Level of Renal Function at the Time of Dialysis Initiation and the Prognosis of Incident Dialysis Patients

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Disclosure of Interests

Nil

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GFR at initiation

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Guidelines pre-2000

Commence dialysis when GFR….

DOQI-NKF guidelines

=10.5ml/min/1.73m^2

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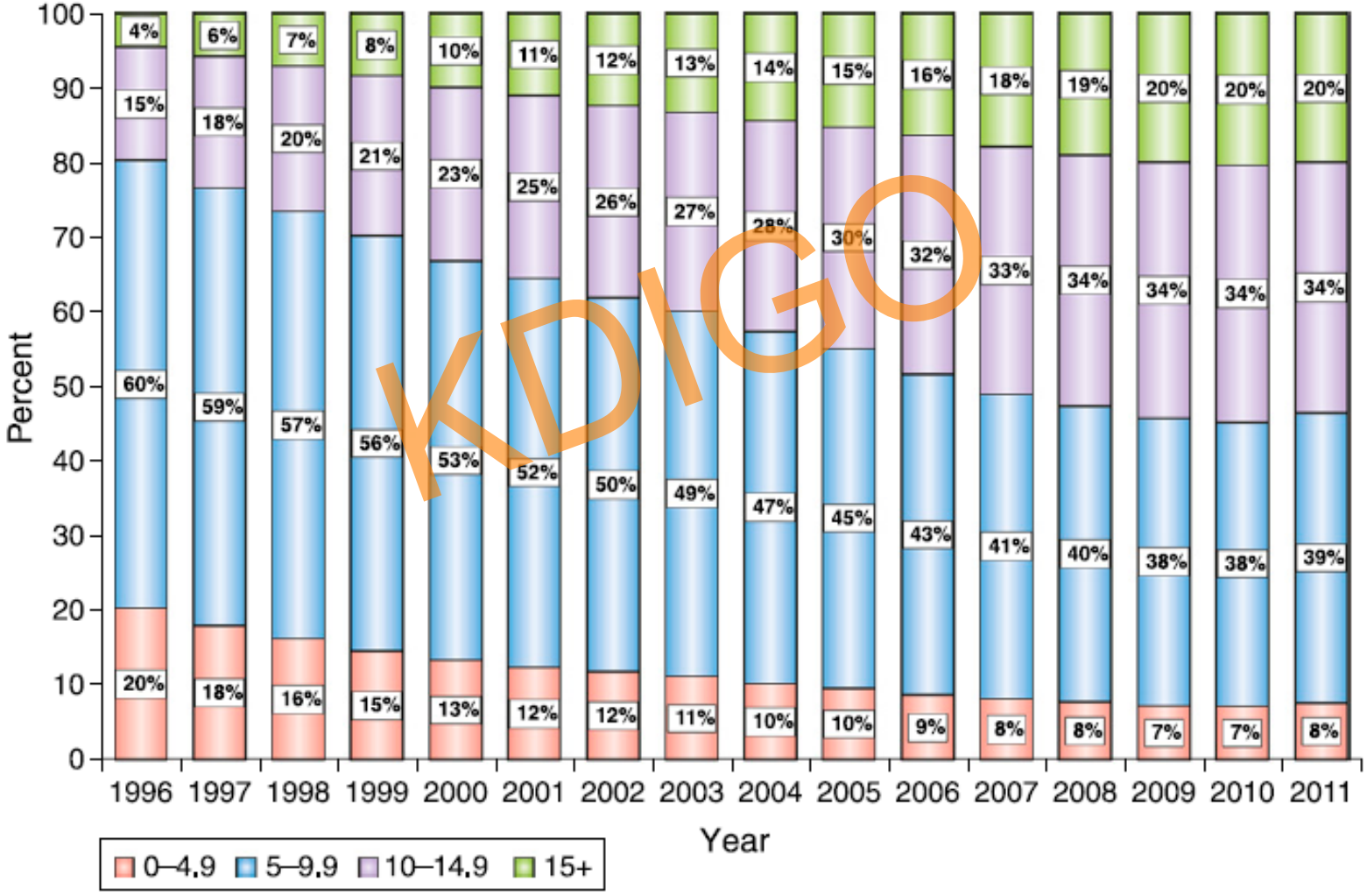
CANADIAN SOCIETY OF NEPHROLOGY

<12ml/min

Rising tide of early start dialysis



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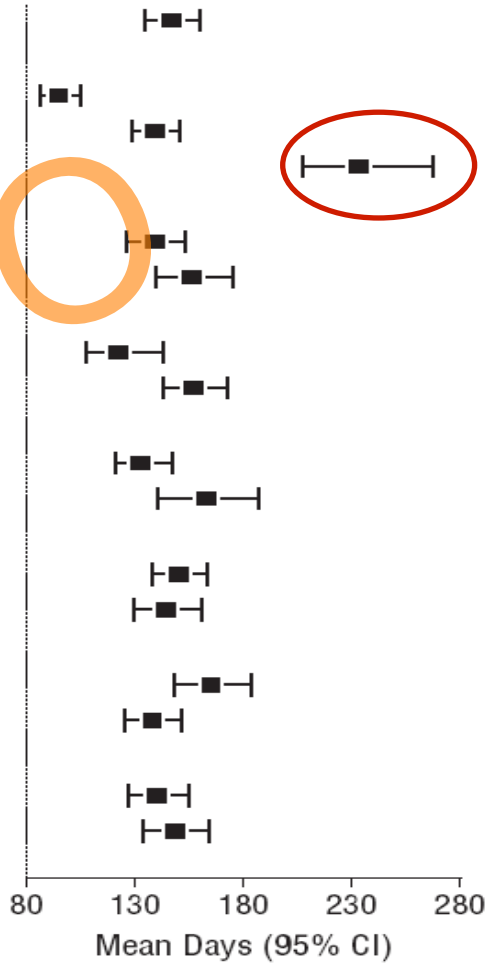
Rosansky SJ & Clark WF. J Am Soc Nephrol 2013;24:1367-70.

Dialysis initiated earlier in all subgroups in 2007 vs 1997

Subgroup	Mean Days	95% CI
All patients	147	134-160
Age, y		
<60	95	86-105
60-74	139	128-150
≥75	233	206-267
Sex		
Male	139	126-153
Female	156	140-176
Race		
Black	122	107-143
Nonblack	157	142-172
Diabetes		
Yes	132	121-148
No	163	140-187
Vascular disease		
Yes	150	138-164
No	144	129-161
Congestive heart failure		
Yes	165	148-184
No	138	125-151
Comorbidities		
≥3	140	127-154
<3	149	134-164



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O'Hare et al. Ann Int Med 2011

prognosis
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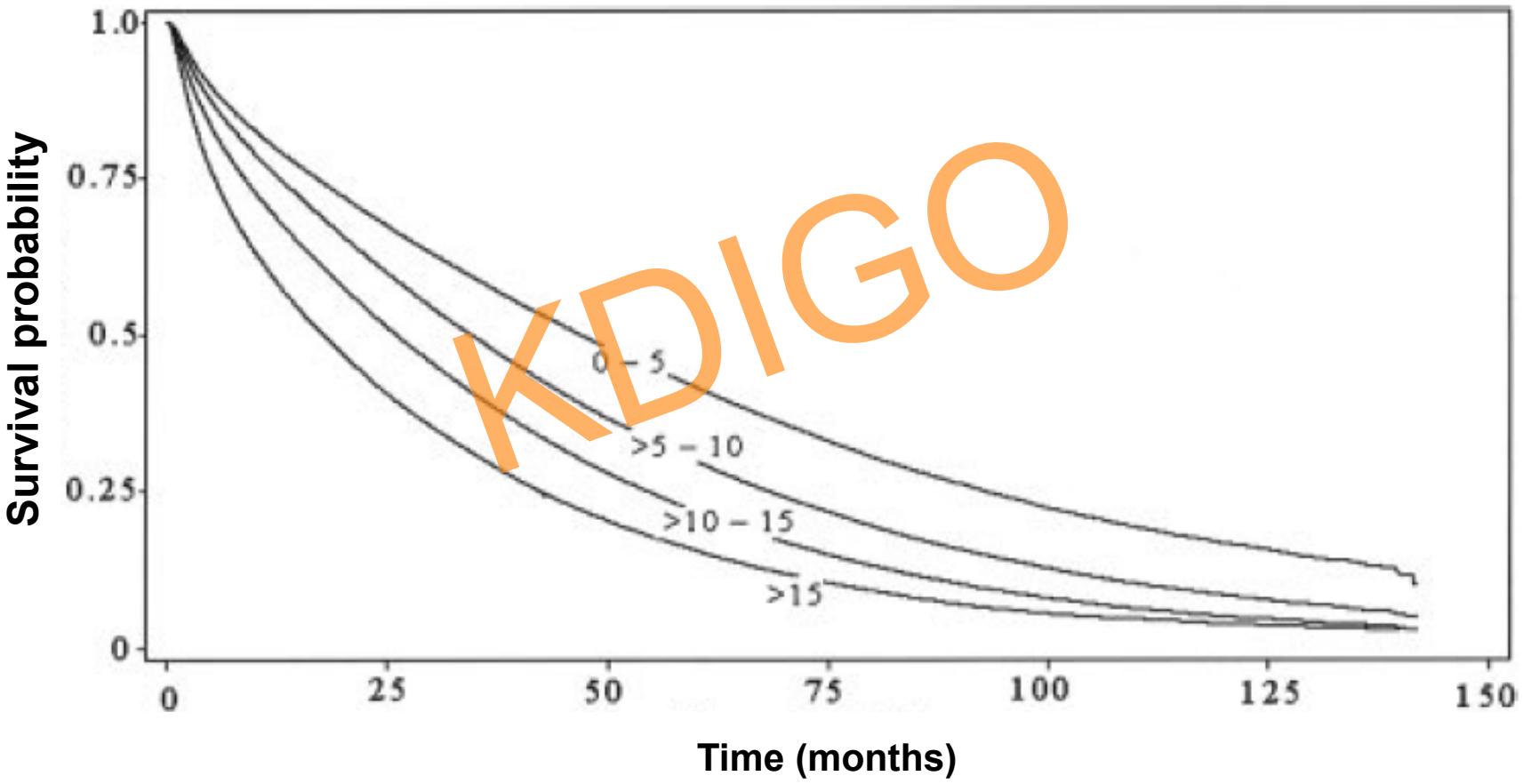
USRDS



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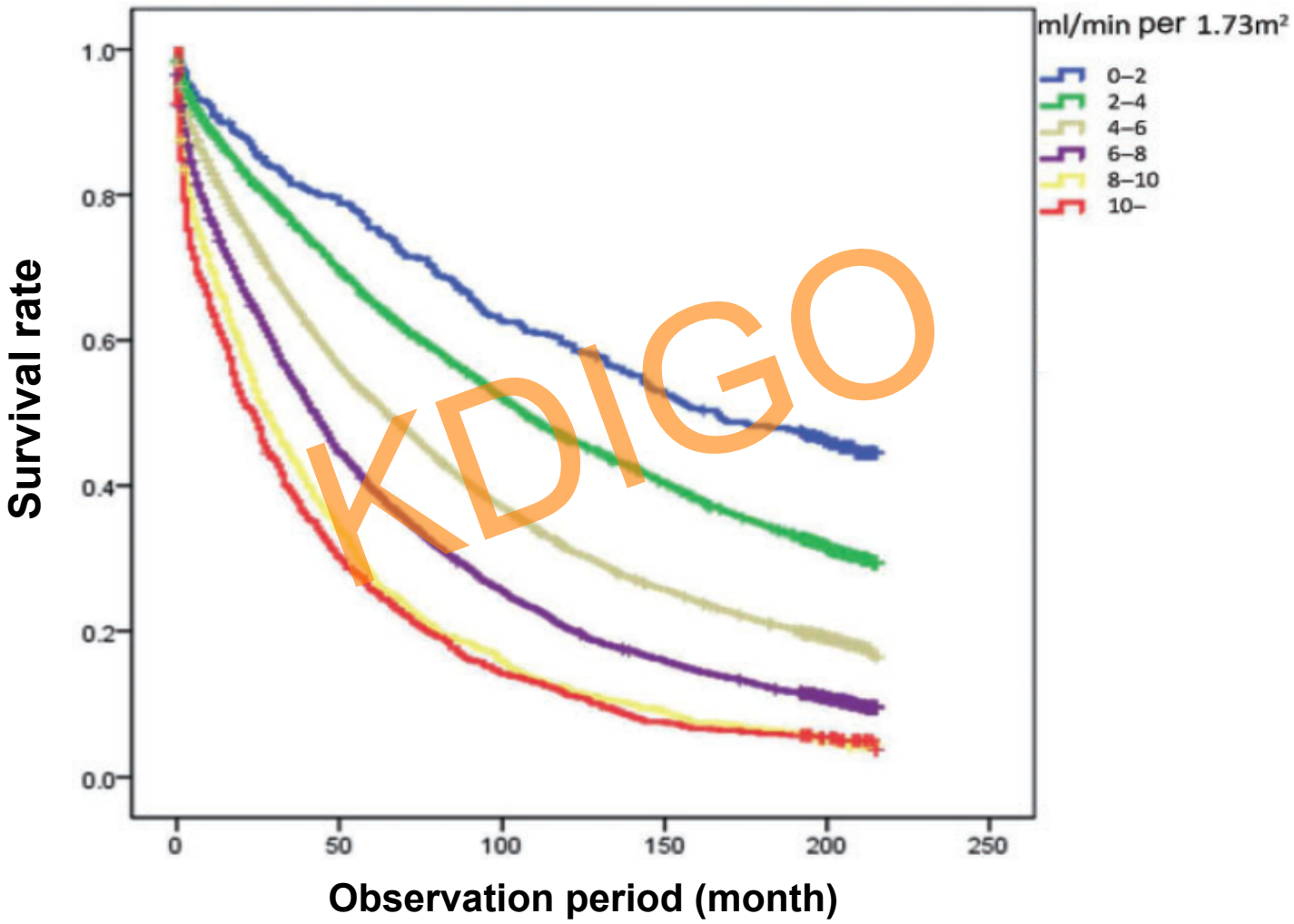
Wright S et al. Clin J Am Soc Nephrol 2010:5:1828–35

Japan



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Yamagata K et al. Ther Apher Dial 2012;16:284–5

IDEAL study outline

Study Population

***Inclusion criteria*:**

- **Progressive CKD**
- **eGFR 10–15 mL/min/ 1.73m^2**
- **≥18 yrs**

***Exclusion criteria*:**

- **Planned KT from living donor next 12 months**
- **Recent cancer diagnosis**
- **Inability to provide informed consent**

2,982 screenings

828 randomisations

- **Early Start 10–14 mL/min/1.73m^2 N=404 (383 started dialysis)**
- **Late Start 5–7 mL/min/1.73m^2 N=424 (386 started dialysis)**

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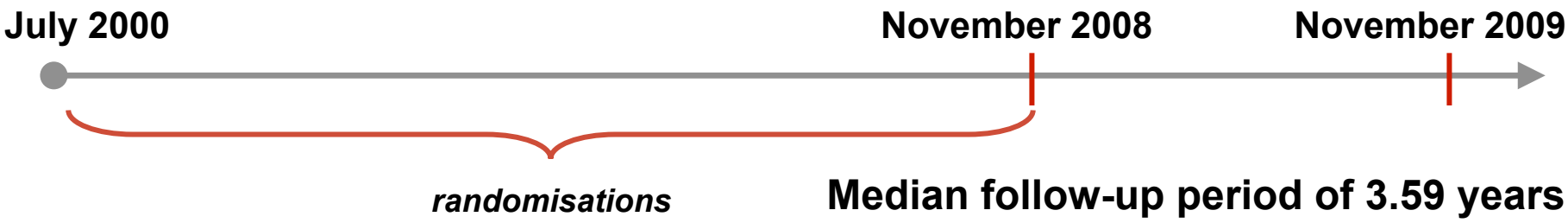
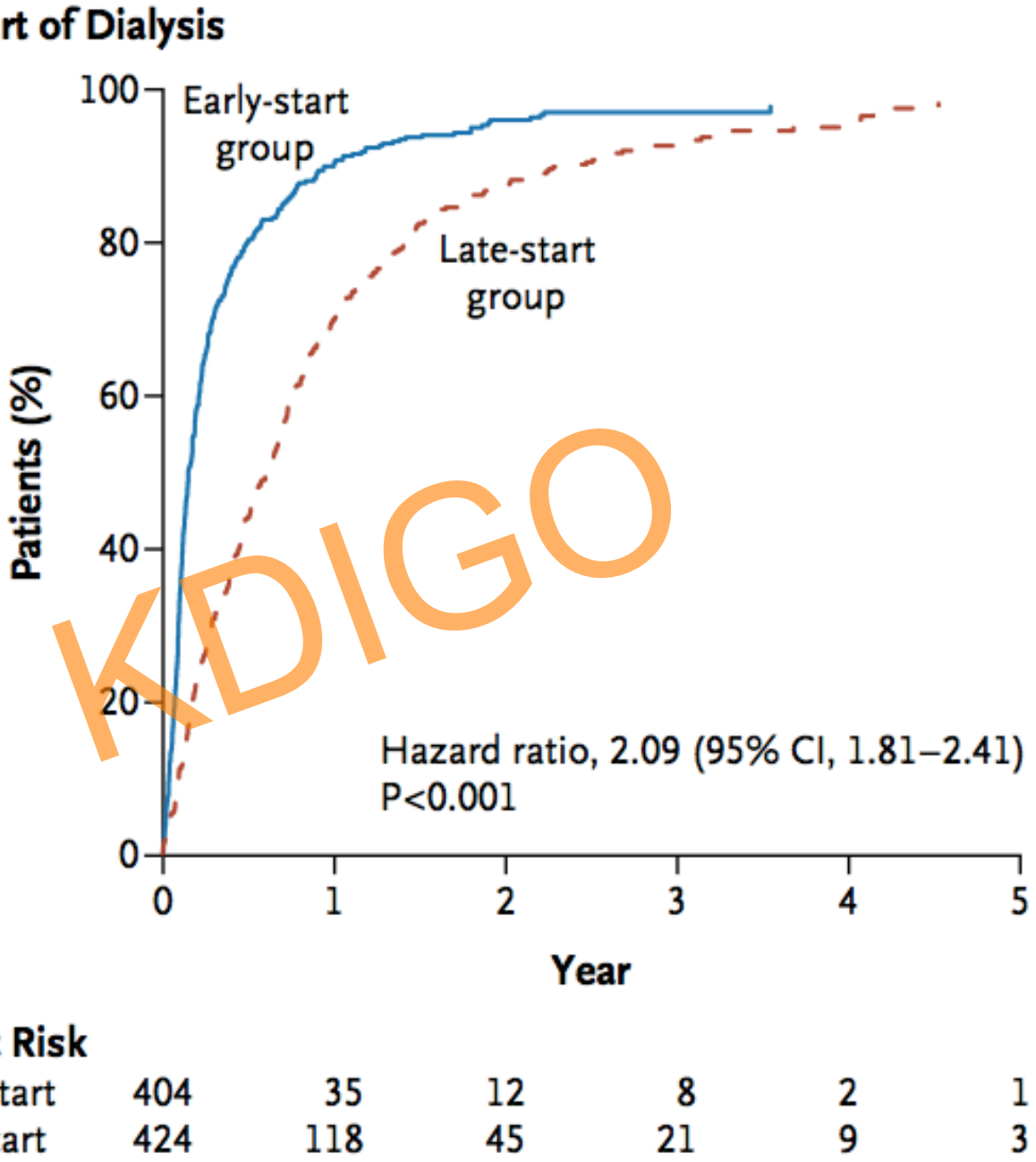


Cooper BA et al. N Engl J Med 2010;363:609–19

32 centres
828 participants
Median f/u 3.59 yrs



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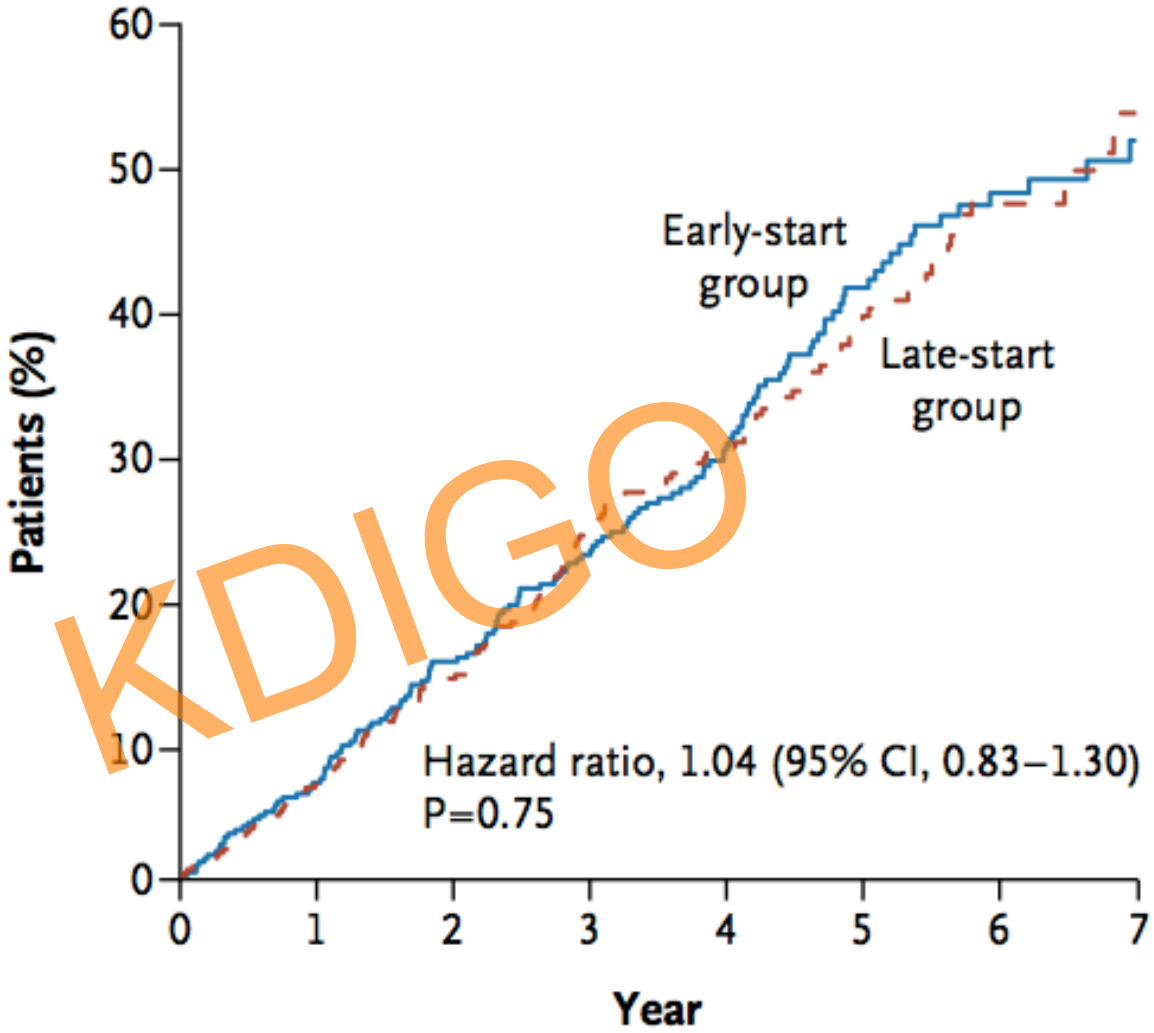
Cooper BA et al. N Engl J Med 2010;363:609–19

Time to Death



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No. at Risk

Early start	404	358	305	249	177	99	59	32
Late start	424	385	333	254	187	115	60	32

Cooper BA et al. N Engl J Med 2010;363:609–19

Summary of secondary outcomes

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

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Cooper BA et al. N Engl J Med 2010;363:609–19

Conclusions

- Early start (vs. late start) dialysis does NOT:
  - Reduce mortality
  - Improve cardiac outcomes
  - Improve nutritional status
  - Decrease infections
  - Decrease hospitalisations
  - Improve quality of life
  - Reduce patient personal costs
  - Reduce costs to the health budget
- **Findings apply to all sub-groups analysed**
- Dialysis should not be started based on eGFR alone

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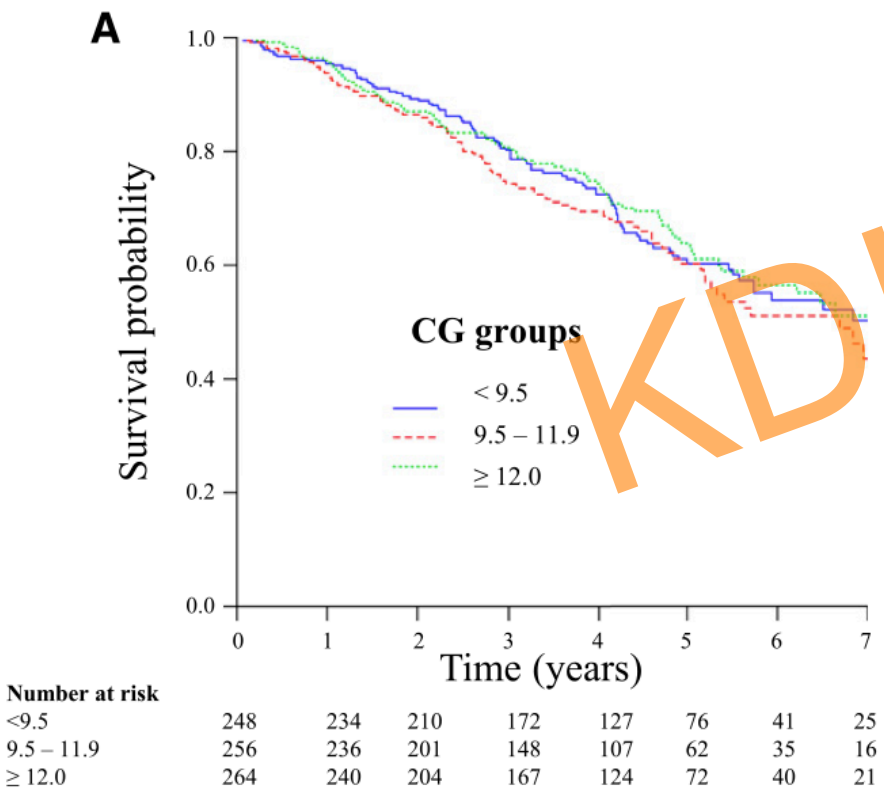
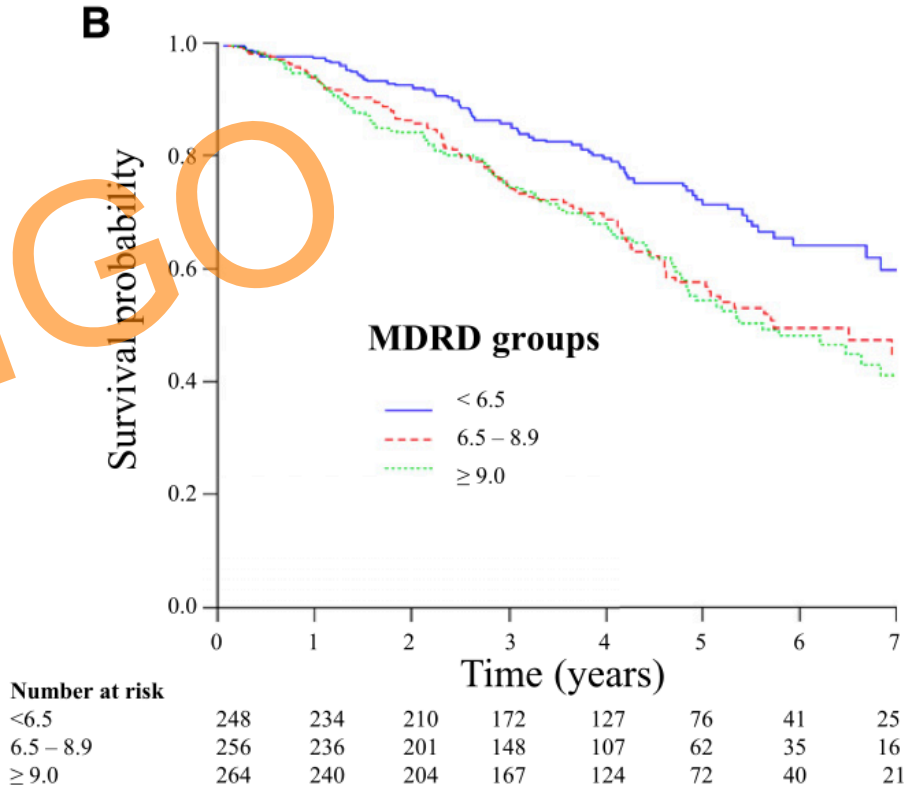
actual GFR at start





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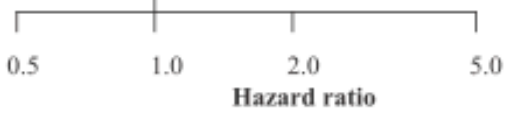
CJASN 2014:9;135–142

Significant difference for MDRD & CKD-EPI, but not with multivariate analysis

older female diabetes CV disease

Model and variables	Hazard ratio	Lower 95% CI	Upper 95% CI	P value
1. C+G GFR				
C+G <9.5 (ref=12.0+)	1.11	0.82	1.49	0.50
C+G 9.5-11.9 (ref=12.0+)	1.29	0.96	1.74	0.09
Age (years)	1.04	1.02	1.05	<.001
Females (ref=males)	1.38	1.07	1.78	<0.01
Caucasian (ref=non-Caucasian)	1.31	0.98	1.74	0.07
Diabetes (ref=no)	2.17	1.64	2.86	<.001
BMI (kg/m^2)	0.97	0.95	0.99	<0.01
Cardiovascular disease* (ref=no)	1.65	1.28	2.11	<.001
2. MDRD GFR				
MDRD <6.5 (ref=9.0+)	0.88	0.63	1.24	0.48
MDRD 6.5-8.9 (ref=9.0+)	1.20	0.90	1.61	0.21
Age (years)	1.04	1.02	1.05	<.001
Females (ref=males)	1.41	1.09	1.81	<0.01
Caucasian (ref=non-Caucasian)	1.25	0.94	1.66	0.13
Diabetes (ref=no)	2.14	1.62	2.82	<.001
BMI (kg/m^2)	0.97	0.95	0.99	0.01
Cardiovascular disease* (ref=no)	1.61	1.26	2.06	<0.01
3. CKDEPI GFR				
CKDEPI <6.0 (ref=8.0+)	0.93	0.67	1.27	0.64
CKDEPI 6.0-7.9 (ref=8.0+)	1.15	0.86	1.54	0.36
Age (years)	1.04	1.02	1.05	<.001
Females (ref=males)	1.41	1.10	1.82	<0.01
Caucasian (ref=non-Caucasian)	1.26	0.95	1.68	0.11
Diabetes (ref=no)	2.12	1.61	2.80	<.001
BMI (kg/m^2)	0.97	0.95	0.99	<0.05
Cardiovascular disease* (ref=no)	1.62	1.26	2.07	<.001



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CJASN 2014:9;135–142

Prognosis in subgroups

age
comorbidity
rate of decline
indication for dialysis
nephrology care

dialysis modality

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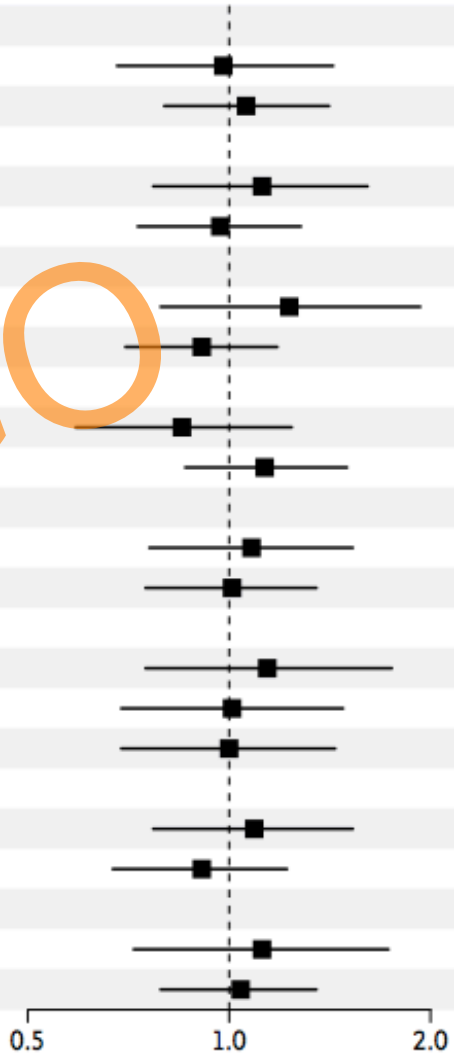
Initiating Dialysis
Early & Late
An Australian and New Zealand Multicentre Nephrology Trial

Mortality risk in subgroups

Subgroup	Early Start	Late Start	P Value for Interaction
	no. of deaths/no. of patients (%)		
GFR C–G			0.74
<12.5 ml/min/1.73 m^2	56/139 (40)	56/137 (41)	
≥12.5 ml/min/1.73 m^2	96/265 (36)	99/287 (34)	
GFR MDRD			0.58
<9.5 ml/min/1.73 m^2	58/195 (30)	57/203 (28)	
≥9.5 ml/min/1.73 m^2	94/209 (45)	98/221 (44)	
Age			0.26
<60 yr	39/180 (22)	38/194 (20)	
≥60 yr	113/224 (50)	117/230 (51)	
Sex			0.28
Female	55/143 (38)	58/143 (41)	
Male	97/261 (37)	97/281 (35)	
Diabetes			0.63
No	65/232 (28)	63/241 (26)	
Yes	87/172 (51)	92/183 (50)	
Body-mass index			0.59
<25.0	40/102 (39)	46/126 (37)	
25.0–29.9	53/143 (37)	52/146 (36)	
≥30.0	59/159 (37)	57/152 (38)	
Baseline history of cardiovascular disease			0.47
No	64/244 (26)	69/262 (26)	
Yes	88/160 (55)	86/162 (53)	
Albumin			0.67
<35 g/liter	38/68 (56)	44/81 (54)	
≥35 g/liter	110/325 (34)	109/336 (32)	



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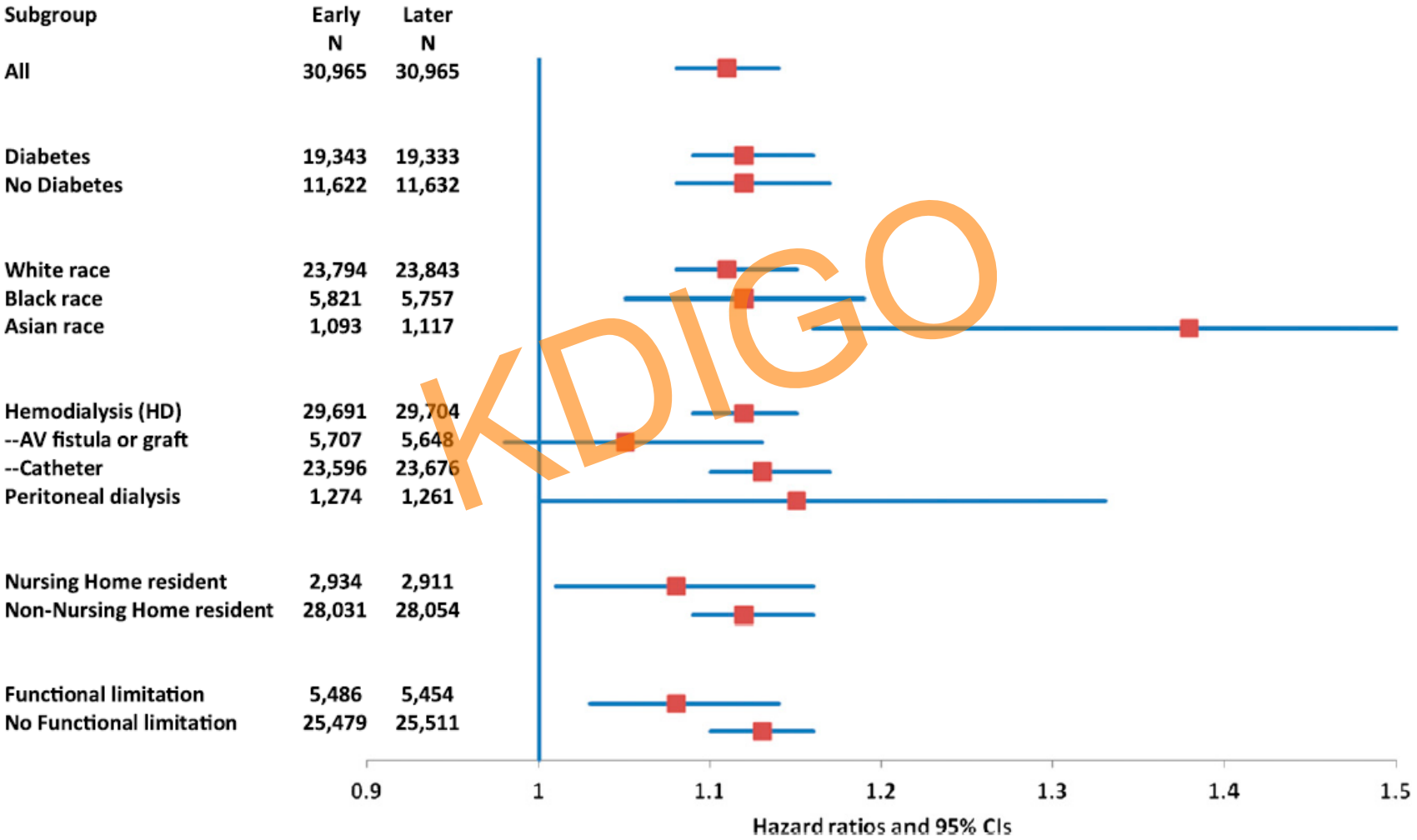
Cooper BA et al. N Engl J Med 2010;363:609–19

Mortality amongst older patients (>67 yrs) initiating dialysis 2006-2008; USRDS



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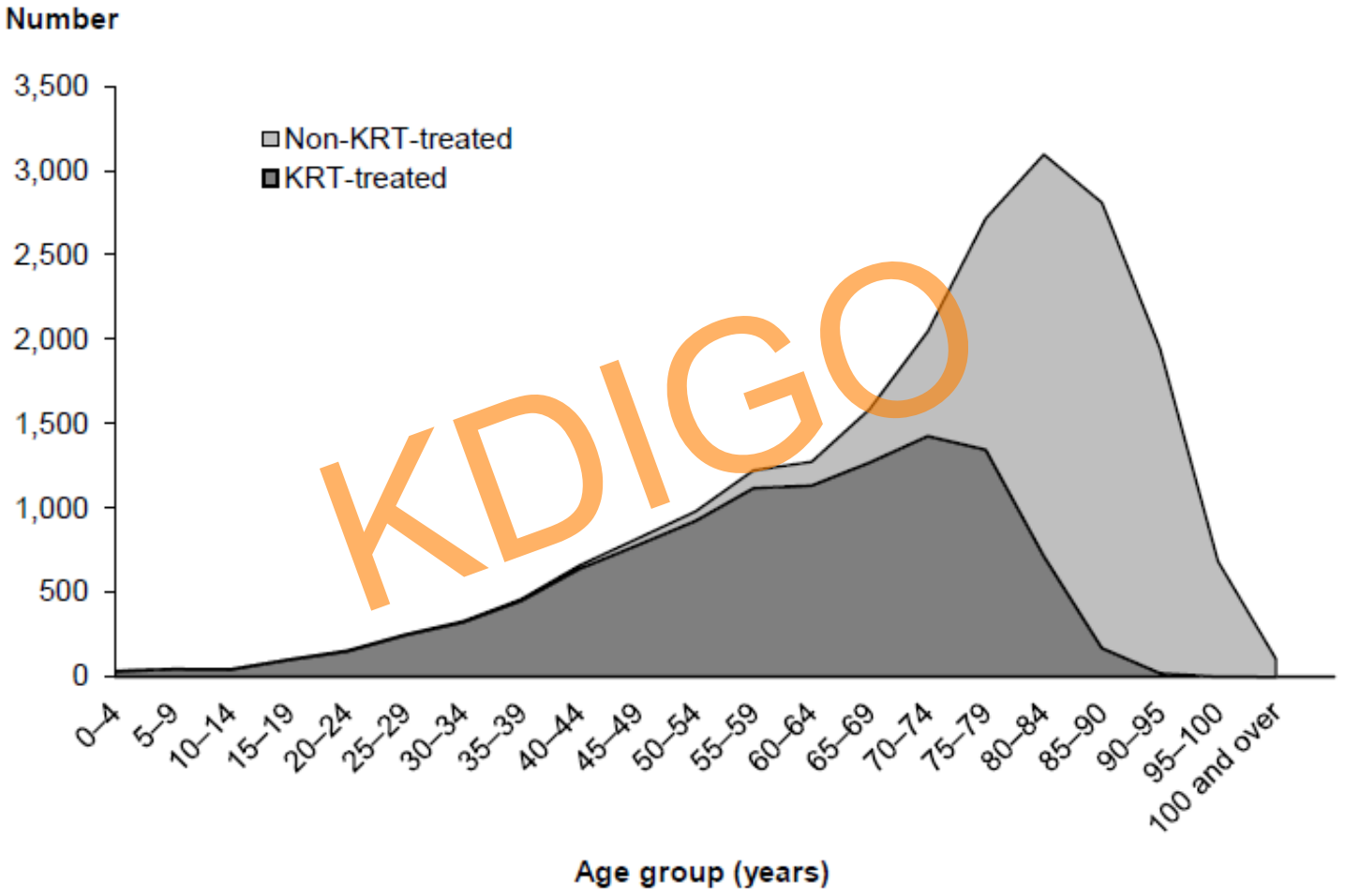
*Hazard ratios greater than 1 indicate greater mortality for early initiators relative to later initiators.

Crews et al J Am Soc Nephrol 2014;25:370-379

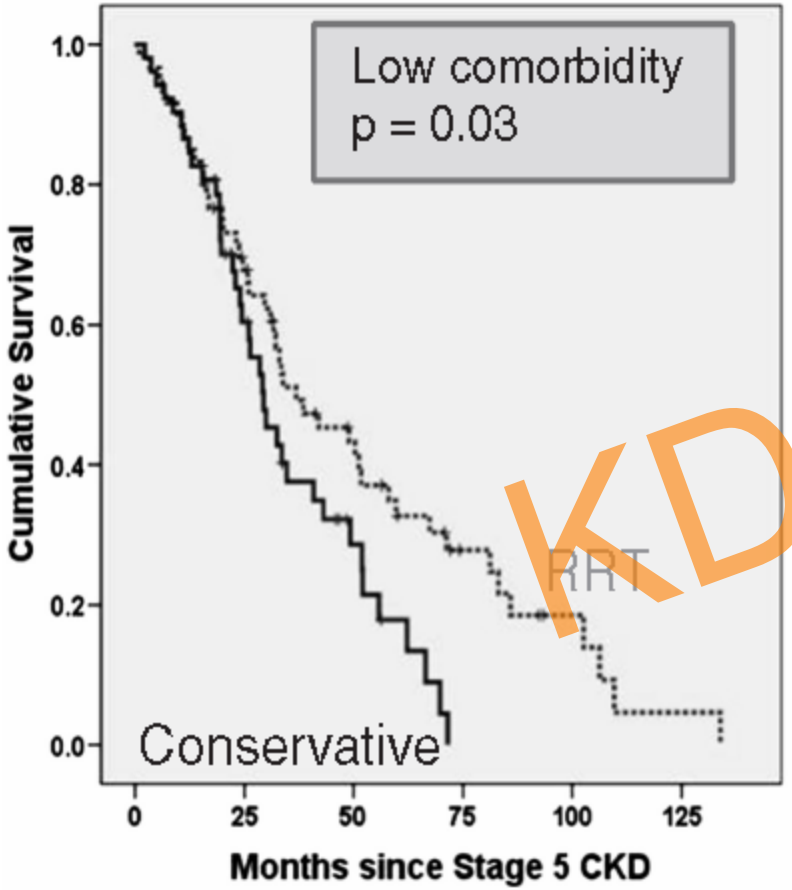
RRT vs Conservative care for ESKD in the elderly

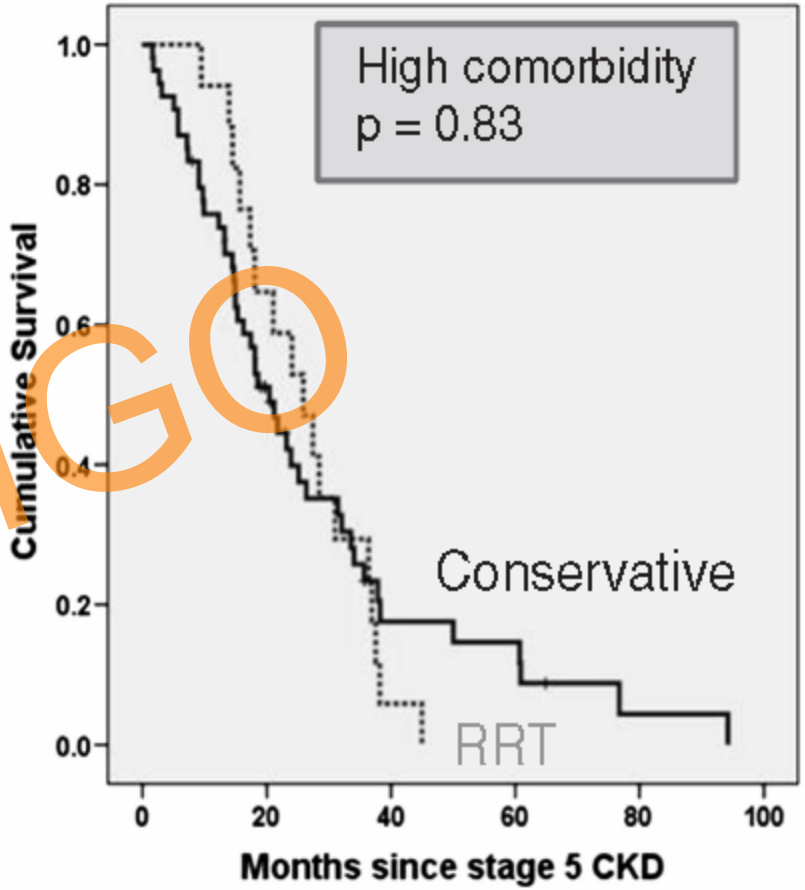


Source: Linked ANZDATA Registry, AIHW National Mortality Database and National Death Index.

End-stage kidney disease in Australia, AIHW June 2011

Survival depends on co-morbidities





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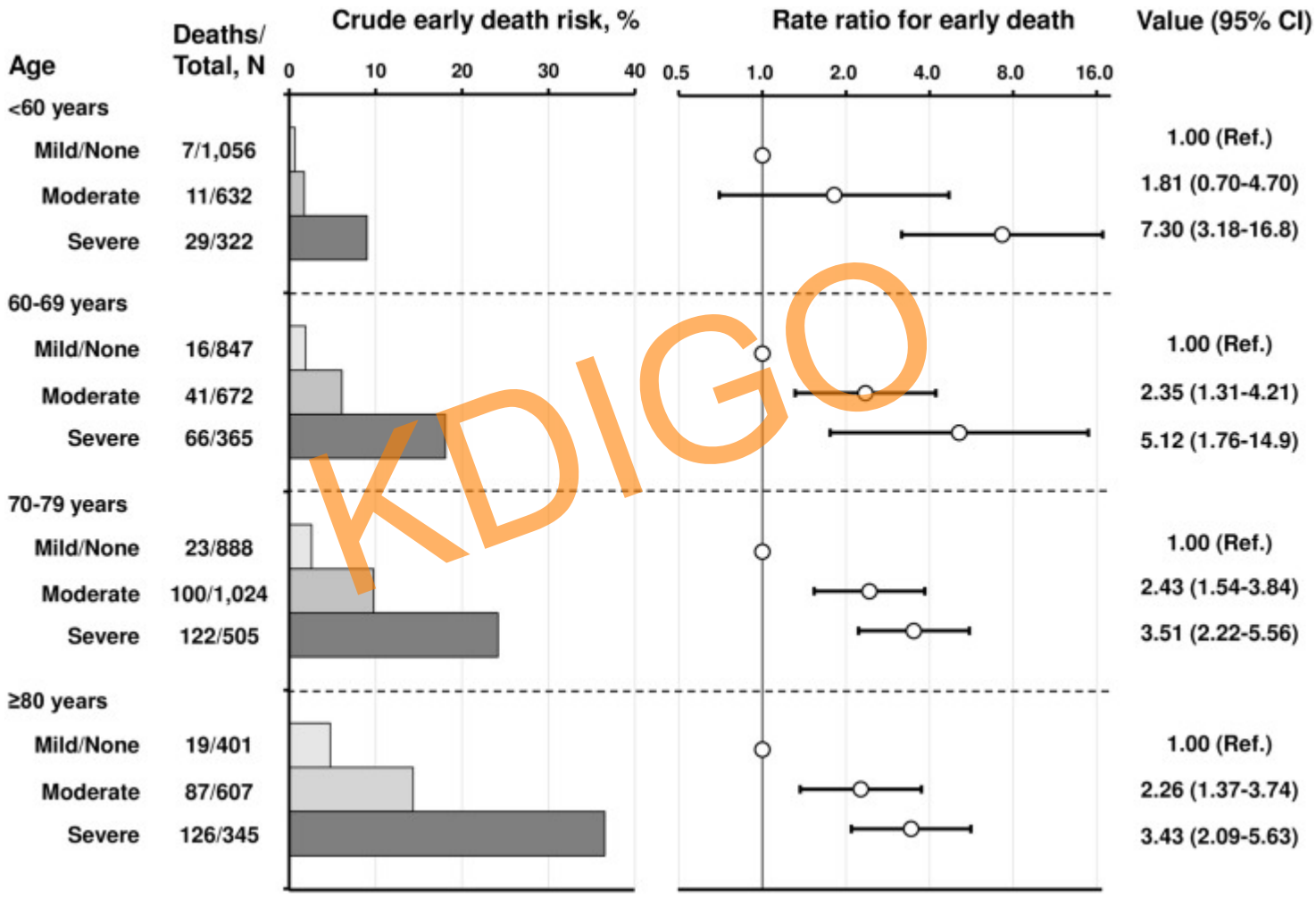
also age >75-80

Chandna SM. *et al. NDT* 2010

Functional status



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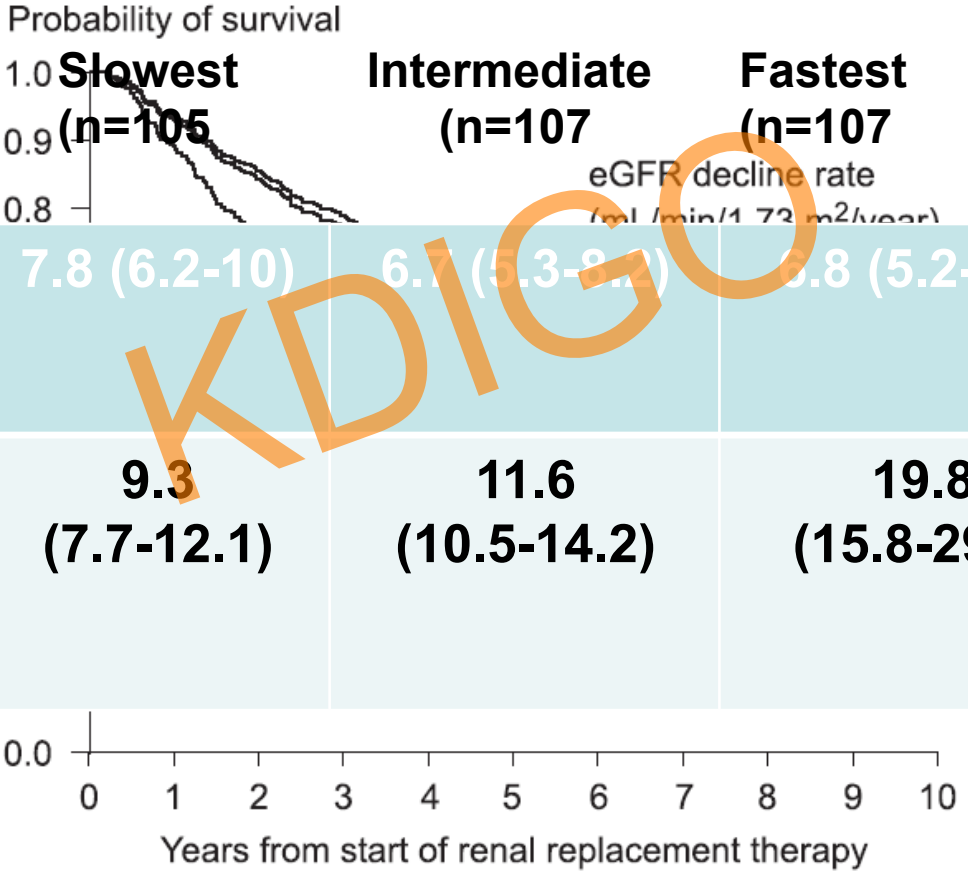
Risk of death <3m of start

Yazawa M et al. PLoS One 2016; 11(6)

Rate of decline is more important than absolute eGFR at dialysis initiation

eGFR decline rate tertiles (ml/min/m2)



	Slowest (n=105	Intermediate (n=107	Fastest (n=107	P value
eGFR at RRT start	7.8 (6.2-10)	6.7 (5.3-8.2)	6.8 (5.2-8.5)	< 0.005
eGFR 12 mths prior to RRT	9.3 (7.7-12.1)	11.6 (10.5-14.2)	19.8 (15.8-29.5)	<0.001

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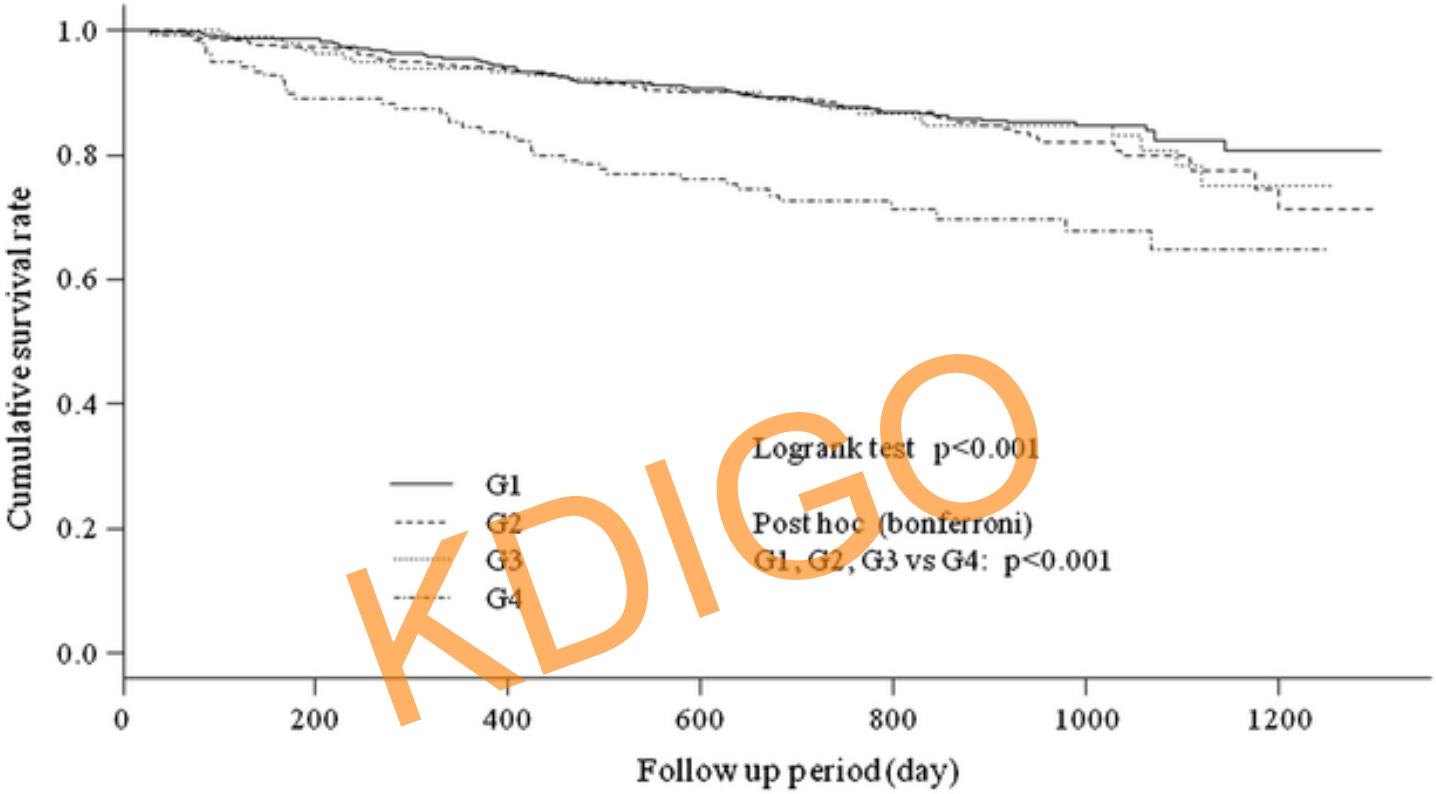
Haapio et al. Nephrol Dial Transplant 2012

Rate of decline…cardiac symptoms



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G1	555	543	515	463	294	154	30
G2	417	402	377	339	220	131	23
G3	183	174	167	154	99	56	10
G4	137	120	111	92	55	34	5

Higher rate of decline over 3m before start

→ **more cardiac symptoms at start**
greater mortality, CV mortality

Inaguma D et al. Clin Exp Nephrol 2016: April

Indication for dialysis

Greater mortality risk if dialysis commenced because of…

volume overload or hypertension

vs

eGFR
uraemic symptoms
other or unknown

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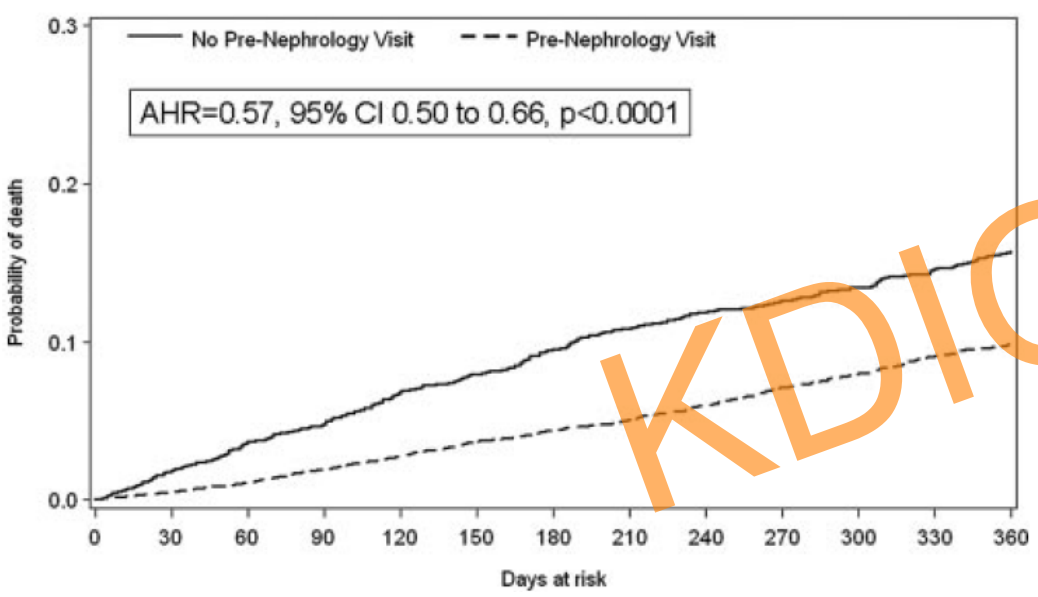
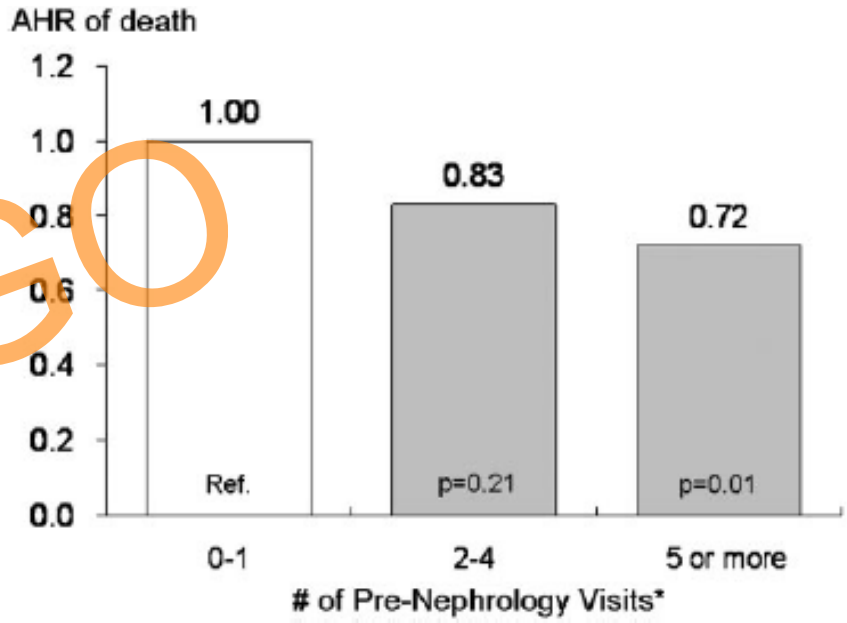
n =461 (437 HD)
retrospective
median F/U 2.4y

Rivara MB et al. AJKD 2016; e

Early start vs early referral





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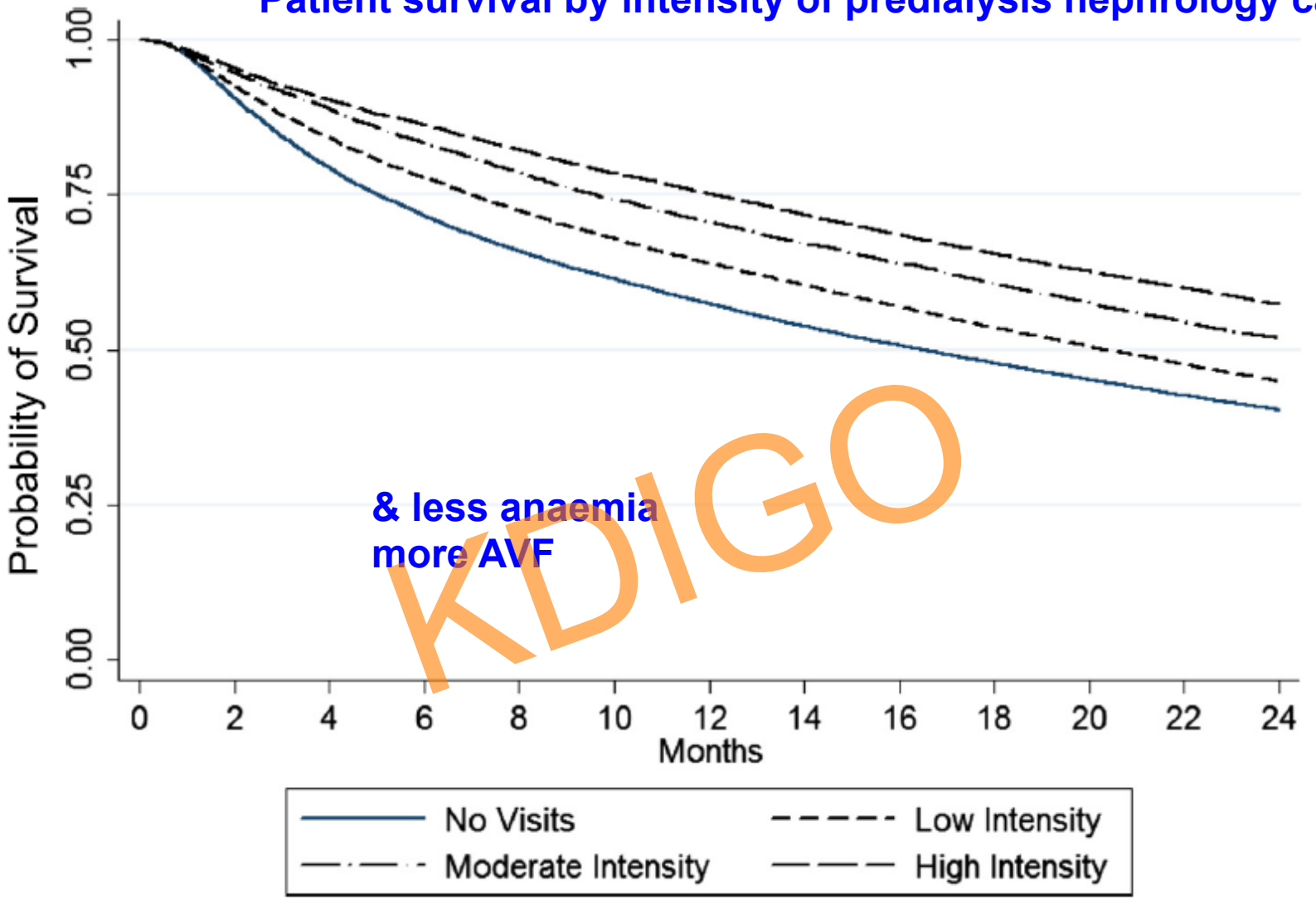
DOPPS
n = 8500
HD

Hasegawa et al
Clin J Am Soc Nephrol 4: 595–602, 2009

Patient survival by intensity of predialysis nephrology care



& less anaemia
more AVF

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VA &/or Medicare
retrospective, >66y
n = 58,014

Fischer MJ et al. BMC Nephrol 2016;17:103

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Initiating Dialysis Early & Late
An Australian and New Zealand Multicentre Nephrology Trial

Characteristics of those who started dialysis early vs late

GFR (ml/min/m2)	<6 (n=188)	6.5-8.9 (n=255)	>9 (n=325)	P (Tertile 1 vs 2=3)
Age (yrs)	55.2±12.6	57.9±11.7	63.5±11.5	<0.001
Female (%)	47	37	25	<0.001
White (%)	60%	71%	77%	0.001
BMI	29.3±6.4	29.9±6.1	28.2±5.7	0.49
Diabetes as primary renal disease (%)	35	35	34	0.79
Co-morbidity (%)				
Diabetes	43	44	42	0.99
CVD	30	36	60	0.02
PVD	15	18	19	0.22
CCF	20	27	33	0.007

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Indications for (early start) dialysis

Stage 5 CKD +

refractory fluid overload

refractory hyperkalemia

refractory hypertension

pericarditis

'uraemic cachexia'

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Not

GFR values

symptoms attributable to another disease

age

primary disease

Guidelines

2012

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5.3: TIMING THE INITIATION OF RRT

5.3.1: We suggest that dialysis be initiated when one or more of the following are present: symptoms or signs attributable to kidney failure (serositis, acid-base or electrolyte abnormalities, pruritus); inability to control volume status or blood pressure; a progressive deterioration in nutritional status refractory to dietary intervention; or cognitive impairment. This often but not invariably occurs in the GFR range between 5 and 10 ml/min/1.73 m^2. (2B)

Intent-to-defer

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GFR "protocol violations"

Reason for not starting dialysis in assigned GFR range (protocol violations)	Randomized to early start group but started with GFR < 10ml/min/1.73m^2 (n=75)	Randomized to late start group but started with GFR >7ml/min/1.73m^2 (n=322)
Uremia	5	234
Physician discretion	10	25
Fluid overload	1	28
Delay in access creation	21	1
Patient refusal	13	3
Unavailability of resources	6	6
Delayed follow up	6	.
Sudden unexpected decline in GFR	6	.
Malnutrition	.	5
Hyperkalaemia	.	4
Malaise and fatigue	.	3
Sudden unexpected improvement in GFR	.	2
Other reasons*	7	11

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NEJM Supplement: online 2010

Symptoms at dialysis initiation

TABLE 3. *Symptom at dialysis initiation*

Symptom	%	Median age		%Male	Underlying renal disease (%DMN)
		Years	Range		
Nausea, appetite loss	46.3%	60	18–98	57.3%	27.7%
Congestive heart failure	19.8%	64	18–99	52.5%	40.5%
Intractable edema	6.1%	61	18–88	56.4%	49.7%
Oliguria	4.5%	62	20–90	60.9%	19.9%
Neuropathy	7.1%	57	21–88	62.5%	27.8%
Unrecovered acute exacerbation of renal function	1.8%	64	18–90	53.3%	17.8%
Other uremic symptom	5.5%	70	26–93	61.4%	33.6%
No symptom	8.8%	58	18–88	65.4%	20.6%

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K Yamagata et al, Therapeutic Apheresis and Dialysis 2012

Late-start IDEAL = intention to defer

Predicting risk of starting dialysis early

Age*		**0.98**	**0.97**	**0.99**
Sex female*		1.15	0.93	1.42
Whites		**0.79**	**0.63**	**0.99**
Smoking	Current	0.84	0.60	1.17
	Former	1.13	0.91	1.41
	Never	1.00	1.00	1.00
Comorbidities	Diabetes	**1.51**	**1.23**	**1.86**
	IHD	**1.28**	**1.00**	**1.63**
	Hyperlipidemia	0.87	0.70	1.07
Cause of ESRF	Diabetes	**1.54**	**1.24**	**1.90**
	Glomerulonephritis	1.19	0.90	1.56
	Polycystic Kidney Dise	0.92	0.67	1.25

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younger, non-white, diabetes, ischaemic heart disease

Risks of intent-to-defer

Impact on the ability to train & remain on home-based therapy

Accumulation of comorbidities

- General ill health
- Access creation problems if delayed placement

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Home-based therapy uptake

	Home HD and PD	Non-home therapy
Early	156	129
Late	144	152

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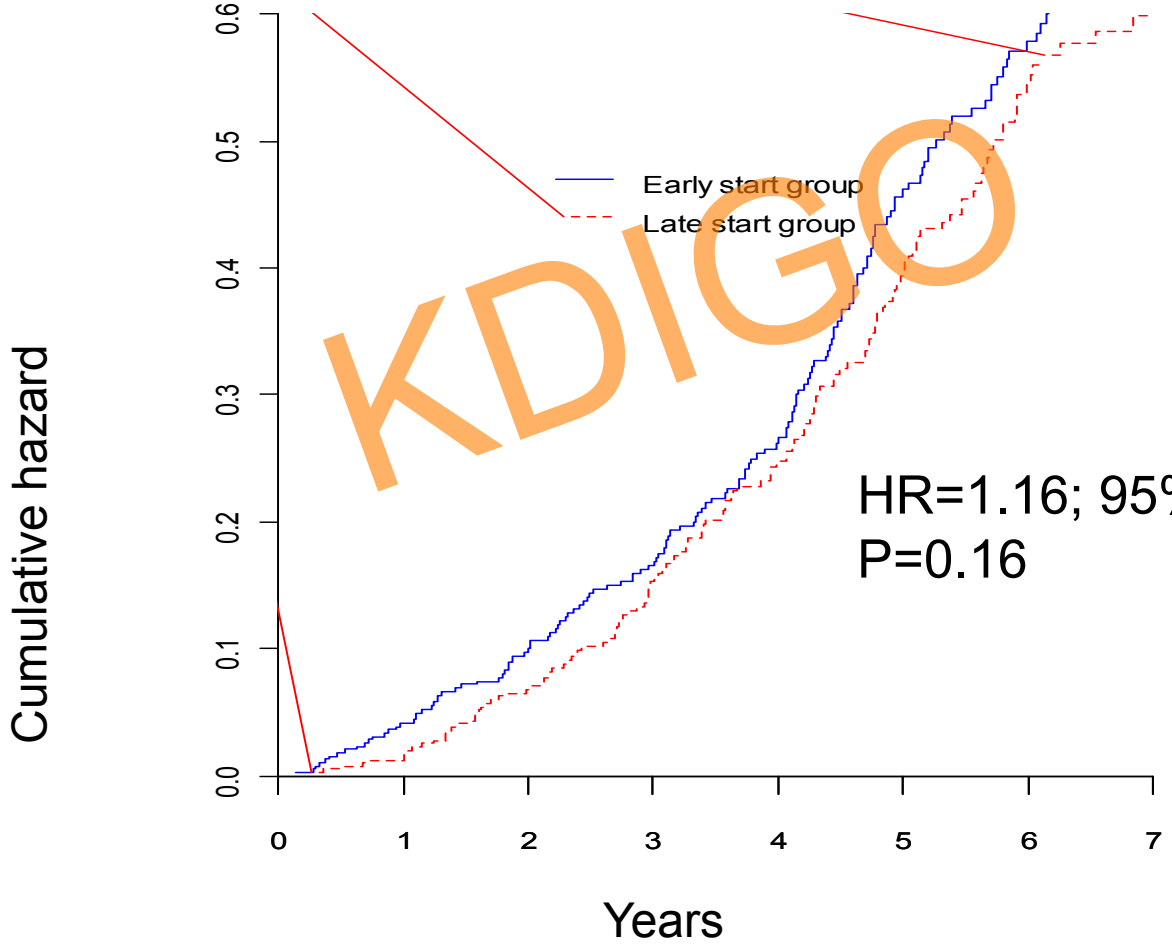
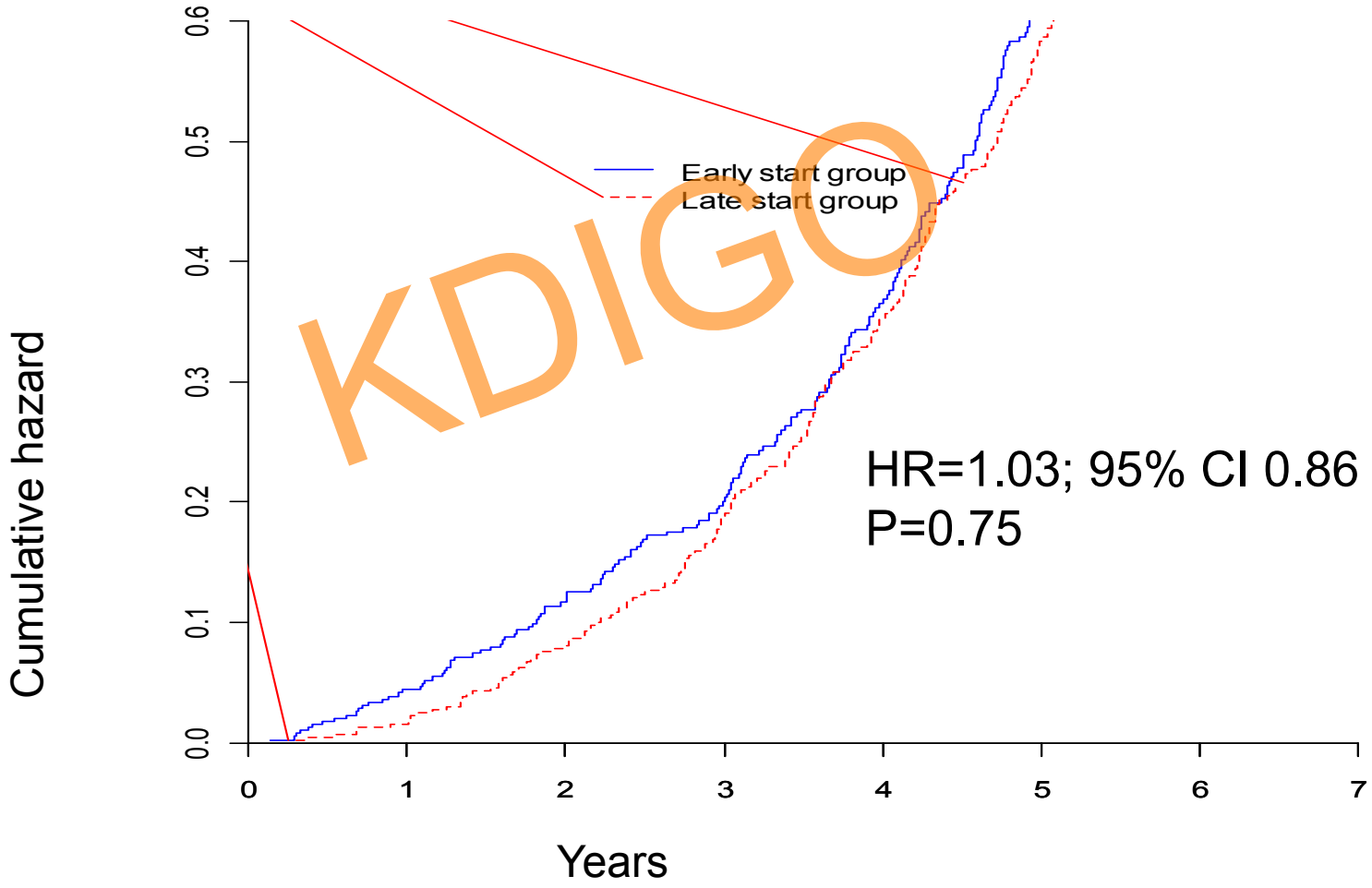
P=0.16

Patient Survival – Home dialysis



HR=1.16; 95% CI 0.93 to 1.46
P=0.16

Treatment Survival – Home dialysis



Temporary dialysis catheter usage in the IDEAL trial at the first dialysis treatment:

15 early-start patients (3.7%)

35 late-start patients (8.3%)

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(Don’t forget access creation!)

Conclusions: Intent-to-defer

Some patients will need close supervision:

- **diabetes**
- **ischaemic heart disease**
- **high risk racial groups**

Some patients should do well:

- **older**
- **few comorbidities**

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Is an age specific approach to dialysis initiation warranted?

Functional status, co-morbidity, frailty and falls risk, ability to self transfer

Co-morbidity – IHD, PVD, dementia, poor nutritional status

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"Would I be surprised if this person died in the next 12 months?"

Early referral important to gauge rate of decline and functional trajectory

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