Supplement to: Decline of kidney function preceding dialysis initiation in chronic kidney disease patients: a systematic review and meta-analysis

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Supplementary Data

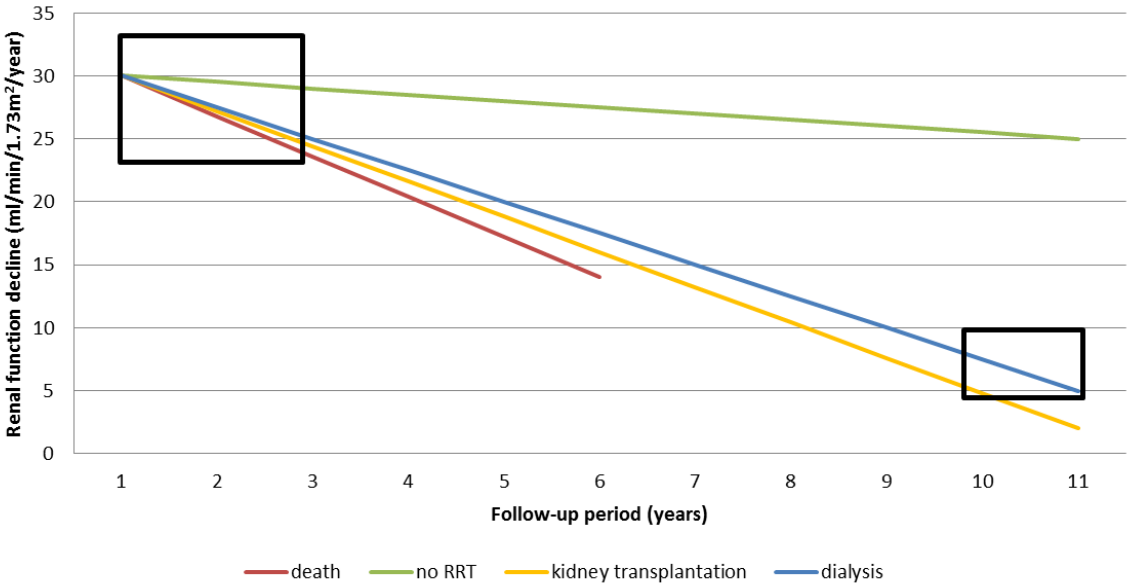


Figure S1. Graphical representation of the hypothetical difference between patients from CKD 3-5 cohorts and dialysis-based studies. In CKD 3-5 cohorts, CKD 3-5 patients are followed from a certain point in the pre-dialysis phase and only a part of the patients starts dialysis therapy. The annual eGFR decline during the pre-dialysis period is the overall decline rate for all four subgroups (green, blue, yellow and red line). However, in dialysis-based studies, patients on dialysis are selected (blue line) and their associated eGFR decline is determined in a specified period before dialysis initiation. Black boxes represent the duration of the pre-dialysis period over which the eGFR declines are reported.

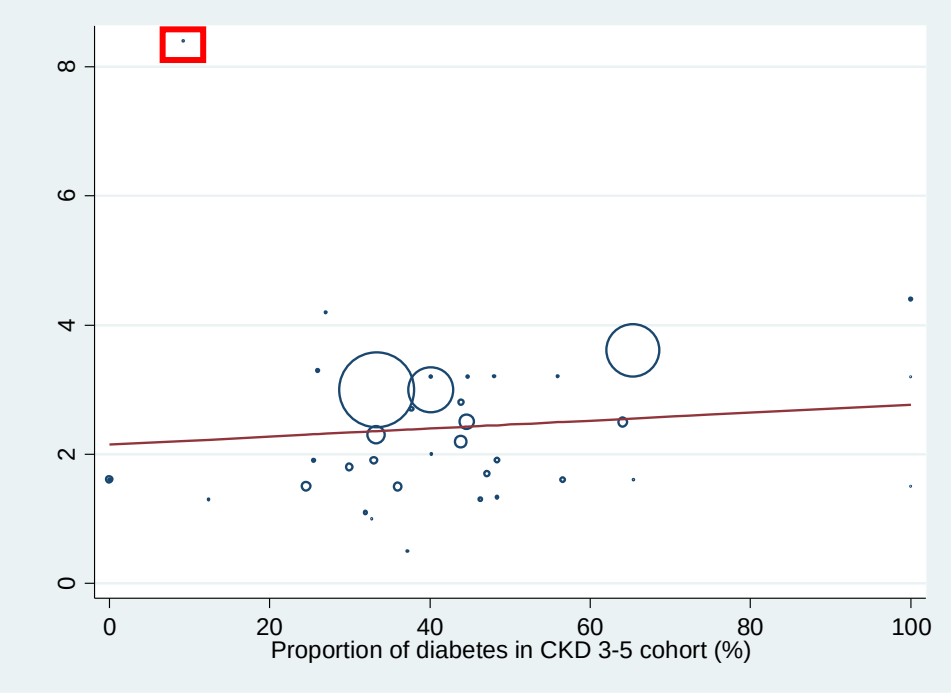


Figure S2A. Meta-regression plot for proportion of diabetes and mean annual eGFR decline [all CKD 3-5 cohorts]. Red box represent the sole outlier reported by Lucas et al.[31]

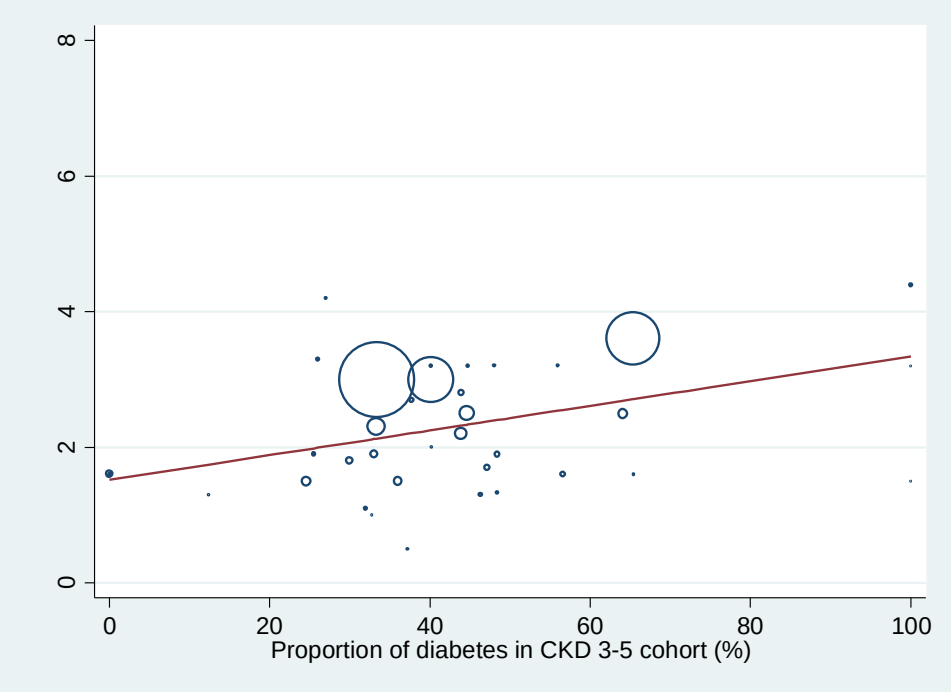
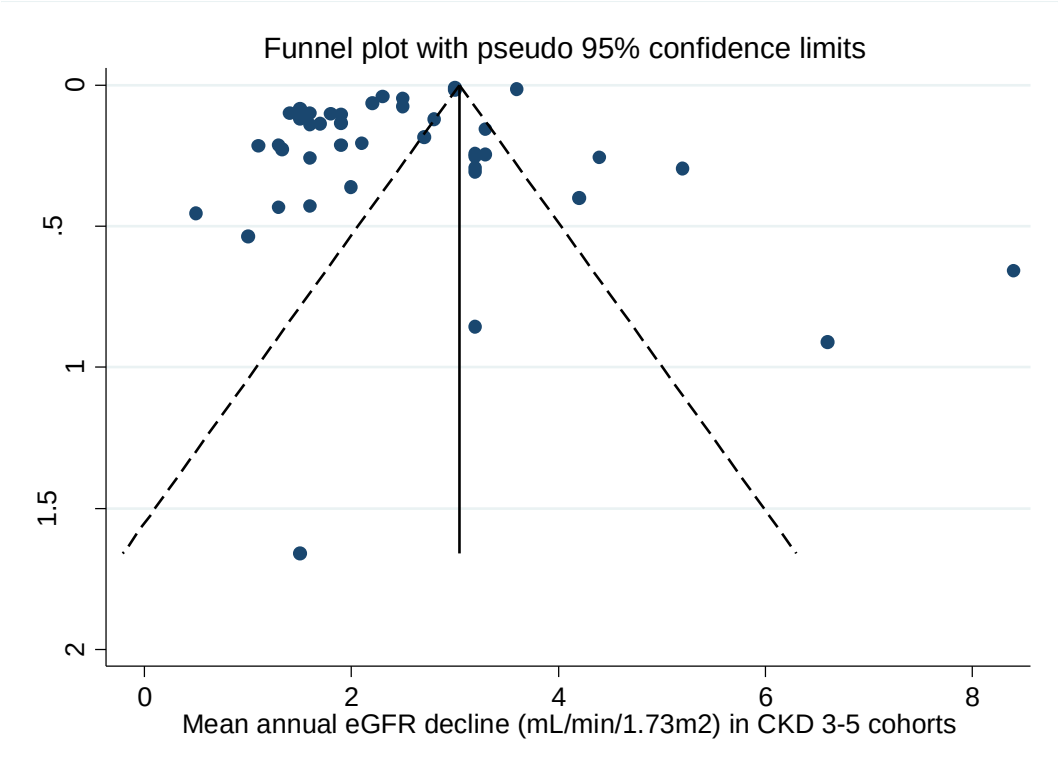


Figure S2B. Meta-regression plot for proportion of diabetes and mean annual eGFR decline [all CKD 3-5 cohorts, except the sole outlier]



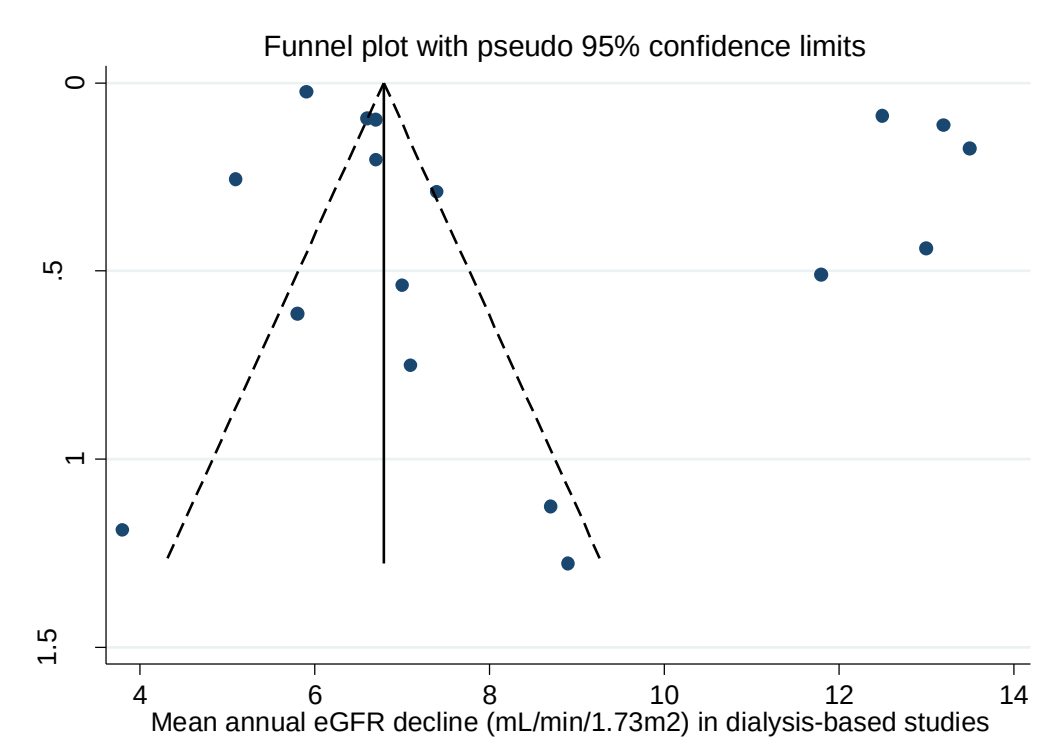


Figure S3. Association between study size and eGFR magnitude represented in funnel plots for CKD 3-5 cohorts and dialysis-based studies

Supplementary material 1

Inception cohort

In the current meta-analysis we distinguished between CKD 3-5 cohorts and dialysis-based studies. To clarify the difference between these study types from a methodological point of view, we elaborate on the concept of an inception cohort. An inception cohort is a group of individuals identified and assembled for subsequent study at a well-defined point in the course of the specified health condition. In this case the inception cohort requires identification of all CKD 3-5 patients and follow-up kidney function decline over time. In such an inception cohort patients are included irrespective of their outcome, thus, patients with long-term stable or even recovering kidney function are included as are those whose kidney disease progresses and start dialysis. Failure to select an inception cohort often severely biases studies on the natural history of disease, e.g. kidney disease progression.[1] It follows that dialysis-based studies do not comply with this definition and could give biased estimates of kidney function decline in CKD 3-5 patients.

[1] Porta M. *Dictionary of Epidemiology.* New York, NY: Oxford University Press, 2016

Supplementary material 2

Search strategy (PubMed, Web of Science, Cochrane, EMBASE)

PubMed

(((("pre-dialysis"[tw] OR pre-dialy*[tw] OR "predialysis"[tw] OR predial*[tw] OR "chronic renal"[tw] OR "chronic kidney"[tw] OR "Renal Insufficiency, Chronic"[Mesh] OR "Kidney Failure, Chronic"[Mesh] OR "end stage renal"[tw] OR "end stage kidney"[tw] OR "CKD"[tw] OR "ESRD"[tw] OR "ESKD"[tw]) AND ("Glomerular Filtration Rate"[Mesh] OR "eGFR"[tw] OR "GFR"[tw] OR "glomerular filtration rate"[tw] OR "renal function"[tw] OR "kidney function"[tw] OR renal function*[tw] OR kidney function*[tw]) AND **("slope"[tw] OR "slopes"[tw] OR slope*[tw] OR "decline"[tw] OR declin*[tw] OR "trajectory"[tw] OR "trajectories"[tw] OR trajector*[tw] OR "deteriorate"[tw] OR "ascend"[tw] OR "descend"[tw] OR "accelerate"[tw] OR "decelerate"[tw] OR deteriorat*[tw] OR ascend*[tw] OR descend*[tw] OR accelerat*[tw] OR decelerat*[tw] OR "chronic kidney disease progression"[tw] OR "ckd progression"[tw] OR "renal progression"[tw] OR "progression of CKD"[tw] OR "progression of chronic kidney disease"[tw] OR "progression of chronic renal failure"[tw] OR "progression of renal diseases"[tw] OR "progression of renal failure"[tw] OR "progression of kidney disease"[tw] OR "kidney progression"[tw] OR "progression"[tiab] OR progress*[tiab])** AND ("Renal Dialysis"[mesh] OR "Dialysis"[mesh] OR "dialysis"[tw] OR "hemodialysis"[tw] OR "renal replacement therapy"[tw] OR "Renal Replacement Therapy"[Mesh] OR "Hemofiltration"[tw] OR "Hemodiafiltration"[tw] OR "Kidney Transplantation"[tw] OR "Haemofiltration"[tw] OR "Haemodiafiltration"[tw] OR "Renal Transplantation"[tw]) AND **("initiation"[tw] OR initiat*[tw] OR "start"[tw] OR start*[tw] OR "commencing"[tw] OR commenc*[tw] OR "beginning"[tw] OR begin*[tw] OR "entering dialysis"[tw])**) OR ((("pre-dialysis"[tw] OR pre-dialy*[tw] OR "predialysis"[tw] OR predial*[tw] OR "chronic renal"[tw] OR "chronic kidney"[tw] OR "Renal Insufficiency, Chronic"[Mesh] OR "Kidney Failure, Chronic"[Mesh] OR "end stage renal"[tw] OR "end stage kidney"[tw]) AND ("3"[ti] OR "4"[ti] OR "5"[ti] OR "three"[ti] OR "four"[ti] OR "five"[ti] OR "iii"[ti] OR "iv"[ti] OR "v"[ti]) AND ("stage"[ti] OR "stages"[ti] OR "late"[ti]) AND ("Glomerular Filtration Rate"[Mesh] OR "eGFR"[tw] OR "GFR"[tw] OR "glomerular filtration rate"[tw] OR "renal function"[tw] OR "kidney function"[tw] OR renal function*[tw] OR kidney function*[tw]) AND **("slope"[tw] OR "slopes"[tw] OR slope*[tw] OR "decline"[tw] OR declin*[tw] OR "trajectory"[tw] OR "trajectories"[tw] OR trajector*[tw] OR "deteriorate"[tw] OR "ascend"[tw] OR "descend"[tw] OR "accelerate"[tw] OR "decelerate"[tw] OR deteriorat*[tw] OR ascend*[tw] OR descend*[tw] OR accelerat*[tw] OR decelerat*[tw] OR "chronic kidney disease progression"[tw] OR "ckd progression"[tw] OR "renal progression"[tw] OR "progression of CKD"[tw] OR "progression of chronic kidney disease"[tw] OR "progression of chronic renal failure"[tw] OR "progression of renal diseases"[tw] OR "progression of renal failure"[tw] OR "progression of kidney disease"[tw] OR "kidney progression"[tw] OR "progression"[tiab] OR progress*[tiab])**))) NOT ("Animals"[mesh] NOT "Humans"[mesh]) NOT (("Case Reports"[ptyp] OR "case report"[ti]) NOT ("Review"[ptyp] OR "review"[ti])) NOT ("editorial"[ptyp] OR "comment"[ptyp])

Embase

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Web of Science

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COCHRANE

((("pre-dialysis" OR pre-dialy* OR "predialysis" OR predial* OR "chronic renal" OR "chronic kidney" OR "chronic kidney disease" OR "chronic kidney failure" OR "end stage renal" OR "end stage kidney" OR "CKD" OR "ESRD" OR "ESKD" OR "end stage renal disease") AND ("Glomerulus Filtration Rate" OR "eGFR" OR "GFR" OR "glomerular filtration rate" OR "Kidney Function" OR "renal function" OR "kidney function" OR renal function* OR kidney function*) AND **("slope" OR "slopes" OR slope* OR "decline" OR declin* OR "trajectory" OR "trajectories" OR trajector* OR "deteriorate" OR "ascend" OR "descend" OR "accelerate" OR "decelerate" OR deteriorat* OR ascend* OR descend* OR accelerat* OR decelerat* OR "chronic kidney disease progression" OR "ckd progression" OR "renal progression" OR "progression of CKD" OR "progression of chronic kidney disease" OR "progression of chronic renal failure" OR "progression of renal diseases" OR "progression of renal failure" OR "progression of kidney disease" OR "kidney progression" OR "progression" OR progress*)** AND ("renal replacement therapy" OR "Dialysis" OR "dialysis" OR "hemodialysis" OR "renal replacement therapy" OR "Hemofiltration" OR "Hemodiafiltration" OR "Kidney Transplantation" OR "Kidney Transplantation" OR "Haemofiltration" OR "Haemodiafiltration" OR "Renal Transplantation") AND **("initiation" OR initiat* OR "start" OR start* OR "commencing" OR commenc* OR "beginning" OR begin* OR "entering dialysis"))** OR ti/ab/kw (("pre-dialysis" OR pre-dialy* OR "predialysis" OR predial* OR "chronic renal" OR "chronic kidney" OR "chronic kidney disease" OR "chronic kidney failure" OR "end stage renal" OR "end stage kidney" OR "CKD" OR "ESRD" OR "ESKD" OR "end stage renal disease") AND ("Glomerulus Filtration Rate" OR "eGFR" OR "GFR" OR "glomerular filtration rate" OR "Kidney Function" OR "renal function" OR "kidney function" OR renal function* OR kidney function*) AND **("slope" OR "slopes" OR slope* OR "decline" OR declin* OR "trajectory" OR "trajectories" OR trajector* OR "deteriorate" OR "ascend" OR "descend" OR "accelerate" OR "decelerate" OR deteriorat* OR ascend* OR descend* OR accelerat* OR decelerat* OR "chronic kidney disease progression" OR "ckd progression" OR "renal progression" OR "progression of CKD" OR "progression of chronic kidney disease" OR "progression of chronic renal failure" OR "progression of renal diseases" OR "progression of renal failure" OR "progression of kidney disease" OR "kidney progression" OR "progression" OR progress*)**) AND TI ("3" OR "4" OR "5" OR "three" OR "four" OR "five" OR "iii" OR "iv" OR "v") AND ("stage" OR "stages" OR "late")

Supplementary material 3

References of excluded full text articles, which were based on the same outcome and patient population as final included studies (n=10):

1. Chang JM, Chen SC, Huang JC, Su HM, Chen HC. Anemia and Left Ventricular Hypertrophy With Renal Function Decline and Cardiovascular Events in Chronic Kidney Disease. *American Journal of the Medical Sciences.* 2014;347(3):183-189.
2. Chen SC, Chang JM, Liu WC, et al. Brachial-ankle pulse wave velocity and rate of renal function decline and mortality in chronic kidney disease. *Clin J Am Soc Nephrol.* 2011;6(4):724-732.
3. Chen SC, Chang JM, Tsai YC, et al. Left atrial diameter and albumin with renal outcomes in chronic kidney disease. *Int J Med Sci.* 2013;10(5):575-584.
4. de Goeij MC, Liem M, de Jager DJ, et al. Proteinuria as a risk marker for the progression of chronic kidney disease in patients on predialysis care and the role of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker treatment. *Nephron Clin Pract.* 2012;121(1-2):c73-c82.
5. Goicoechea M, Garcia d, V, Verdalles U, et al. Allopurinol and progression of CKD and cardiovascular events: long-term follow-up of a randomized clinical trial. *Am J Kidney Dis.* 2015;65(4):543-549.
6. Liu WC, Hung CC, Chen SC, et al. Association of hyperuricemia with renal outcomes, cardiovascular disease, and mortality. *Clin J Am Soc Nephrol.* 2012;7(4):541-548.
7. Nacak H, van DM, de Goeij MC, Rotmans JI, Dekker FW. Uric acid: association with rate of renal function decline and time until start of dialysis in incident pre-dialysis patients. *BMC Nephrol.* 2014;15:91.
8. Rigalleau V, Garcia M, Lasseur C, et al. Large kidneys predict poor renal outcome in subjects with diabetes and chronic kidney disease. *BMC Nephrol.* 2010;11:3.
9. Tsai YC, Hung CC, Kuo MC, et al. Association of hsCRP, white blood cell count and ferritin with renal outcome in chronic kidney disease patients. *PLoS One.* 2012;7(12):e52775.
10. Tsai YC, Tsai JC, Chiu YW, et al. Is fluid overload more important than diabetes in renal progression in late chronic kidney disease? *PLoS One.* 2013;8(12):e82566.

Table S1. General characteristics of CKD 3-5 cohorts

First author and year of publication*	No. of participants and population studied	Aim of the study	Setting, country (year of baseline)	Mean [±SD] age[a]	% male	% DM	Renal function equation used	Mean [±SD] duration of pre-dialysis period (years)[a]	Mean [±SD] initial /baseline eGFR (ml/min/1.73 m^2)[a]	Unadjusted mean [±SD] annual eGFR decline (ml/min/1.73 m^2/year)[a,b]	Number/percentage of subjects initiated dialysis, had ESRD, died	Renal function at start of dialysis	Loss to follow-up (LTFU) (n + reason)
Barrett 2011	474 CKD 3-4 patients	compare nurse-coordinated model of care (E, n=238) and usual care (U, n=236) on achievement of treatment targets for surrogate outcomes (i.a. change in kidney function)	Five urban centers, Canada (2005)	Median 67 (IQR 61.5; 72)	E=55 female U=56 female	E=31 U=33	Re-expressed (175) 4-variable MDRD	Median 742 (IQR 614-854) days	E=Median 42 (IQR 40,46) U= median 42 (IQR 37, 46)	-1.9 (95%CI: -1.2; -2.6) over 20 months (adjusted for baseline eGFR)	N=3 dialysis (E=2, U=1) N=9 died (E=7, U=2)	N.R.	10% (20 LTFU, 27 withdrawal)
Brown 2012	499 CKD 3-5 patients	rate of CKD progression in non-obese (n=368) and obese (n=131) subjects	CRISIS, UK	Non-obese: 65 [±15] Obese: 60 [±13]	Non-obese: 61 Obese: 59	0	Original (186) 4-variable MDRD	Nonobese: 38 [±21] months Obese: 39 [±21] months	< 60 ml/min /1.73m^2	Non-obese: −1.77 [±5.68] Obese: −1.28 [±6.13]	92 RRT (72 non-obese, 20 obese) 56 died (47 non-obese, 8 obese)	N.R.	<9% (44 were excluded before analysis due to withdrawal from the study, lost or insufficient data or patient discharge)
Chen 2011	415 CKD 3-5 pre-dialysis patients	association between echo-cardiographic left ventricular structural and functional parameters and progression to start dialysis and rate of renal function decline	Kaohsiung Medical University Hospital, Taiwan (2007)	66.6 [±12.1]	63.9	56.6	Original (186) 4-variable MDRD	27.3 [±11.1] months	27.3 [±14.0]	-1.58 [±0.14 =SEM]	76 (18.3%) HD	N.R.	Unclear
Chen 2012	186 stage 3-5 CKD patients	assessing whether the combination of brachial-ankle pulse wave velocity (baPWV) and the ratio of brachial pre-	Regional hospital in southern Taiwan (2009)	63.4 [±12.5]	123/ 186 = 66.1%	Low baPWV; low bPEP/ bET(n=46): 32.6 Low baPWV; high bPEP/bET (n=47): 34.0 High	Original (186) 4-variable MDRD	22.1 [±13.4] months	Low baPWV; low bPEP/ bET (n=46): 36.5 [±19.0] Low baPWV; high bPEP/ bET (n=47): 41.1 ± 13.3 High baPWV;	-1.33 [±SE 0.23]	2 HD	N.R.	Unclear

		ejection period (bPEP) to brachial ejection time (bET) is useful in identifying stage 3-5 CKD patients at risk for adverse renal outcomes				baPWV; low bPEP/bET (n=47): 61.7 High baPWV; High bPEP/bET (n=46): 65.2			low bPEP/ bET (n=47): 33.5 ± 17.1 High baPWV; High bPEP/ bET (n=46): 30.3 ± 15.6				
Chen 2013	3393 patients with CKD stage 3-5	association of dyslipidaemia with RRT and CKD progression	ICKD study, Taiwan (2002)	63.5 [±13.5]	42.2[c]	44.6	Original (186) 4-variable MDRD	1150.3 [±577.6] days	24.7 [±15.1]	Median -2.2 (IQR -5.6; -0.1)	N=957 HD N=116 PD N=7 renal transplant N death unspecified	N.R.	Unclear (90 in the first 3 months, not further described)
Chen 2014	1862 ND CKD 3-5 patients	determining whether eGFR AUC% is associated with renal outcomes in progression to RRT	ICKD, Kaohsiung Medical University Hospital and Kaohsiung Municipal Hsiao-Kang Hospital, Taiwan (2002)	63.6 [±13.4]	58.2	40.2	Original (186) 4-variable MDRD	28.7 [±14.0] months	27.2 [±14.2]	-0.17 [±0.03] per month[d]	N=564 (30.3%) start RRT	N.R.	Unclear
Chen 2015	1206 CKD 3B-5 patients	evaluating the effect of a multidisciplinary (MDC, n=592) care program versus non-multidisciplinary (non-MDC, n=614) i.a. on dialysis incidence, eGFR decline [e]	National Taiwan University Hospital (2007)	MDC: 62.16 [±13.16] Non-MDC: 61.93 [±13.68]	MDC: 57.9 Non-MDC: 53.6	MDC: 44.3 Non-MDC: 45.0	Original (186) 4-variable MDRD	Median 2.43	MDC: 22.41 [±11.64] Non-MDC: 22.05 [±12.14]	MDC: -2.57 [±6.64] non-MDC: -3.74 [±10.40]	<u>MDC:</u> 230 (38.9%) RRT (148 (64.3%) HD, 73 (31.7%) PD, 9 (3.9%) Tx) <u>Non-MDC:</u> 319 (52.0%) RRT (216 (67.7%) HD, 100 (31.3%) PD, (0.9%) Tx) Death: MDC: 7.6% Non-MDC: 5.9%	MDC: 4.47 Non-MDC: 4.40	Unclear
Chen 2016	1891 patients with baseline eGFR <45	effect of change in proteinuria (UPCR≤0.3, n=1261 and UPCR>0.3, n=630) on composite endpoint was dialysis start and renal death before	6 hospitals in nationwide multidisci-plinary pre-ESRD care program, Taiwan (2008)	UPCR≤0.3: 67 [±13] UPCR>0.3: 65 [±13]	UPCR≤0.3: 59.8 UPCR>0.3: 51.1	UPCR≤0.3: 46.9 UPCR>0.3: 51.3	Original (186) 4-variable MDRD	32.0 [±12.3]	UPCR≤0.3: 25.10 [±10.54] UPCR>0.30: 20.96 [±10.24]	-1.93 [±5.89]	60 deaths (39 UPCR≤0.30; 21 UPCR>0.30) 307 dialysis (153 UPCR≤0.30; 154 UPCR>0.30)	N.R.	Unclear
Chiu 2008	433 patients with CKD stages 3-5	investigating rate and predictors of renal progression and	National Taiwan University Hospital (2007)	65.6 [±14.1]	61.7	33.3	Original (186) 4-variable MDRD	Median 27.8 months	27.2 [±14.3]	2.99 [SE±0.20]	123 (28.4%) RRT (102 HD, 19 PD, 2 transplantation) 41 (9.5%) died	N.R.	22

		pre-ESRD mortality in Taiwanese under nephro-logists' care											
Chue 2011	225 CKD 2-4 patients	investigating impact of serum phosphate, simultaneously with pulse wave velocity and augmentation index on combined end-point of start dialysis or ≥25% eGFR decline	Queen Elizabeth University Hospital, Birmingham (2004)	59 [±13]	60	12	Original (186) 4-variable MDRD	Median 924 days (IQR 637-1176)	43 [±19]	-0.11 [±0.54] per month	11 (5%) died	N.R.	Unclear
Conway 2009	396 CKD 4 patients	Identifying factors associating mortality and commencing RRT	Health Boards, Ireland and Scotland (1998)	71.6 (median)	50.5	N.R.	eGFR[f]	Median 3.76	Mean 22.5	Median (IQR) age <65 (n=112): −2.25 (−4.2; 0.6), Age 65–74 (n=150): −1.38 (−3.2; +0.4), Age ≥75 (n=134): −0.86 (−2.3; +1.2)	89 (22.5%) RRT 180 (45.5%) died 20 (5.1%) no RRT	Mean at RRT: 8.0, 8.4, 9.8 in those aged <65 years, 65–74 and ≥75 years, resp.	10, no reason described
Dattolo 2016	342 CKD 5 patients	role of ACE-I (ACE-I n=188; no ACE-I n=154) in slowing the progression of renal damage	Santa Maria Annunziata Hospital, Florence, Italy (2002)	ACE-I: median 70 (IQR 68-73) No ACE-I: median 72 (IQR 69-75)	ACE-I: 63 No ACE-I: 62	ACE-I: 33 No ACE-I: 32	re-expressed (175) 4-variable MDRD	In months 1st-2nd quartile (Q): 17 [±19] 3rd Q: 14 [±18] 4th Q: 11 [±14] (from table 2)	ACE-I: median 10.2 (IQR 9.8-10.8) No ACE-I: median 10.1 (IQR 9.6-10.7)	ACE-I: -0.96 [±1.1] No ACE-I: -3.12 [±2.1]	201 (59%) dialysis 81 (24%) no RRT 60 (17%) died	Dialysis 10 [±4] No RRT: 12 [±5] Dead: 10 [±5]	Unclear
Drüeke 2006	603 CKD 3-4 patients	Effect of complete (group 1, n=301) versus partial correction of anemia (group 2, n=302) on cardiovascular outcomes	CREATE trial (2000)	Group 1: 59.3 [±14.6] Group 2: 58.8 [±13.7]	Group 1: 57 Group 2: 51	Group 1: 27 Group 2: 25	Cockcroft -Gault	12 months[g]	Group 1: 24.9 [±6.3] Group 2: 24.2 [±6.0] (Cockcroft Gault, decline is also based on this formula)	Group 1: 3.6 [±6.7] Group 2: 3.1 [±5.3][g]	238 dialysis (127 group 1, 111 group 3) 52 died (31 group 1; 21 death group 2)	N.R.	15% (89 withdrew (excluding those with reason of death): 27 adverse events, 37 withdrawal of consent or lack of cooperation,

													other 25 unclear)
Goicoechea 2010	113 patients with an eGFR <60	the effect of allopurinol (n=57) versus control group (n=56) in reduction of inflammatory markers and renal disease progression	Hospital General Universitario Gregorio Marañón, Spain (2007)	Allopurinol: 72.1 [±7.9] Control: 71.4 [±9.5]	N.R.	Allopurinol: 39 Control: 36	4-variable MDRD (unclear which one)	23.4 [±7.8] months	Allopurinol: 40.6 [±11.3] Control: 39.5 [±12.4]	Allopurinol: +1.3± (SE1.3) Control: -3.3± (SE 1.2) over 24 months	2 dialysis 2 deaths	N.R.	9 (6 control and 3 allopurinol), no reason specified
De Goeij 2011	508 incident CKD 4-5 patients on pre-dialysis care	association between blood pressure and CKD progression	PREPARE-1, The Netherlands (1999)	Median 63 (IQR 50-73)	57	27	Original (186) 4-variable MDRD	Median 351 (IQR 144-365) days	13.1 [±5.8]	-0.35 [±0.75] per month [h]	23% HD 22% PD 5% died	N.R.	1%, reason not specified
Golper 2015	123 patients receiving arterio-venous fistula (AVF) creation	investigating eGFR decline in progressive CKD before and after successfully created AVF	Vanderbilt Nephrology Clinic, USA (2005)	Median 68 (IQR 59.0-76.0)	59 (41 female)	56	Original (186) 4-variable MDRD	Median 638 days before AVF creation; 549 days after AVF creation	28.3 [±11.93]	Before AVF: -5.90 (95%CI: -5.28; -6.51); after AVF: -0.46 (95%CI: -1.05; 0.14)	72 HD 6 transplanted 37 no RRT 4 died	N.R.	4, no reason specified
Gouva 2004	88 predialysis patients (SCr 2.0-6.0 mg/dl) with non-severe anemia	Whether early (n=45) compared to deferred (n=43) EPO treatment can slow down CKD progression	14 participating hospitals, Greece (2000)	Early: 66.7[±10.4] deferred: 64.2[±12.2]	Early: 25/45= 55.6 deferred: 25/43= 58.1	N.R.	Cockcroft -Gault	Median 22.5 (IQR 16-24) months	Early: 25.7 [±9.1] Deferred: 22.3 [±6.0]	At 12 months: Early: 21.9 [±9.4] deferred: 16.1 [±6.3] [i]	28 RRT (10 early, 18 deferred) 7 died (3 early, 4 deferred)	Early: 11.1 [±1.5] deferred: 11.0 [±1.8]	3, no reason specified
Halimi 2016	986 DM type II patients with CKD	assessing blood pressure and proteinuria control after a 2-year follow-up	ALICE-PROTECT cohort, France (2010)	Mean 70	74	100	MDRD (not specified which)	23 [±2.4] months [j]	40 [±20.3]	at year 2: 33.9 [±20.9] [i,j]	72 dialysis, 60 died	N.R.	296 (all lost contact; 257 without com-plications, 39 by year two, with compli-cations)
Heaf 2011	1441 patients with an initial eGFR < 60 and follow-up for at least 2 years	Determining rate of GFR loss in CKD population, before ESRD and influence of ACE inhibitors on it	Herlev hospital, Denmark (1986)	58.7 [±14.9]	57	N.R.	Original (186) 4-variable MDRD	5.5 [±3.8]	30.8 [±15.1]	-1.47 [±4.54]	420 (29%) ESRD	N.R.	Unclear
Hsieh 2017	2408 CKD 3-5 patients	investigating uric acid in association with all-cause mortality, CVD	CKD care program, Changhua Christian Hospital, Taiwan	65.7 [±12.6]	56.9	Q1 n=605: 43.8 Q2 n=600: 44.5 Q3 n=604:	Original (186) 4-variable MDRD	1107.2 [±789.6] days	24 [±12.9]	-1.72 [±6.7]	563 (23.3%) deaths, 652 (27%) RRT (490 HD, 162 PD)	Death: 18.3 [±12.9] RRT: 4.85 [±2.12]	Unclear

		mortality, RRT, rapid renal progression	(2001)			51.66 Q4 n=599: 48.58							
Inaguma 2016	2966 CKD patient under nephrology care	Identifying risk factors for CKD progression to ESRD (for separate CKD stages: G3a (n=306), G3b (n=1045), G4 (n=1149), G5 (n=466)	CKD-JAC study, Japan (2007)	60.3 [±11.6]	62.1 (females 37.9)	37.7	eGFR[k]	Median 3.9	28.9 [±12.2]	G3a: -1.925 [±5.681] G3b: -2.056 [±5.924] G4: -3.182 [±14.189] G5: -3.754 [±6.374]	N.R.	N.R.	121 withdrawn, excluded, or LTFU (were excluded from original 3087 patients)
Jones 2006	726 CKD 3-5 patients [l]	Investigating decline in kidney function prior to and following nephrology referral and its association with mortality	General Hospital Southampton, UK (1997)	72 [±14]	61	N.R.	Original (186) 4-variable MDRD	pre-referral: up to 5 years post referral: Median 2.9 (IQR 1.3–4.1)	median 29 (IQR 18–38) at referral	Median (IQR) pre-referral: -5.4 (-13; -2) post referral: -0.35 (-3; 3)	178 (25%) died 73 (10%) RRT	N.R.	Unclear
Khan 2017	621 CKD 3-4 patients	investigate rate and predictors of CKD progression in NDD-CKD cohort under nephrologist care	Hospital University Sains Malaysia (2004)	61.09 [±6.57]	52.7	40.1	CKD-EPI	> 10 y	33.25 [±4.7]	-3.01 [±0.40]	113 (18%) died 270 RRT (135 of CKD stage 3; 135 CKD stage 4)[m]	N.R.	41% (430: 321 LTFU and 109 referral other healthcare center, were excluded prior analysis)
Khan 2016	333 non dialysis CKD patients with GFR <60	assessing the role of diuretics on adverse renal outcomes	Tertiary care hospital, Malaysia	64.5 [±6.43]	57	64	CKD-EPI	1	23.7 [±7.1]	-2.5 [±1.4]	36 (11.5%) dialysis (28 HD and 8 PD) 2 death	N.R.	N=21, 9 discontinuation of diuretics
Kikuchi 2017	728 CKD 2-5 patients	association of combination of low BMI and serum albumin level with rapid CKD progression	CKD-ROUTE study, Japan (2010)	66.9 [±13.3]	70.1	40.1	eGFR[k]	<2	31.1 [±18.1]	-3.2 [±6.6]	283 (38.9%) dialysis or eGFR decrease of ≥ 30%	N.R.	26% (255 LTFU, excluded prior analysis)
Kuo 2015	56 CKD 3b-5 patients out of 149 CKD 1-5 patients [n]	If compliance index derived from digital volume pulse predicts renal function progression, i.a.	National Cheng Kung University Hospital, Taiwan (2008)	64 [±10]	79	48	CKD-EPI	51 [±12] months	30 [±10]	-3.24 [±2.16]	8 HD, 2 PD	N.R.	Unclear
Levin 2008	4231 patients with an eGFR < 30	Risk factors for rapid progression of kidney disease	BC CKD Registry, (2000)	66.8 [±14.5]	56	33	eGFR (unclear)	Median 31 (IQR 19-43) months	Progression ≤ 2.2 (50% of total): 22.1 [±6.1]	Median -2.18 (IQR -5.14; 0.21)	1608 dialysis 71 transplanted 510 died	N.R.	unclear (1% lost to follow-up in first 2 years)

		and death							Progression 2.3-5.0 (24% of total): 21.5 [±6.0] Progression > 5.0 (26% of total): 21.9 [±5.6]				
Lewis 2004	1094 African Americans with GFR 20-65	comparison iGFR and eGFR with time to halving of GFR or doubling serum creatinine	AASK Study, US (1995)	55 [±11]	61 (39 were female)	N.R.	eGFR= 329 x $(Scr)^{-1.096}$ x$(age)^{-0.294}$ x (0.736 if female)	<5	45.7 [±13.0] (from reference 10/11)	-1.64 [±SE 0.10] (overall linear slope)	88 ESRD 78 deaths	N.R.	Unclear
Lim 2014	2144 CKD 3-4 patients	investigating serum calcium as an independent prognostic marker of rapid renal function progression	Integrated CKD care program Kaohsiung Medical University Hospital, Taiwan (2002)	64.2 [±13.5]	64.7 (35.3 female)	43.8	Original (186) 4-variable MDRD	Median 1085 (IQR 682-1673) days	33.2 [±11.9]	median -1.9 (IQR -5.4; 0.5)	294 (13.7%) RRT 270 (12.6%) death	N.R.	Unclear
Lin 2013	4061 CKD 3b-5 patients	investigating changes in eGFR and risk factors of initiating dialysis	27 pre-dialysis clinics, Taiwan (2007)	70.1 [±12.3]	56.4	46.3	Original (186) 4-variable MDRD	15.0 [±10.9] months	22.4 [±11.0]	0.47 [±SE 0.42]; -1.27 [±SE 0.32]; -2.69 [±SE 0.39] for stages 3b, 4, and 5	558 (13.7%) dialysis (484 HD, 74 PD) 94 (2%) deaths	N.R.	795 (19.6%) (defined as not uploaded data > 1 year prior to end of study period)
Lucas 2008	284 prevalent or incident CKD subjects (overall cohort of n=4259)	racial differences (253 African American and 31 white) in the incidence and progression of HIV-related CKD	Johns Hopkins HIV Clinical Cohort, Maryland (1990)	White: median 46 (IQR 40-54) African: Median 41 (IQR 37-49)	White: 65 African: 60	White: 6 American: 10	Original (186) 4-variable MDRD	Mean 4.5 (mean for all 4259 patients, unclear for 284 patients)	White: Median 52 (IQR 45-56) African: Median 45 (IQR 33-53)	White: -1.5 (95%CI: -5.0; 2.0) African: -9.2 (95% CI -10.6; -7.9) *after baseline GFR adjustment	100 (35%) ESRD	N.R.	Unclear
McCaughan 2014	539 adult recipients of first, deceased donor transplants with a functioning graft at 12 months	comparing eGFR decline rate in renal transplant recipients (with n=140; without graft failure, n=399) and between those returned to dialysis or not	Belfast City Hospital, Northern Ireland (1986)	without: 45 [±14.1] With: 40 [±14.2]	without: 62 with: 71	without: 9 with: 6	Original (186) 4-variable MDRD	Median 11 years and 9 months	Unclear	-2.1 [±4.8] (based on 464 patients)	234 dialysis (192 HD, 26 PD) 140 death	Transplant (n=134): 9.7 [±3.8] Transplant -naive (n=100): 9.1 [±2.9]	Unclear
Meuleman 2015	416 incident predialysis	identifying illness	PREPARE-2, The Netherlands	Median 68.5 (IQR	66.3	25.5	Original (186) 4-	Median 12.4 (IQR	16.92 (95% CI 16.28;	−1.92 (95% CI −2.35; -1.50)[n]	29 (7.0%) died 32 (7.7%) kidney	10.5 [±4.4]	19% (total 77: 17 recovered

	patients receiving specialized predialysis care	perceptions and its association with disease progression	(2004)	55.7–75.6)			variable MDRD	5.3–21.9) months	17.56)[o]		transplant 55 (13.2%) no RRT 223 (53.6%) dialysis (138 HD, 85 PD)		kidney function, 48 refused further treatment, 8 transfer other center, 4 other reason)
Nacak 2015	2466 patients with CKD 3-5 and baseline uric acid	baseline uric acid in association with renal function decline and time to RRT	Swedish Renal Registry – Chronic Kidney Disease (SSR-CKD), Sweden (2005)	68.98 [±13.59]	65.4	36.0	re-expressed (175) 4-variable MDRD	Median 26 [IQR 16.3; 38.6]	24.95 [±9.80]	−1.48 (95% CI−1.65; −1.31)	12.6% (N=311) HD 7.1% (N=175) PD 1.8% (N=44) transplanted 26.4 (N=652) died	N.R.	Unclear
Peeters 2014	788 patients with Cockcroft-Gault 20-70 ml/min	effect of adding nurse practitioner support to physician care (intervention, n=395) versus physician care alone (control n=393) on renal endpoints	MASTERPLAN study, The Netherlands (2004)	Intervention 58.9 [±13.1] control: 59.3 [±12.8]	Intervention: 67 control: 68	Intervention: 26 control: 23	re-expressed (175) 4-variable MDRD	Median 5.7	Intervention: 35.9 [±14.2] control: 35.2 [±12.9]	Intervention -1.26 [±SE 0.12] Control: -1.71 [±SE 0.12]	166 RRT (77 intervention, 89 control) 105 died (50 intervention, 55 control)	N.R.	11 (from reference list), no reason specified
Portoles 2013	405 CKD 3 patients	investigate onset of anemia of renal origin and its association with the evolution of kidney disease	NADIR-3 study, Spain (2005)	67 (range 22-78)	69.9 (30.1 female)	32.8	Original (186) 4-variable MDRD	Max. 36 months	39.1 [±9.1]	End of follow-up 36.0 [±12.3] (mean 1.1 ml/min without variance) [i]	13 started RRT 26 died	N.R.	11% (43 drop-outs: 12 invest. criteria, 13 moved other hospital, 3 withdrew consent, 15 other reasons)
Rigalleau 2007	89 patients with diabetes and eGFR <60	investigating difference in subjects with normo- (n=15), micro- (n=36) and macro-albuminuria (n=38) on CKD progression and death	Centre Hospitalier Universitaire de Bordeaux, France (2001)	64 [±11]	55.1 (Normo: 66 female Micro: 52 female macro: 29 female)	100	Original (186) 4-variable MDRD	Mean 3.2 months (calculated based on Normo: 40 [±8] Micro: 38 [±11] macro: 37 [±13] months)	All: 41.3 [± 13.1] Normo: 45.6 [±8.9] Micro: 43.8 [±12.2] macro: 37.2 [±14.5]	(measures end of follow-up) Normo: 45.8 [±8.5] Micro: 43 [±12.8] macro: 29.5 [±21.1] [i]	10 death (3 micro-, y macro-) 12 dialysis (2 micro-, 10 macro-)	N.R.	Unclear
Schulman 2015	999 ITT placebo population from 1999 non-dialysis patients with	Whether addition of AST-120 (n=1000) to standard therapy (n=999) can slow the progression of	EPPIC-1 and EPPIC-2 trial, US (2007)	55.6 [±14.6]	60.3	N.R.	eGFR (equation not specified)	N.R.	22.04 [±7.23]	Fast decliners (N=499): -10.22 [±SE 0.43] Slow decliners (n=500): -	321 ESRD 103 death	10.44 [±4.99] (derived from table 6)	Unclear

	moderate to severe CKD [p]	renal disease								0.28 [±SE 0.26]			
Tan 2015	62 CKD 3-4 patients with type 2 diabetes and proteinuria	follow-up post-trial study on the association of intervention/ community care (CC, n=30) and usual care (UC, n=32) on all-cause mortality or composite renal event (ESRD)	DEFEND study, New Zealand (2004)	CC: 63 [±6.6] UC: 60 [±7.1][q]	35/65=53.8[p]	100	Original (186) 4-variable MDRD	Median (IQR) in months Original trial: 17 (11–21) Post-trial: CC: 47.5 (20.25-82.53) UC: 52 (24.5-68)	CC: 36 [±15] UC: 39 [±14]	CC: Median −3.1 (IQR −5.5, −2.3) UC: median −5.5 (IQR −7.1, −3.0)	30 dialysis or ESRD 16 died	N.R.	Unclear
Tangkiatkumjai 2017	339 CKD 3-5 patients [r]	association between medication adherence (low, n=62); high, n=233) and CKD progression	Chulalongkorn University & Srinakharinwirot University, Thailand (2012)	68 [±12]	48 (52 female)	65	Thai re-expressed (175) 4-variable MDRD	Median 12 (range 9-16) months	39 [±12]	Low: -4.4 [±6.7] high: -0.9 [±7.4]	18 (6%) started dialysis 28 (8%) died	N.R.	16 (5%), reason unspecified
Tsai 2012	428 CKD patients not requiring dialysis	association between depressive symptoms and progression to requirement of maintenance dialysis	Kaohsiung hospital, Southern Taiwan (2007)	57 [±15]	62 (38 female)	30	Original (186) 4-variable MDRD	25.2 [±11.9] months	Median 27 (IQR 11-48)	Median -1.6 (IQR -4.2; 0.1)	119 dialysis 17 died	Median 4.0 (IQR 3.4; 5.5)	50 (11.7%), no reason specified
Tsai 2014	472 non dialysis CKD stage 4-5 patients	association of fluid status and CKD progression	Kaohsiung hospital, Southern Taiwan (2011)	65.4 [±12.7]	54.4	43.9[s]	Original (186) 4-variable MDRD	Median 17.3 (IQR 14.0-19.1) months	15.4 [±7.5]	Median -2.0 (IQR -5.2; 0.1)	71 (15%) dialysis (65 HD; 6 PD) 0 died	N.R.	Unclear
Xie 2016	26246 patients who entered CKD stage 4	eGFR trajectories in association with kidney disease outcomes and mortality	US Veterans Affairs Healthcare system, USA (2007)	73.17 [±8.41]	97.0	65.3	CKD-EPI	Median 4.34 (IQR 1.72; 5.00)	44.63 [±17.45]	Median -3.44 (IQR -6.05; -1.65)	37% (N=9809) composite endpoint of kidney failure (eGFR <15), dialysis or transplantation. 36% (N=14550) died	N.R.	Unclear

Abbreviations: N.R. not reported; HD=hemodialysis; PD=peritoneal dialysis, CKD=chronic kidney disease, RRT=renal replacement therapy, ESRD=end-stage renal disease

* Published between January 2000 and December 2016 (both finally published and epubs published in advance).

[a] Indicated as mean [±SD], unless indicated otherwise.

[b] Negative values represent a faster decline rate of GFR; positive values represent slower decline rate of GFR.

[c] Derived from table 1, however in the first paragraph of the results is stated 1909/3303=58%.

[d] Decline rate is derived from table 2, but there is no unit of decline rate mentioned in the table. The method section states that the decline rate is calculated per year. However, in the example of figure 2 the unit is per month. For current meta-analysis, we assumed that the decline rate was calculated per month.

[e] Cited from the article "A total 1382 patients were enrolled, including 721 multidisciplinary care group and 661 nonmultidisciplinary care group patients. Using age, sex, chronic kidney disease stage, and diabetes mellitus status as variables, 592 multidisciplinary care recipients were matched to 614 nonmultidisciplinary care patients".

[f] $eGFR = 175 \times [0.011312 \times (SCr - c)/m]^{-1.154} \times age^{-0.203}$ (× 0.742 if female); *C* and *M* are correction factors required to correct individual laboratory results to ID-MS values as determined by NEQAS.

[g] decline rate over first 12 months of follow-up, GFR decline rate is not provided over the full follow-up period.
[h] Mean decline in GFR was calculated for 436 patients, who had ≥2 eGFR measurements to estimate the kidney function decline rate.
[i] Decline rate was calculated based on mean difference between initial baseline eGFR measure and GFR measured at the end of follow-up. Standard deviations of initial baseline eGFR value(s) were pooled with SDs from GFR value(s) at the end of follow-up. The derived mean ±SD was divided by the mean follow-up time (in years) to calculate the mean annual eGFR decline.
[j] Of 986 patients, 630 patients were followed for 2 years. The mean follow-up is calculated over these 630 patients. Furthermore, the mean decline rate is 3.2 ml/min/1.73m^2 following the results, but no variance (SD or SE) is described. Therefore, we used the baseline GFR with the GFR given at year 2 to calculate the mean GFR decline with corresponding SD. The GFR value at year to is also based on these 630 patients.
[k] eGFR (ml/min/1.73 m^2) = 194 x Serum creatinine$^{-1.094}$ xAge$^{-0.287}$ x 0.739 (if female).
[l] All baseline characteristics are at moment of referral for nephrology care.
[m] Based on the sentence: "Out of 372 progressed patients, 93 (21%) patients with CKD stage 3 progressed to stage 4, 42 (10%) to non-dialysis dependent (NDD) stage 5 and 135 (31%) progressed to RRT. On the other hand, 15(8%) and 135(31%) patients with CKD stage 4 progressed to NDD stage 5 and RRT respectively." However, the total number of patients in this sentence exceeds the number of 372 progressed patients, it concerns 420 patients.
[n] The follow-up period and the number of patients that initiated dialysis were only available for all 149 patients. Other results are based on data from the 56 CKD3b-5 patients, since this is the population of interest for this meta-analysis.
[o] 399 patients had at least one kidney function (eGFR) estimation and were included for calculation of renal function decline.
[p] Based on 999 pooled placebo ITT population, no decline for AST-120 group. Other possibility of renal function at begin and end of follow-up for calculating decline not possible, because no mean follow-up known.
[q] from the complete DEFEND trial of 65 patients (ref: Hotu C *et al*. *Nephrol Dial Transplant* 2010; **25**: 3260–6.)
[r] Results are based on 295 patients: patients lost to follow-up and died during 12 months were excluded.
[s] In table 1 the percentage of patients with diabetes is 35.4%.

Table S2. General characteristics of dialysis-based studies

First author and year of publication*	No. of participants	Aim of the study	Setting, country (year of baseline)	Mean [±SD] age[a]	% male	% DM	Dialysis modality	Renal function measure	Mean [±SD] duration of pre-dialysis period (years)[a]	Mean [±SD] initial /baseline eGFR (ml/min/1.73 m^2)[a]	Unadjusted mean [±SD] of estimated annual decline (ml/min/1.73 m^2/year)[a, b]	Mean [±SD] GFR at dialysis initiation/RRT (ml/min/1.73 m^2)[a]
Ambrogi 2009	342	rates and patterns of eGFR evolution preceding dialysis initiation, divided in linear (N=185) and nonlinear decline (N=157)	AVENIR study, Loraine France (2005)	67.8 [±14.8]	61.1	44.4	N.R.	Original (186) 4-variable MDRD	10.0 [±9.7] months	20.3 [±16.9]	-13.2 [±2.1]	Linear: 9.1 [±3.2] Nonlinear: 10.8 [±3.6]
Beltrán 2009	63	identifying differences in survival between dialysis start after graft failure (GF, n=25) or native kidney failure (NF, n=38)	University hospital Dr Peset Valencia, Spain (1996)	GF: 63.5 [±13.6] NF: 56.8 [±19.5]	GF: 56 NF: 63.2	N.R.	HD	abridged MDRD	24 months	N.R.	GF: -0.83 [±0.4]/month NF: -0.42 [±0.2]/month	GF: 8.66 [±3.13] NF: 7.72[±2.32]
Bhan 2007	63	identifying factors associated with lack of access of fistula creation (with fistula creation n=30, without n=33)	Academic university hospital Dalhousie, Canada (2005)	With: 59 [±16] without: 64 [±15]	With: 80 without: 73	With: 43 without: 55	HD	MDRD, equation not specified	2	With: 13.3 [±6.1] Without: 18.0 [±8.4]	With: 0-1y:-4.7 [±3.5] 1-2y: 1.42 [±3.9] Without: 0-1y:-12.1 [±9.9] 1-2y: 0.54 [±10.4]	With: 7.5 [±3.5] Without: 8.6 [±3.3]
Eyre 2008	122	effects of low-protein diets (LPD, n=61) compared to controls (n=61) on nutritional status, morbidity, and mortality at the start of dialysis	Sahlgrenska University Hospital, Germany (1988)	Mean (range) LPD: 65.4 (37-85) Control: 64.3 (21-83)	67	N.R.	39% HD 61% PD	Original (186) 4-variable MDRD	6 months	N.R.	LPD: 4.08 [SEM ±0.48] Controls: 13.32 [SEM ±2.04]	LPD: 7.1 [±SEM 0.5] Controls: 6.9 [±SEM 0.4]
Haapio 2012	319	association between eGFR decline pattern and long-term survival on RRT	Finnish Registry for Kidney Diseases, Finland (1998)	Median 60 (IQR 47-69)	61	N.R.	37% PD	re-expressed (175) 4-variable MDRD	12 months	Median 13.3 (IQR 9.7;18.7)	-6.6 [±1.7] [c]	Median 7.1 (IQR 5.6;8.8)
He 2016	77	course of GFR decline 12 months before and after start of PD	Toronto General Hospital, Canada (2008)	63.1 [±15.1]	54.5	37.7	PD	original(186) 4-variable MDRD	1	N.R.	-0.59 [±0.55] per month	7.4 [±3.2]
Hsu 2016	661	quantify proportion of incident HD patients with an abrupt decline in kidney function prior to HD start and whether this pattern is associated with early death after initiating maintenance HD therapy	CRIC study, USA (2003)	56.3 [±11.3]	61.3 (38.7 female)	70.5	HD	eGFR (CRIC equation)[d]	3.3 [±1.9]	32.6 [±10.4]	-6.7 [±2.5] [c]	10.4 [±4.4] [d]
Inaguma 2017	1292	association between eGFR decline in the 3 months prior to dialysis initiation and survival afterwards	AICOPP, Japan (2011)	67.8 [±12.9]	68.1 (31.9 female)	52.7	92.3% HD	eGFR[e]	3 months	8.72 [±4.63]	-12.96 [±15.76] [c, f]	5.48 [±2.11]
Jeong 2011	160	Case-control study comparing 80 patients with arteriovenous access	University of Ulsan College of Medicine, Korea	AVA: 63.3 [±13.6]	55	55	HD	re-expressed (175) 4-variable	Before Z-point: 12 months	On Z-point: AVA: 11.4 [±3.1] Catheter: 11.3 [±3.2]	Before Z-point AVA:-0.62 [±0.3] Catheter: -0.63	AVA: 6.4 [±2.0] Catheter: 6.1 [±1.9]

		(AVA) creation (=Z-point) before HD with 80 patients with catheter on rate of decline of renal function	(2005)	Catheter: 61.6 [±13.6]				MDRD	after Z-point: AVA: 14.2 [±9.4] Catheter: 5.9 [± 4.1] months		[±0.3] After Z-point AVF: -0.21 Catheter: -0.67 per month [g]	
Jungers 2001	63	evaluation of the rate of kidney function decline and the duration of the predialysis period in patients treated with recombinant erythropoietin (epo+, n=20) or not (epo-, n=43)	Necker Hospital, France (1990)	Epo+: 67.1 [±9.2] Epo-: 58.7 [±13.4]	Epo+: 50 (10/20) Epo-: 81 (35/43)	N.R.	Dialysis (modality unspecified)	Cockcroft-Gault	Months before T0: Epo+: 22.8 [±3.5] Epo-: 22.9 [±5.9] T0-dialysis: Epo+: 16.3 [±12.7] Epo-: 10.6 [±6.1]	Epo+: 10.2 [±1.7] Epo-: 11.9 [±2.4]	Before T0: Epo+: 0.36 [±0.16] Epo-: 0.55 [±0.48] T0-dialysis: Epo+: 0.26 [±0.15] Epo-: 0.57 [±0.44] Per month	Epo+: 7.1 [±1.1] Epo-: 7.7 [±1.3]
Kitai 2015	125	impact of nephrotic range proteinuria (with, n=103) versus without (n=22) on renal function decline during the 3 months prior to hemodialysis initiation	Osaka Red Cross Hospital, Japan (2008)	Without: 71 [±9] With: 63 [±11]	Without: 77.2 With: 72.8	100	HD	eGFR[e]	Median 75 (IQR 66-85) days	without: median 7.1 (IQR 5.9–8.6) with: median 6.2 (IQR 5.5–7.2)	Median 0.98 (IQR 0.51; 1.46) per month	Without: median 6.3 (IQR 5.1–8.0) With: median 5.2 (IQR 4.3–6.0)
Maeda 2011	112	examining effects of AST-120 (n=56) compared to controls (n=56) in suppressing CKD progression and delaying dialysis initiation	Juntendo University Hospital, Japan (2000)	Control: 62.9 [±13.0] AST: 61.0 [±12.9]	Control: 60.7 AST: 67.9	N.R.	Unclear	eGFR[e]	4	Control: 11.0 [±9.3] AST-120: 11.7 [±7.9]	Before baseline: Control: 0.722 [±0.885] AST-120: -1.041 [±1.177] After baseline: Control: -0.859 [±0.978] AST-120: -0.338 [±0.317] Per month	N.R.
O'Hare 2011	666	Estimating magnitude of changes in timing of dialysis initiation between 1997 and 2007 [h]	Health care coorporation program; USRDS, US (1997 vs 2007)	64.2 [±14.1]	53.5	59.9	Unclear	Original (186) 4-variable MDRD	Median 1.9 (IQR 0.9;3.4)	N.R.	-6.7 (95%CI -7.1; -6.3)	8.2 [±4.7]
O'Hare 2012	5606	Investigating different eGFR trajectories in 2 years before long-term dialysis initiation	Veterans Affairs and US Renal Data System, US (2001)	66.2 [±11.5]	98.4 (1.6 women)	50.0	95.5 in-center HD	Original (186) 4-variable MDRD	Median 386 (IQR 179, 585) days	34.5 (pooled median, derived from figure 1)	13.5 [±13.1]	11.8 (pooled median derived from figure 1)
Ramspek 2017	197	Whether fast mGFR decline is a risk factor for mortality on dialysis, in contrast to a fast eGFR decline	NECOSAD-II, The Netherlands (1997)	58.3 [±14.3]	61.4	20.4	54.8% HD 45.2% PD	original (186) 4-variable MDRD	Median 204 (IQR 92-312) days	N.R.	Median 4.7 (IQR 1.8; 9.0)	7.3 [±2.6]
Sumida 2017	6540	comparing the rate of eGFR decline in patients with AVF/AVG (n=3026) and without (with	TC-CKD study, US (2007)	Without: 67.0 [±10.8] With:	Without: 97.9 With: 98.0	Without: 74.8 With: 74.9	HD	CKD-EPI	Median (IQR) Pre-AVF: Without: 1.7 (0.7, 2.9)	N.R.	Median (IQR) Pre-AVF: Without: −6.0 (−10.2, −3.3)	Median (IQR) Without: 13.0 (9.6, 17.7) With: 10.3 (8.0,

		catheter, n=3514)		67.1 [±10.7]					With: 1.4 (0.5, 2.6) Post-AVF: Without: 0.5 (0.5, 0.5) With: 0.5 (0.2, 1.2)		With: −5.6 (−8.8, −3.4) Post-AVF: Without: −16.3 (−26.2, −9.5) With: −4.1 (−4.8, −3.2) [i]	12.9)
Sumida 2016	18 874	eGFR slopes prior to dialysis initiation with cause-specific mortality following dialysis initiation	TC-CKD study, US (2007)	69.1 [±11.3]	98.2	72.2	Unclear	CKD-EPI	Median 4.0 (IQR 3.0, 5.2)	N.R.	Median −5.4 (IQR −9.7, −2.9)	Median 13.0 (IQR9.5, 18.6)

Abbreviations: N.R. not reported; HD=haemodialysis; PD=peritoneal dialysis, CKD=chronic kidney disease, RRT=renal replacement therapy, ESRD=end-stage renal disease

* Published between January 2000 and December 2016 (both finally published and epubs published in advance).

[a] Indicated as mean [±SD], unless indicated otherwise.

[b] Negative values represent a faster decline rate of GFR; positive values represent slower decline rate of GFR.

[c] Decline rate was calculated based on mean difference between initial baseline eGFR measure and GFR measured at the end of follow-up. In this case, meaning the difference between baseline eGFR and eGFR at dialysis initiation. Standard deviations of initial baseline eGFR value(s) were pooled with SDs from GFR value(s) at the end of follow-up. The derived mean ±SD was divided by the mean follow-up time (in years) to calculate the mean annual eGFR decline.

[d] reference for CRIC equation "Anderson AH, Yang W, Hsu CY, et al. Estimating GFR among participants in the Chronic Renal Insufficiency Cohort (CRIC) Study. Am J Kidney Dis. 2012;60(2):250-261"

[e] eGFR (ml/min/1.73 m2) = 194 x Serum creatinine$^{-1.094}$ xAge$^{-0.287}$ x 0.739 (if female). The mean (SD) eGFR at dialysis initiation was calculated over 493 patients.

[f] The eGFR value was calculated following the method described above in note [c]. In table 2 of the article, median (range) eGFR decline values for 3 months prior to dialysis initiation are described for G1 to G4. We reported the eGFR values at the beginning and at the end of follow-up (in this case the moment dialysis is started). This estimation is the most accurate, rather than pooling median (range) eGFR values over the 3 month period and multiply these by 4 to calculate the annual decline.

[g] In the article mean decline rates with SD are given before Z-point and after the Z-point the means are given without variance. Therefore, we calculated the mean [±SD] GFR decline by calculating the difference between eGFR values at the Z-point and at dialysis start, dividing these mean differences by the mean follow-up time from the Z-point to dialysis start (AVA: 14.2 [±9.4] months and controls: 5.9 [±4.1] months).

[h] Only the subgroup of patients was selected for whom a renal function decline was available.

[i] Adjusted eGFR decline: With: −18.1 (−20.6, −15.9) and −8.3 (−8.8, −7.5) Without: −20.6 (−23.5, −17.9) and −58.8 (−68.1, −51.6).

Table S3. Risk of bias assessment of included studies

CKD 3-5 cohorts

First author (year of publication)	Adequate definition and assessment of renal function decline	Adequate loss to follow-up (<10%)	Adequate selection of patients
Barrett 2015	-	-	?
Brown 2012	-	-	-
Chen 2011	-	?	-
Chen 2012	-	?	-
Chen 2013	-	?	-
Chen 2014	-	?	-
Chen 2015	-	?	?
Chen 2016	-	?	?
Chiu 2008	-	-	-
Chue 2011	-	+	?
Conway 2009	-	-	-
Datallo 2016	-	?	-
Drüeke 2006	+	+	?
Goicoechea 2010	-	-	?
De Goeij 2011	-	-	-
Golper 2015	-	-	-
Gouva 2004	+	-	?
Halimi 2016	-	+	?
Heaf 2011	-	?	-
Hsieh 2017	-	?	?
Inaguma 2016	-	-	?
Jones 2006	-	?	?
Kahn 2017	-	+	?
Kahn 2016	-	-	-
Kikuchi 2017	-	+	?
Kuo 2015	-	?	-
Levin 2008	-	?	-
Lewis 2004	-	?	?
Lim 2014	-	?	?
Lin 2013	-	+	?
Lucas 2008	-	?	?
McCaughan 2014	-	?	-
Meuleman 2015	-	+	?
Nacak 2015	-	?	-
Peeters 2014	-	-	?
Portoles 2013	-	+	?
Rigalleau 2007	-	?	?
Schulman 2015	-	?	?
Tan 2015	-	?	?
Tangkiatkumjai 2017	-	-	?
Tsai 2012	-	+	-
Tsai 2014	-	?	-
Xie 2016	-	?	-

?=unclear -=low risk of bias +=high risk of bias

Dialysis-based studies

First author (year of publication)	Adequate definition and assessment of renal function decline	Adequate selection of patients
Ambrogi 2009	-	-
Beltrán 2009	-	?
Bhan 2007	-	-
Eyre 2008	-	?
Haapio 2012	-	-
He 2016	-	-
Hsu 2016	-	?
Inaguma 2017	-	?
Jeong 2011	-	?
Jungers 2001	+	?
Kitai 2015	-	-
Maeda 2011	-	?
O'Hare 2011	-	-
O'Hare 2012	-	-
Ramspek 2017	-	-
Sumida 2017	-	-
Sumida 2016	-	-

?=unclear -=low risk of bias +=high risk of bias