 to 1.30; P=0.75). There was no significant difference between the groups in the frequency of adverse events (cardiovascular events, infections, or complications of dialysis).

Cooper et al, NEJM, 363:609-19; 2010

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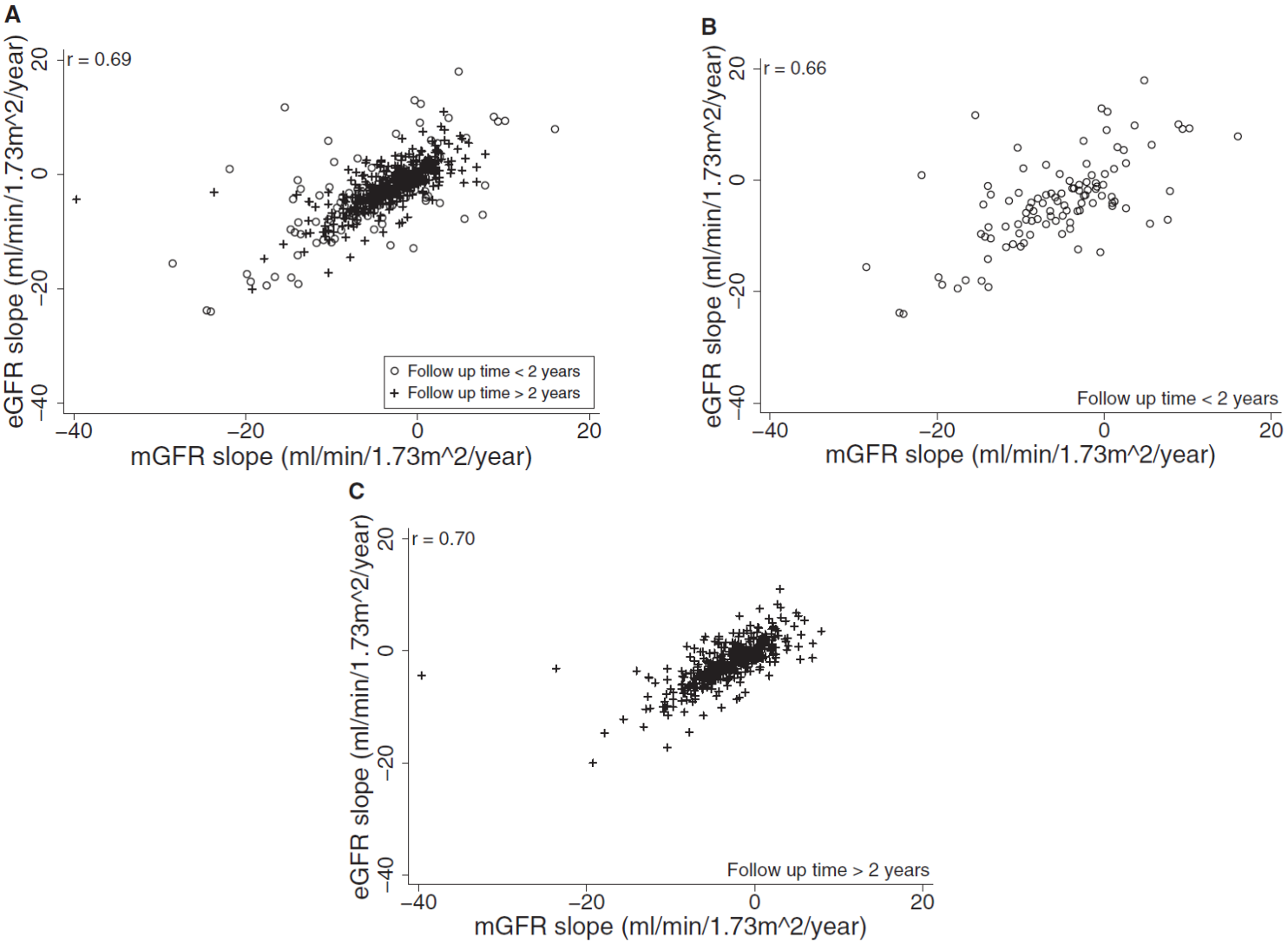
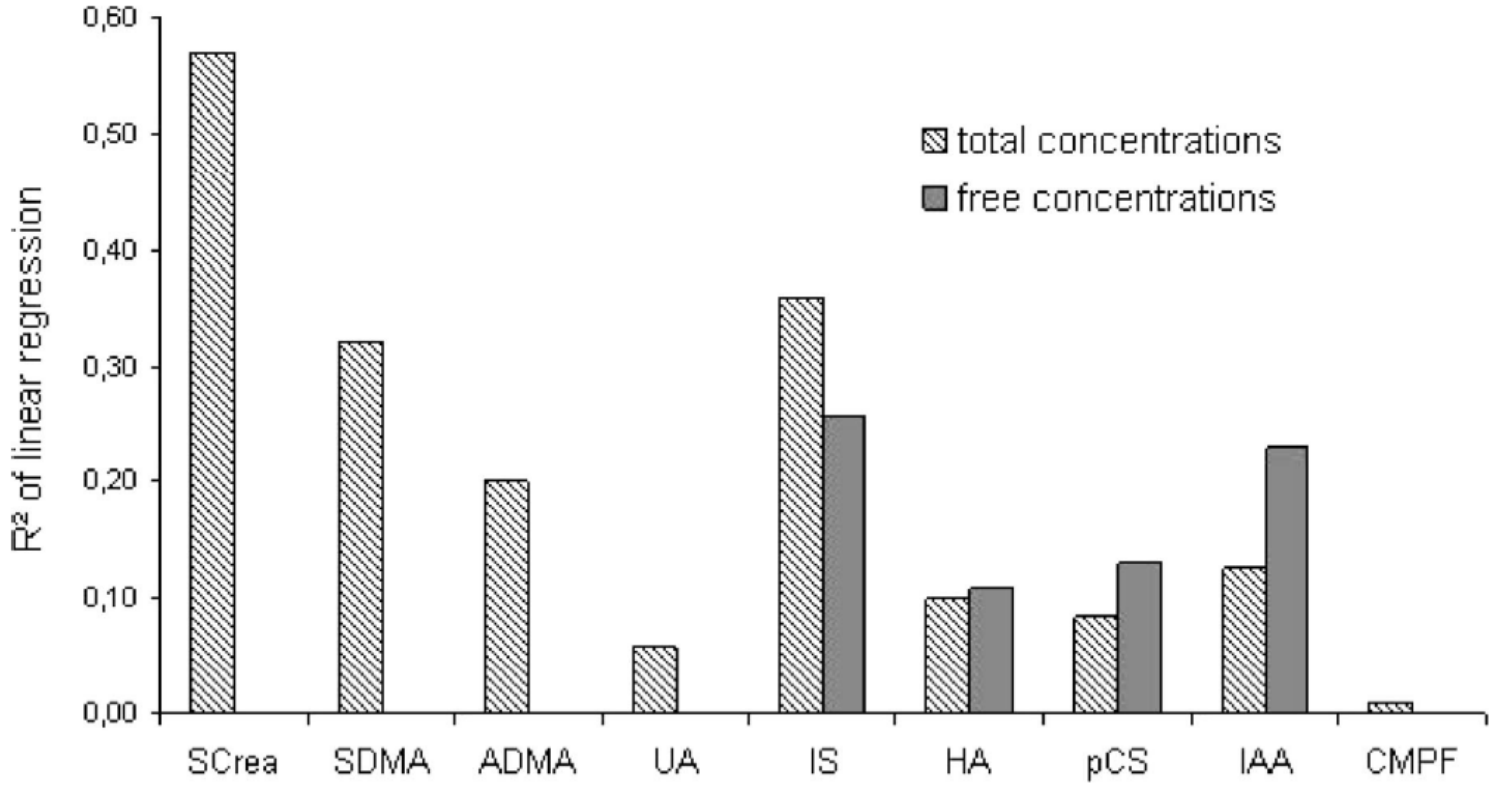
REASONS FOR THESE RESULTS

eGFR ≠ mGFR



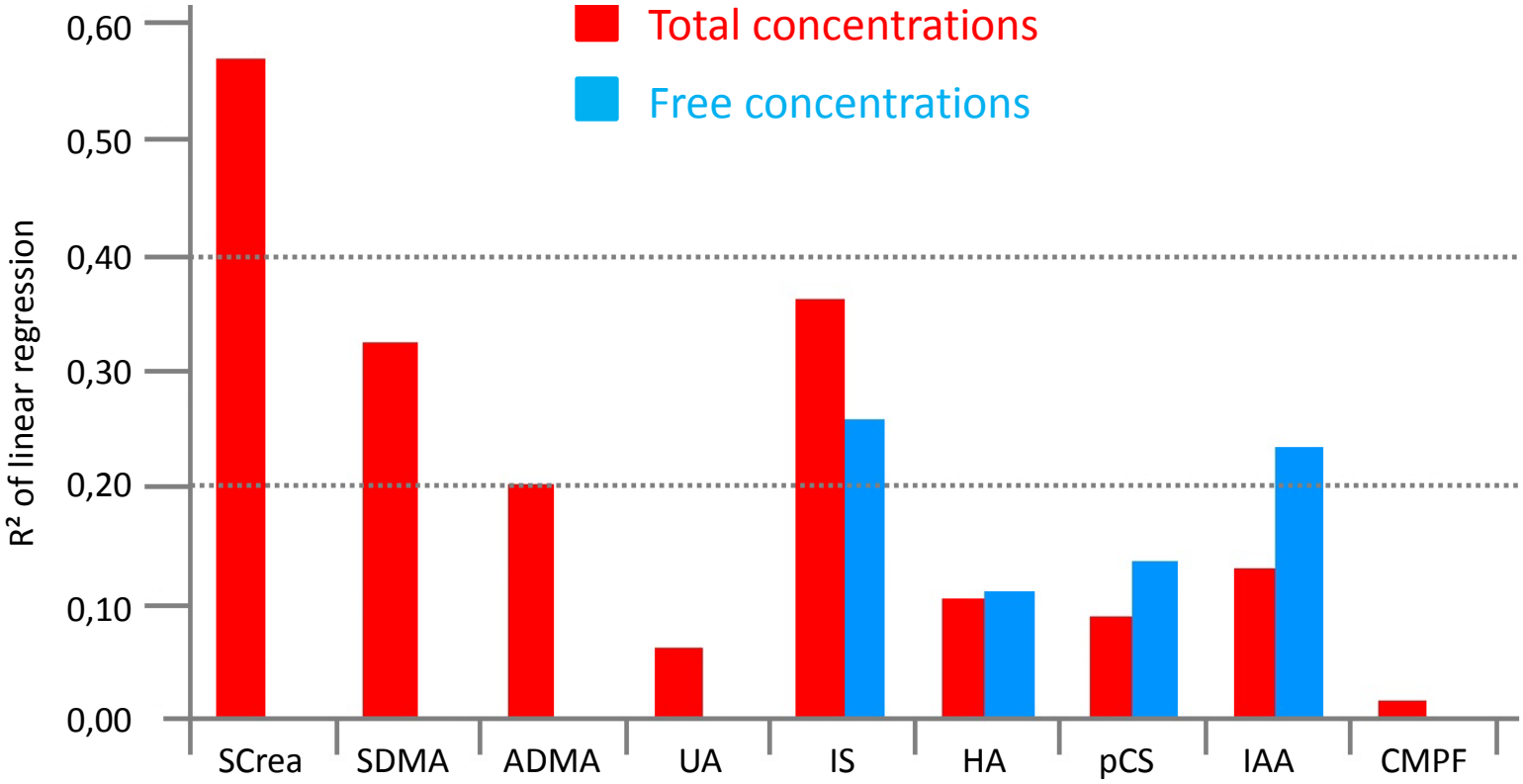
Xie et al, cJASN, 3: 1332-1338; 2008

eGFR ≠ UREMIC STATUS



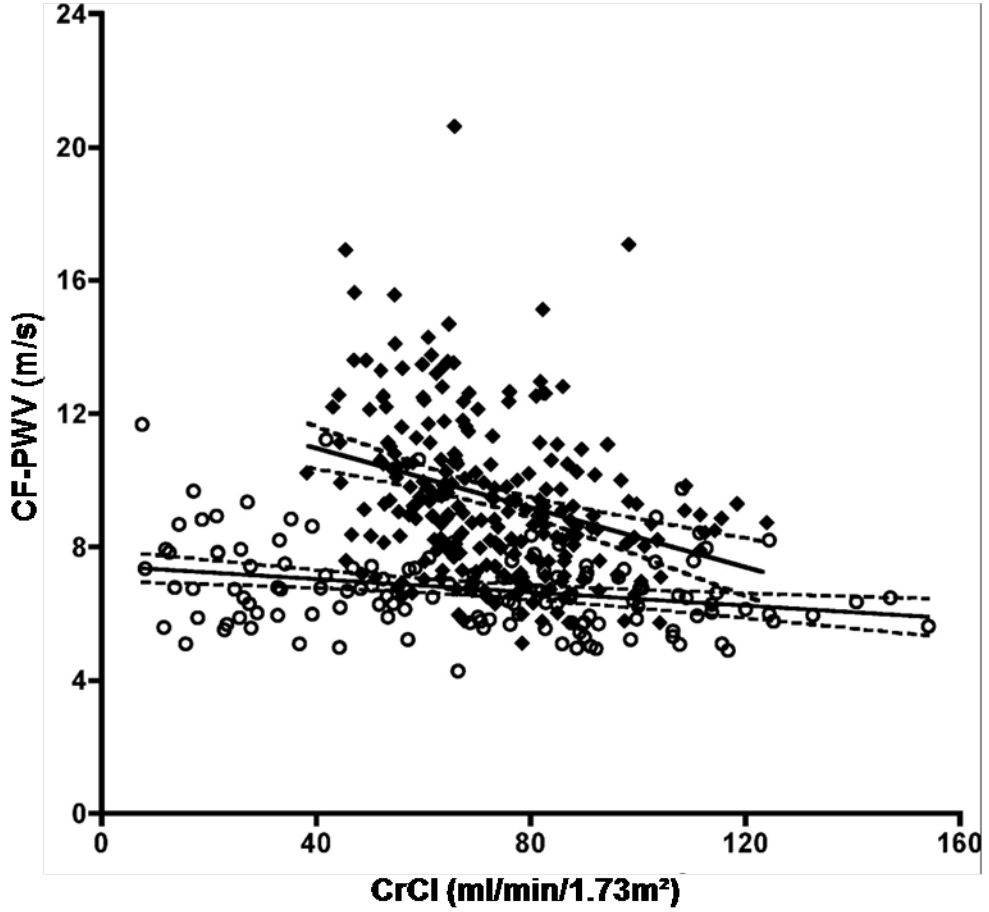
Eloot et al, cJASN, 6: 1266-1273 ; 2011

eGFR ≠ UREMIC STATUS



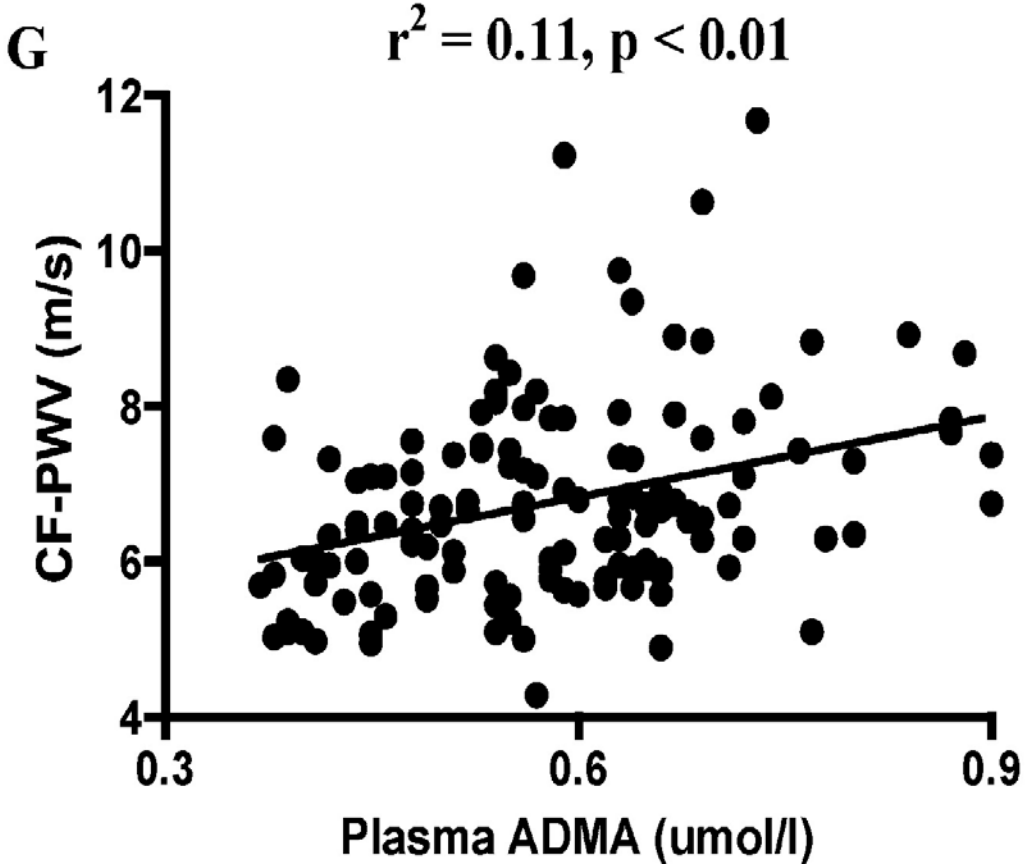
Eloot et al, cJASN, 6:1266-1273; 2011

LACK OF CORRELATION EGFR AND PWV IN NON-DIABETICS



Lilitkarntakul et al, Atherosclerosis, 216: 217-225; 2011

CORRELATION WITH ADMA



Correlation equally maintained with: ET-1, CRP, isoprostanes

Lilitkarntakul et al, Atherosclerosis, 216: 217-225; 2011

ALTERNATIVE FACTORS AFFECTING UREMIC SOLUTE CONCENTRATION / ACTIVITY

- **CONCENTRATION**
  - **Tubular secretion**
  - **Intestinal generation/absorption**
  - **Metabolism**
- **ACTIVITY**
  - **Interference with other solutes**
  - **Competition for protein binding**
  - **Drug effects**

NEW GUIDANCE (1)

- **Guideline I.3**

❑ **(1) Patients with advanced CKD should be prepared for dialysis, kidney transplant or conservative care before their CKD becomes symptomatic. For patients who are expected to require dialysis, this includes advance preparation of appropriate access. This process also includes careful observation for signs and symptoms of uraemia and should, ideally, be started while GFR is >15 mL/min/1.73m2. Supervision in a dedicated clinic for patients with advanced CKD is recommended (1C, Strong recommendation based on low-quality evidence).**

Tattersall et al, NDT, 26: 2082-2086; 2011

NEW GUIDANCE (2)

- **Guideline I.3**
  - **(2) In patients with a GFR <15 mL/min/1.73m2, dialysis should be considered when there is one or more of the following: symptoms or signs of uraemia, inability to control hydration status or blood pressure or a progressive deterioration in nutritional status. It should be taken into account that the majority of patients will be symptomatic and need to start dialysis with GFR in the range 9–6 mL/min/1.73m2 (1A Strong recommendation based on high-quality evidence).**

Tattersall et al, NDT, 26: 2082-2086; 2011

NEW GUIDANCE (3)

- **Guideline I.3**

- **(3) High-risk patients e.g. diabetics and those whose renal function is deteriorating more rapidly than eGFR 4 mL/min/year require particularly close supervision. Where close supervision is not feasible and in patients whose uraemic symptoms may be difficult to detect, a planned start to dialysis while still asymptomatic may be preferred (1C Strong recommendation based on low-quality evidence).**
- **(4) Asymptomatic patients presenting with advanced CKD may benefit from a delay in starting dialysis in order to allow preparation, planning and permanent access creation rather than using temporary access (2C Weak recommendation based on low-quality evidence).**

Tattersall et al, NDT, 26: 2082-2086; 2011

NEW GUIDANCE (4)

- **Guideline 1.1.1**

❑ **Renal function should not be estimated from measurements of blood urea or creatinine alone. Cockcroft and Gault equation or reciprocal creatinine plots should not be used when the GFR is <30 mL/min/1.73m2 or to determine the need for dialysis. The MDRD-eGFR is useful in identifying CKD and estimating rate of progression but should not be used to determine the need for dialysis or to estimate renal function in Stage 5 CKD (GFR < 15 mL/min/1.73m2) (1A Strong recommendation based on high-quality evidence).**

Tattersall et al, NDT, 26: 2082-2086; 2011