CTRR
Centre for Transplant and Renal Research

The Westmead Institute FOR MEDICAL RESEARCH

University of Sydney

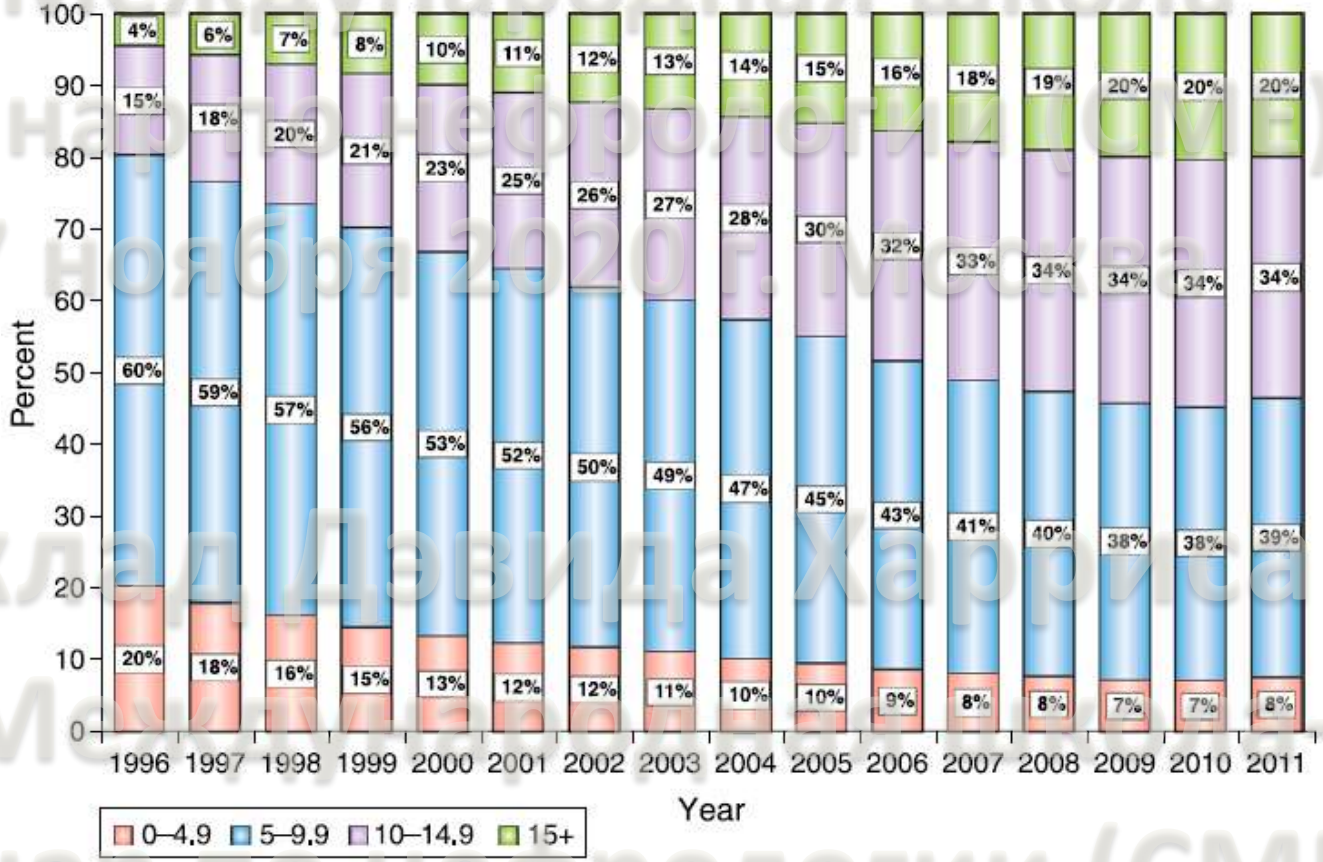
WHEN TO START DIALYSIS FOR PATIENTS WITH KIDNEY FAILURE (ESKD)

DAVID HARRIS

7/11/20

Westmead Hospital

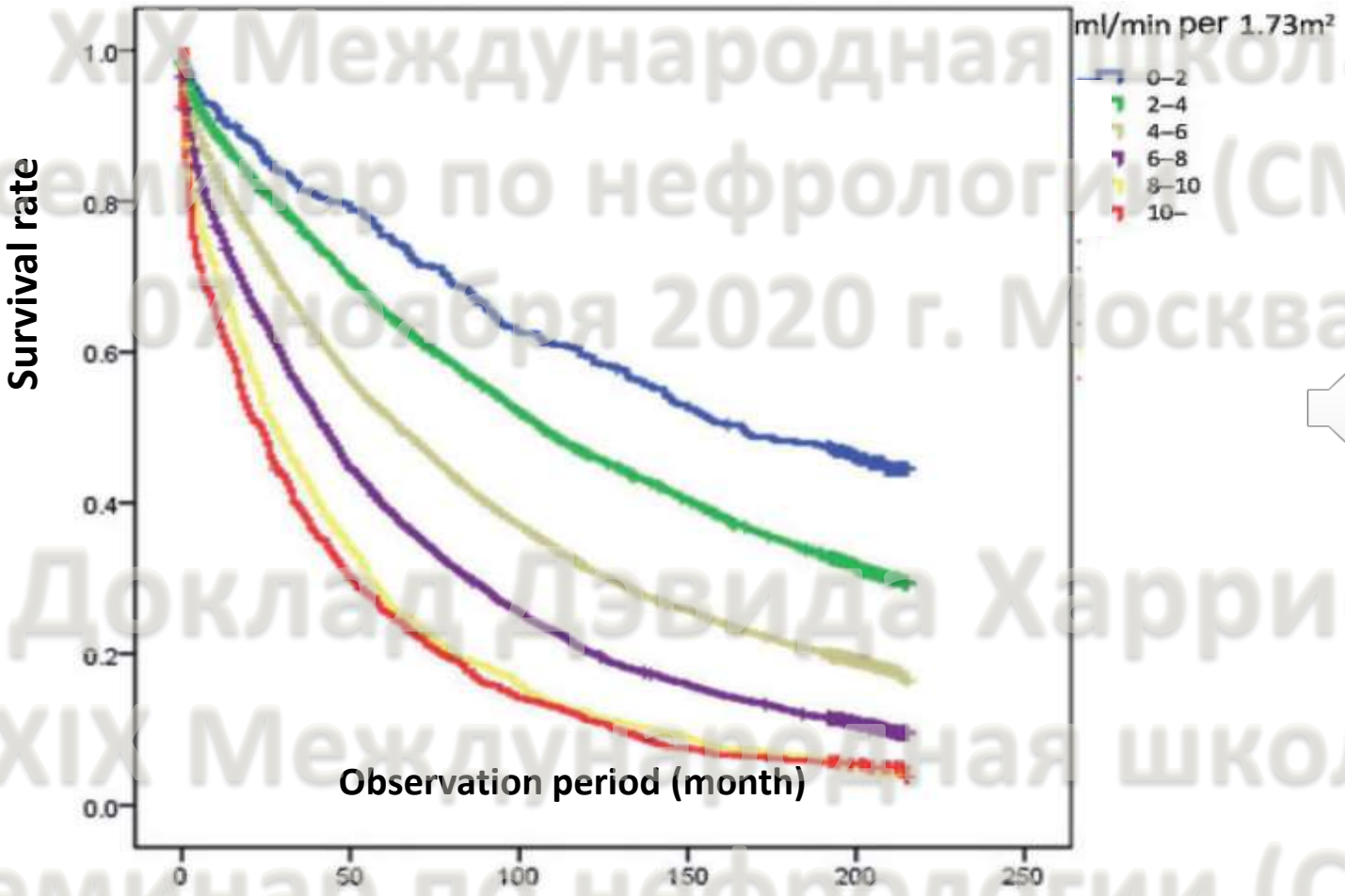
Rising tide of early start dialysis



All subgroups,
esp elderly

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

Japan



Also:

USA

Canada

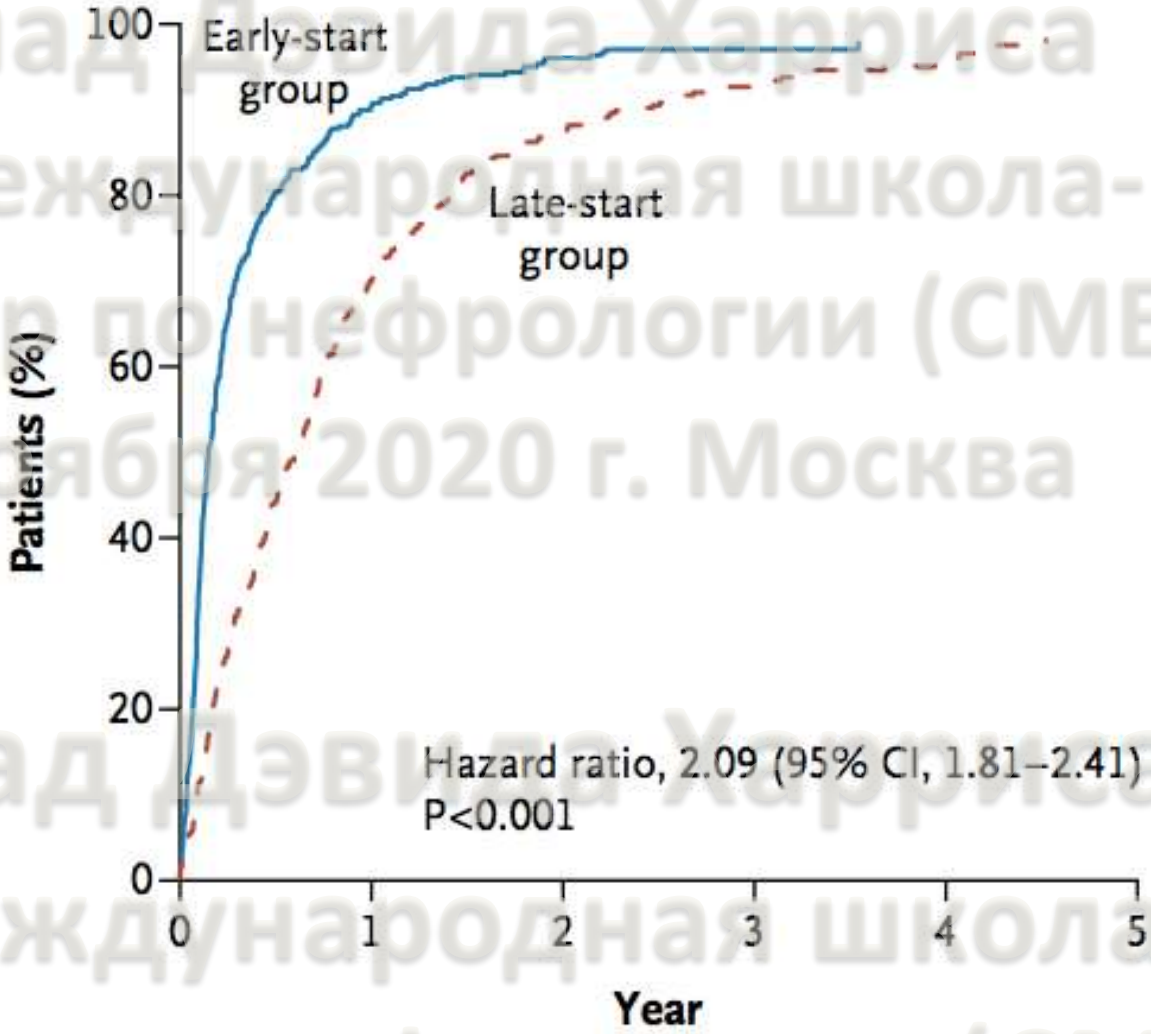
Scotland…

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

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

Time to Start of Dialysis

32 centres
828 participants
Median f/u 3.59 yrs



No. at Risk						
Early start	404	35	12	8	2	1
Late start	424	118	45	21	9	3

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

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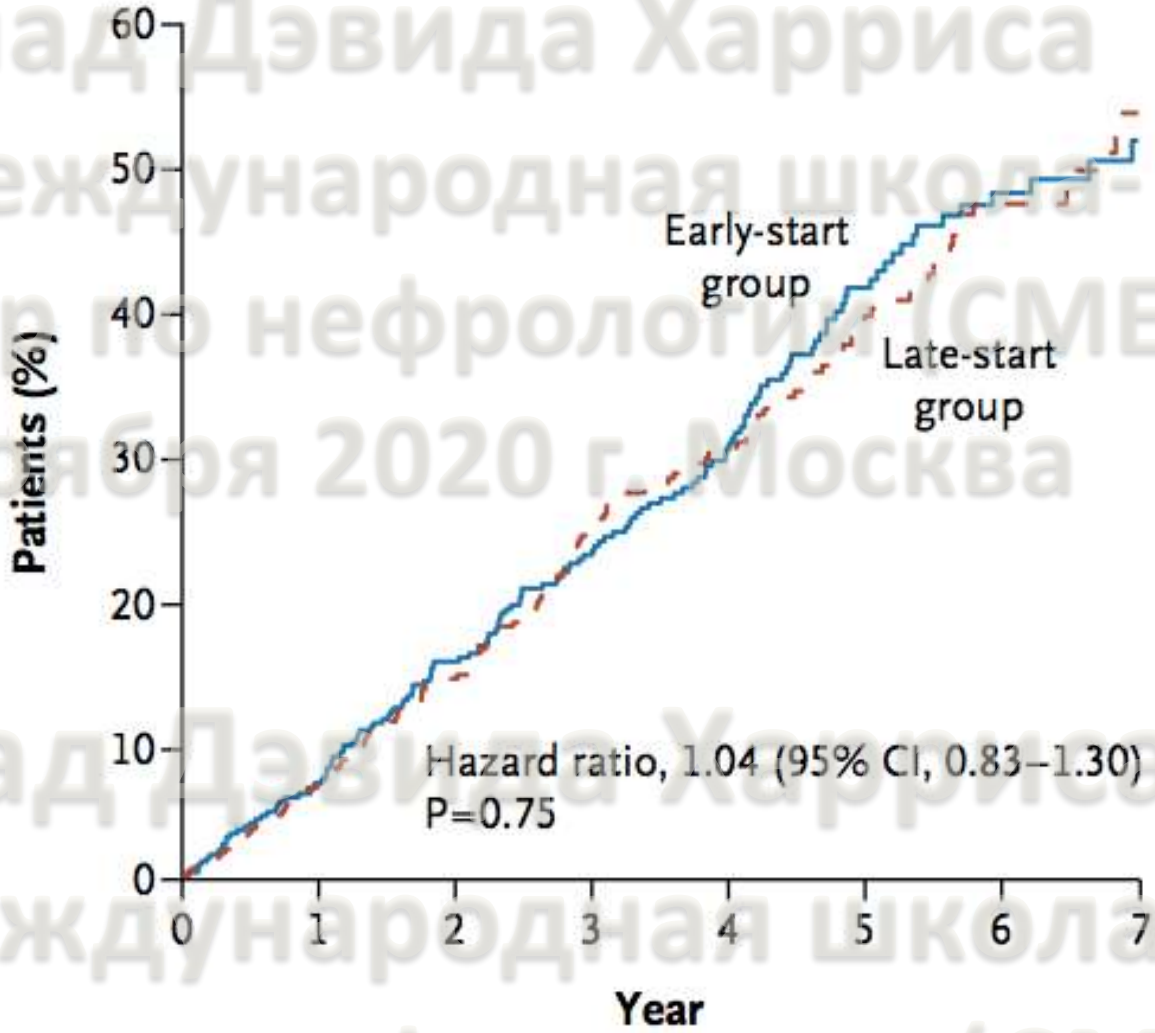
Initiating Dialysis Early & Late
An Australian and New Zealand Multicentre Nephrology Trial

Time to Death



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

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An Australian and New Zealand Multicentre Nephrology Trial

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

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

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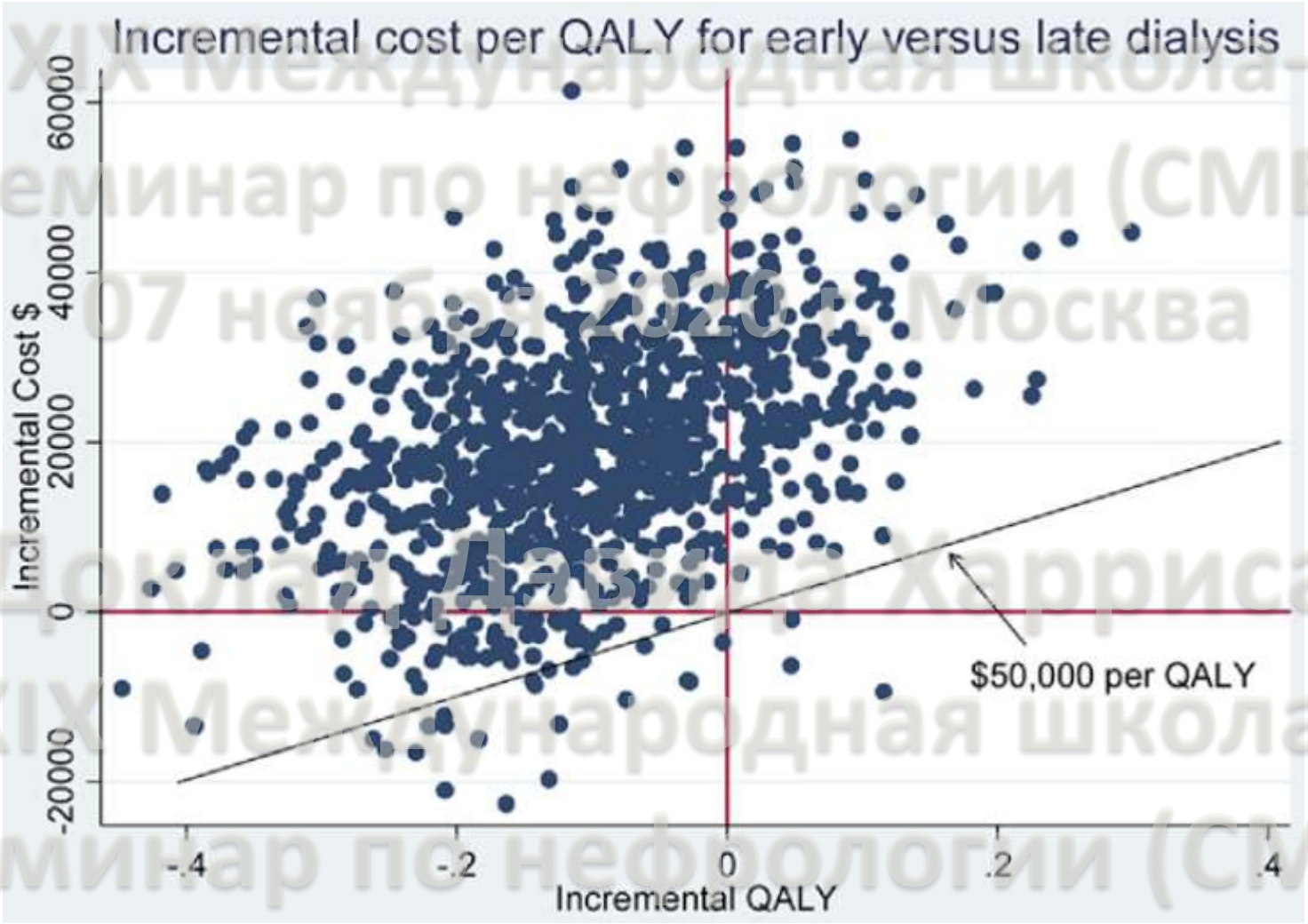
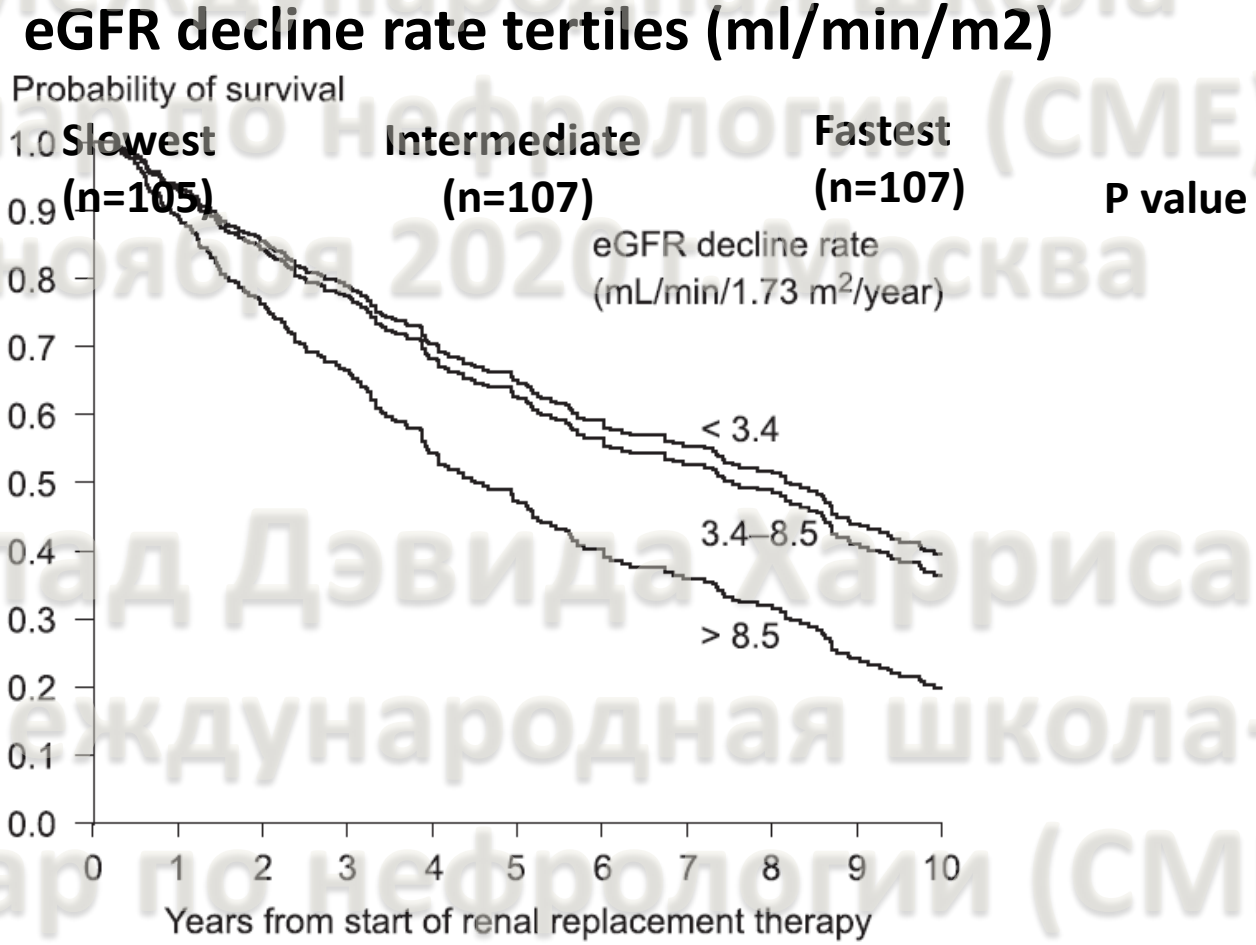
Bootstrap replicates of incremental cost per QALY



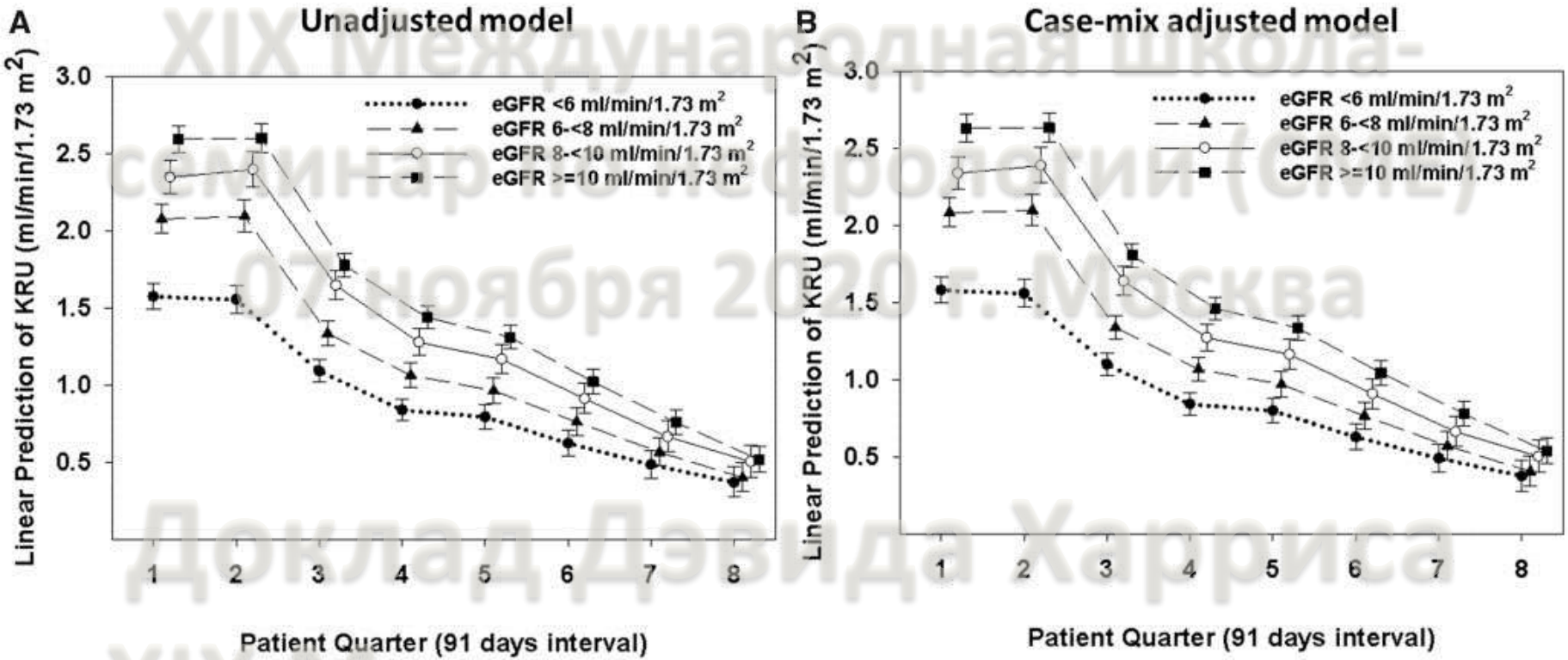
Harris A et al. Am J Kidney Dis 2011;57:707–15

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



Haapio et al. Nephrol Dial Transplant 2012

Decline of residual function



…and associated with higher mortality

Lertdumrongluk P et al. NDT 2020

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

Indications for early start dialysis

Stage 5 CKD +

- Refractory fluid overload
- Refractory hyperkalemia
- Refractory hypertension
- Pericarditis
- ‘Uraemic cachexia’

Not

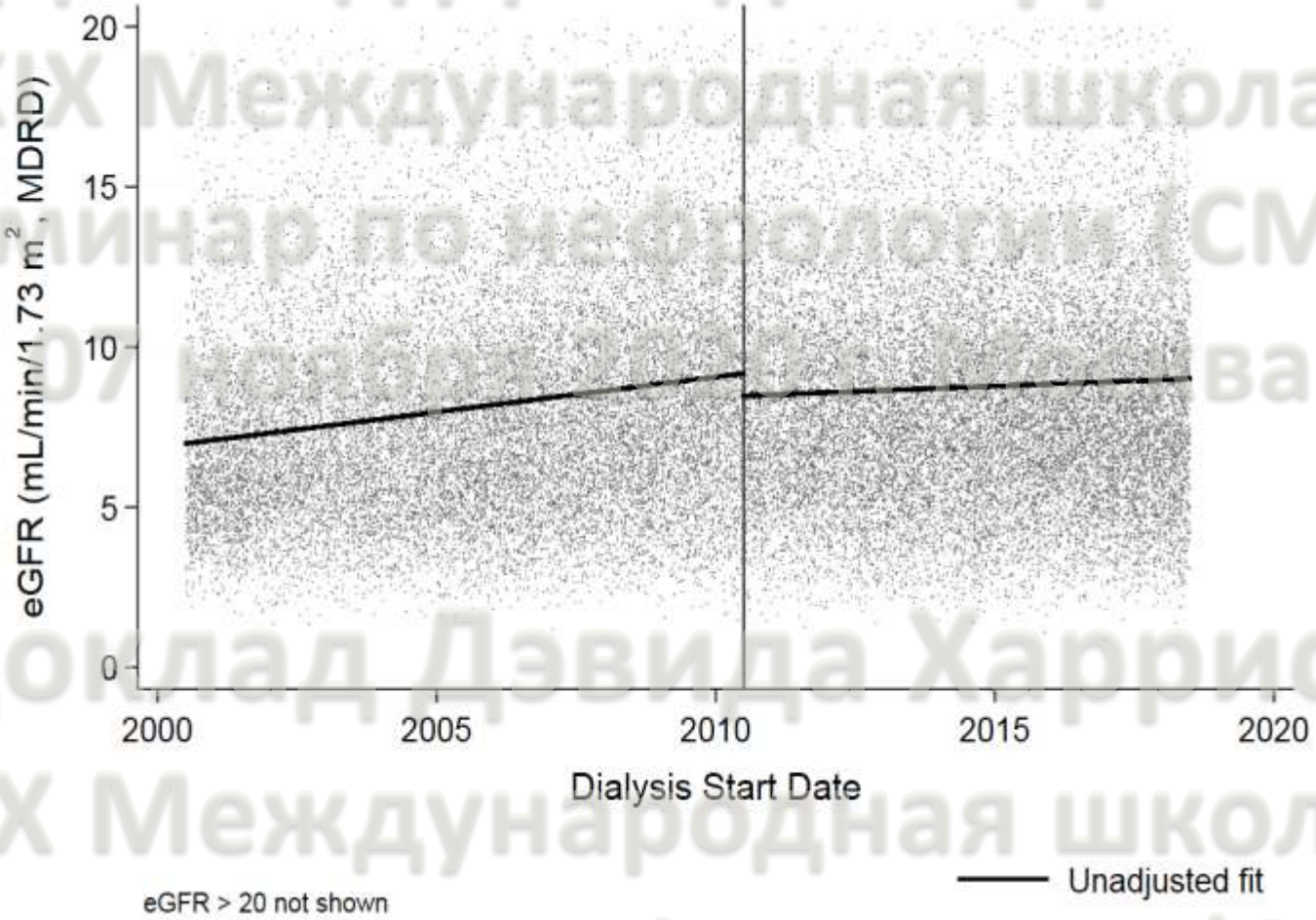
- GFR values
- Symptoms attributable to alternative disease
- Age or primary disease

Guidelines

2012

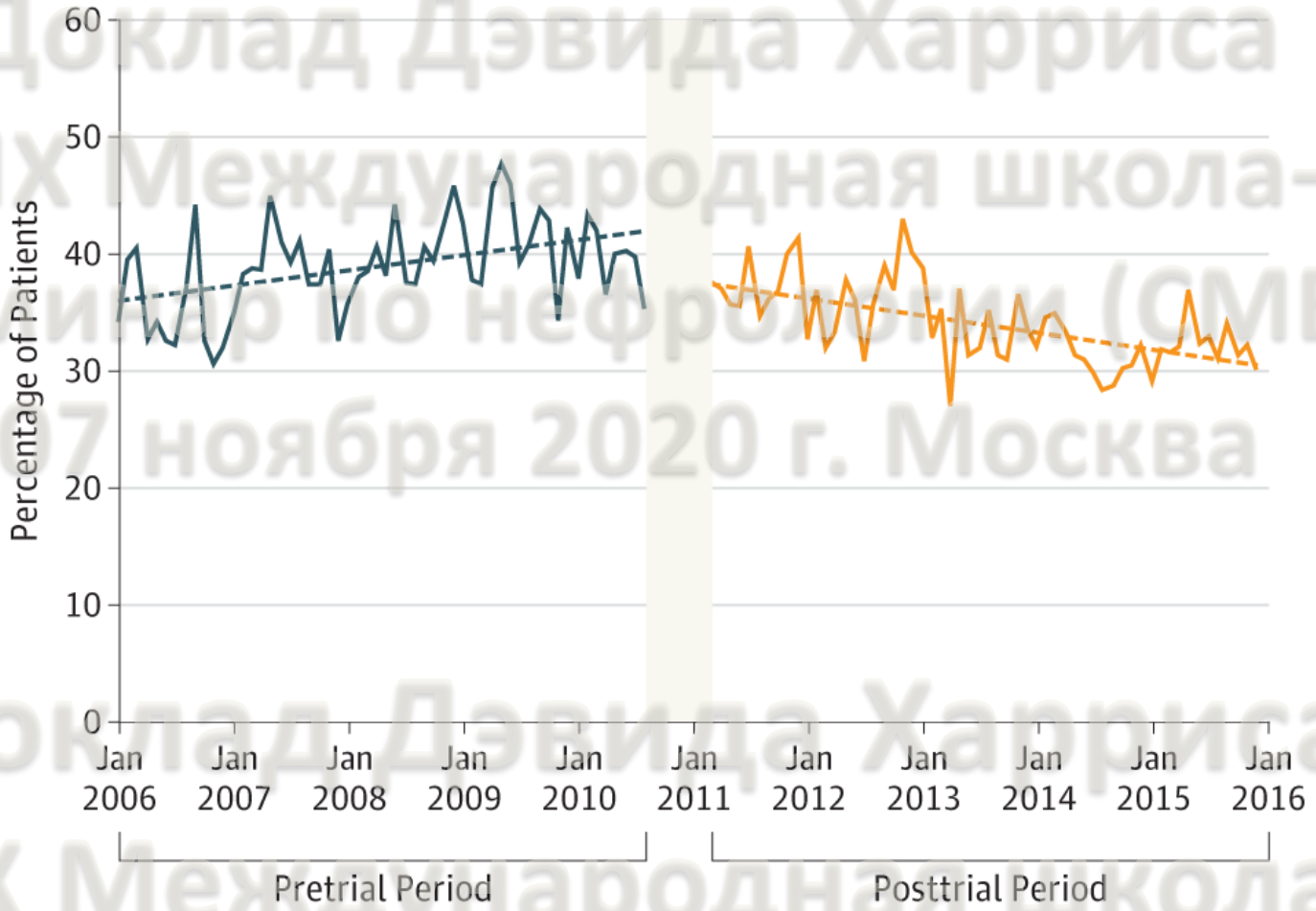
5.3: TIMING THE INITIATION OF RRT

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)



Доклад Дэвида Харриса
XIX Международная школа-семинар по нефрологии (CME)
07 ноября 2020 г. Москва

Dansie KB et al. 2020



Ferguson TW et al. JAMA Intern Med 2019:179:934-41

IDEAL
Initiating Dialysis
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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

Mortality higher:
older
female
diabetes
CV disease

CJASN 2014:9;135–142

Delaying dialysis start

Risks

?ability to train for home-based therapy
accumulation of comorbidities
delayed access creation

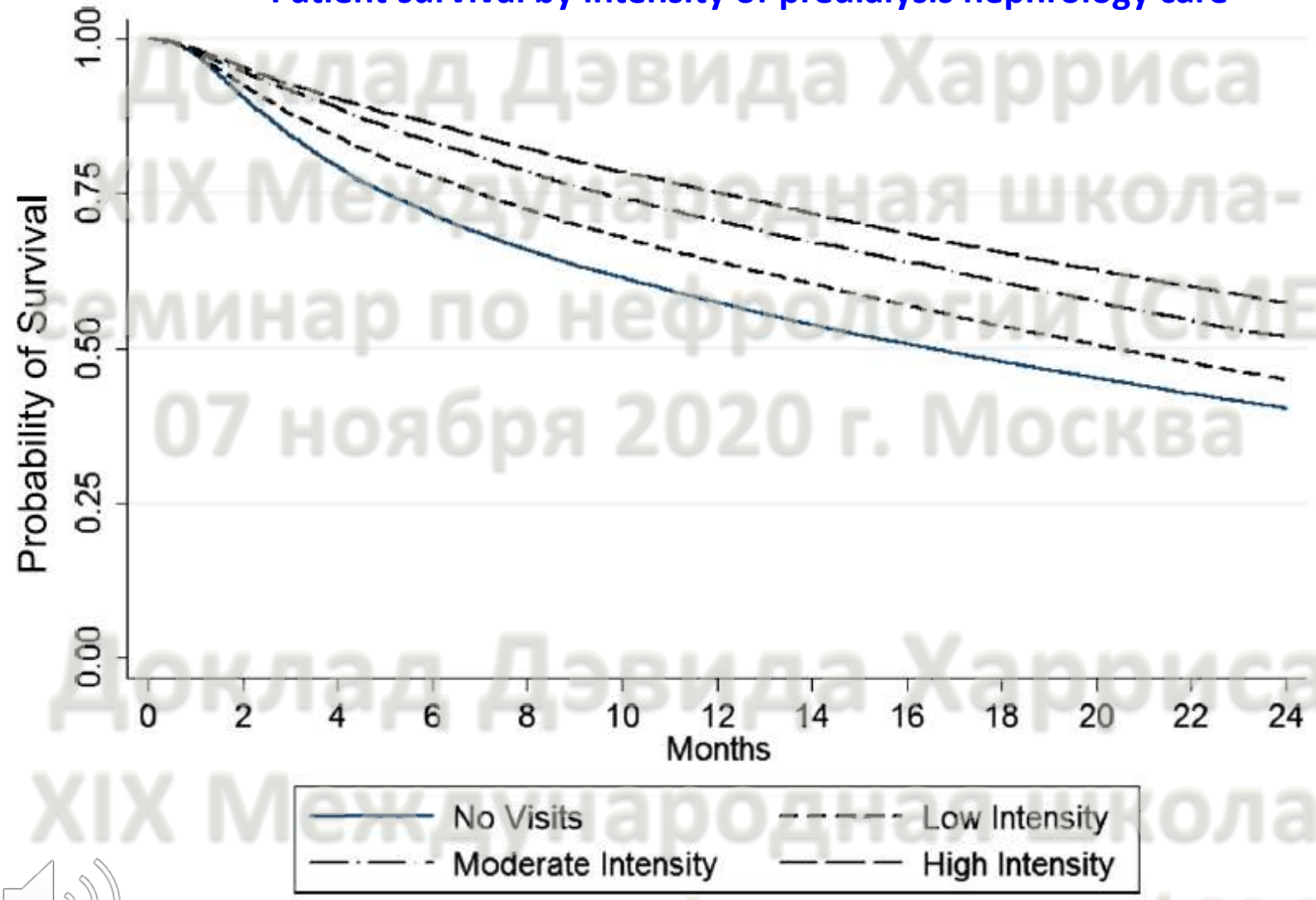
Need close supervision if

diabetes
ischaemic heart disease
high risk racial groups

Should do well if

older
few comorbidities

Patient survival by intensity of predialysis nephrology care



retrospective, >65y
N= 58,000 VA or MC
0, <3, 3-6, >6 visits in 12m

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

Vulnerable patient subgroups

Elderly

Comorbidities

Return from transplant

Pediatric

Pregnancy

KDIGO Controversies Conf. Kid Int 2019;96:37-47

Elderly & co-morbid

Older patients

progress slowly (≤ 3 ml/min/1.73m^2/year)

high mortality rates

high comorbidity –IHD, PVD, dementia, poor nutrition, frailty

die before needing dialysis (if no preemptive early start)

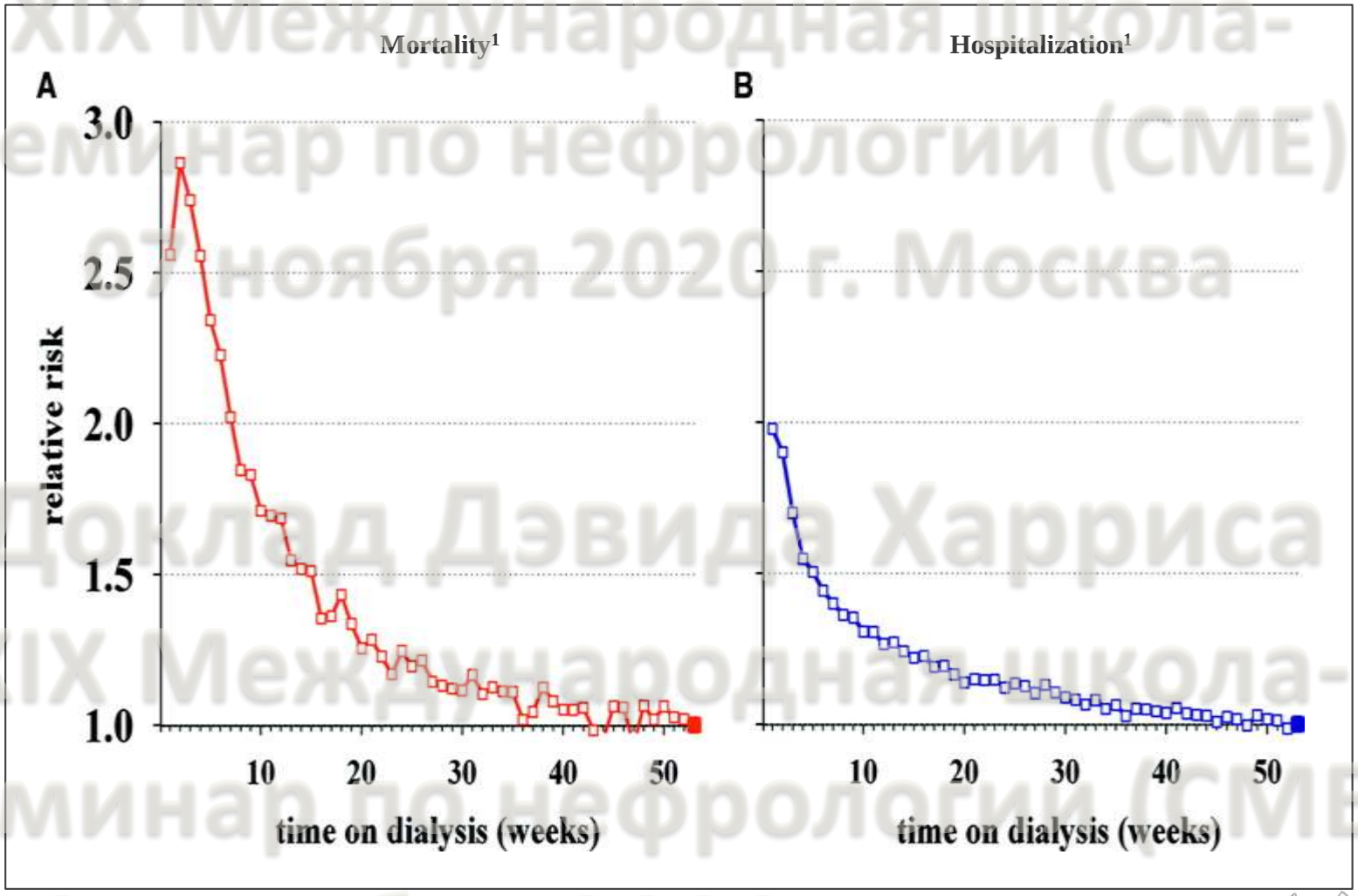
spend longer in hospital if on dialysis

may survive as long with CKM, esp. if co-morbid

early referral to gauge rate of decline & functional trajectory

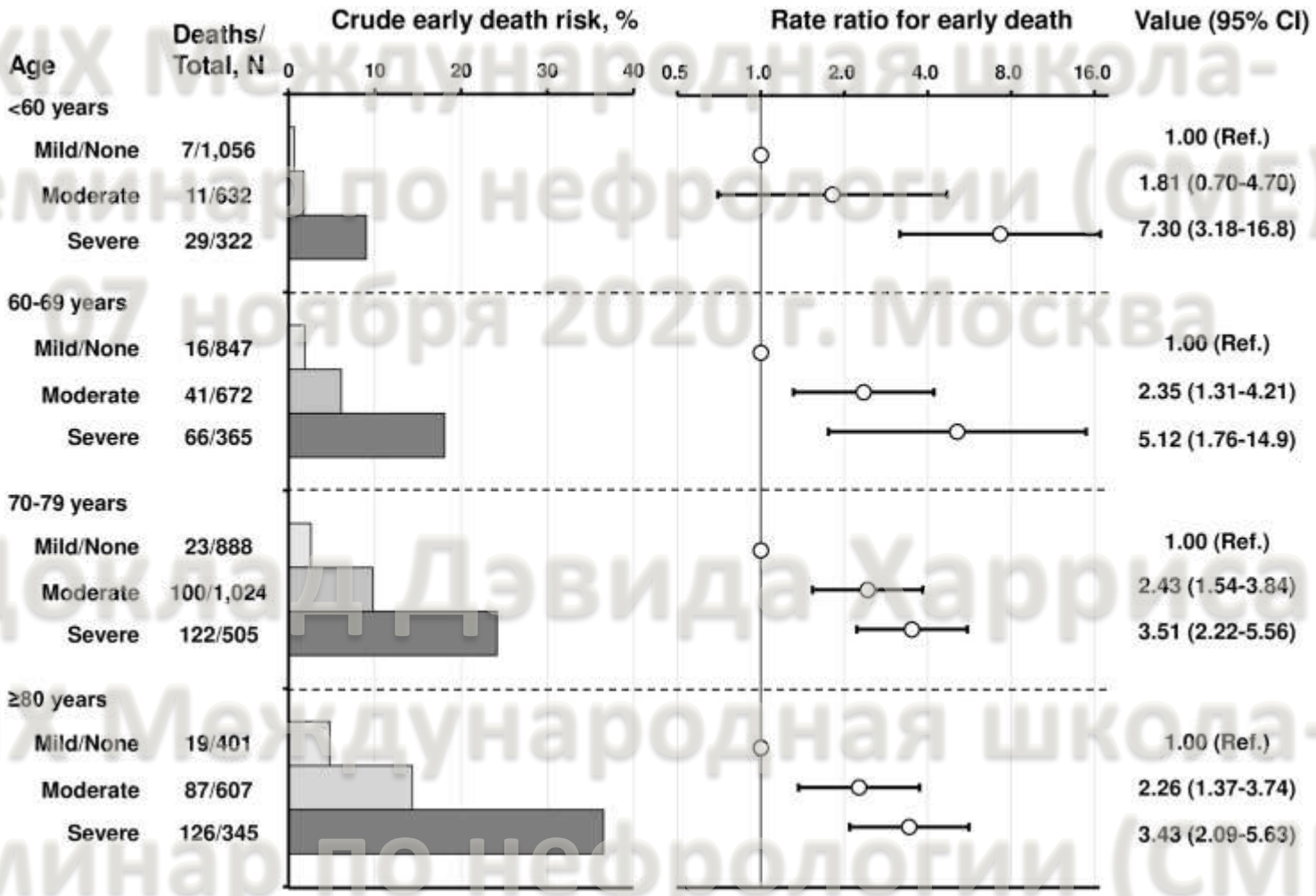
Period of Heightened Risk

The First 90 Days of Starting Dialysis



Chan KE et al. CJASN 2011;6:2642-2649

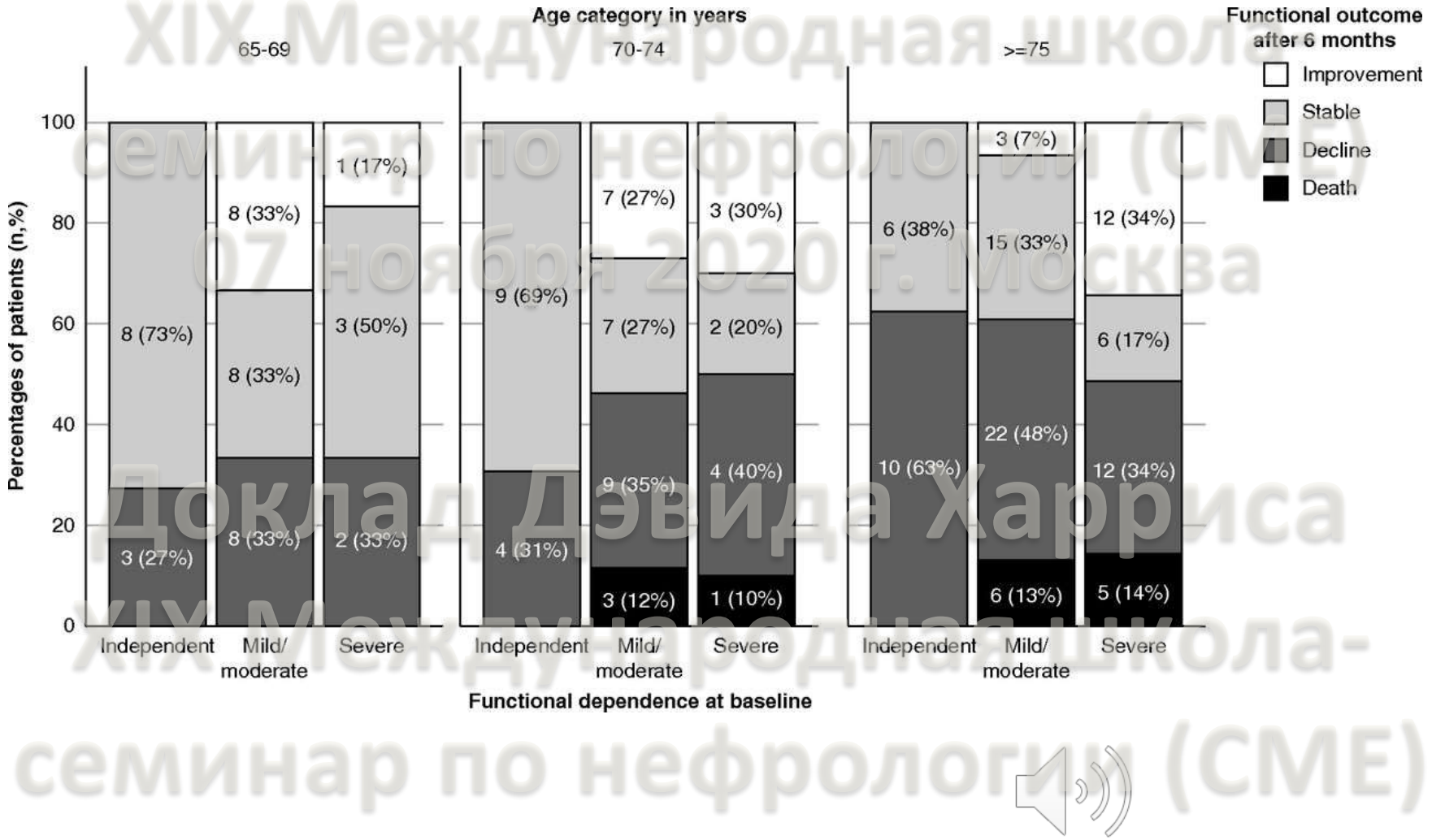
functional disability at start of HD



death within 3mon

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

Change in functional status over 6 months from dialysis initiation according to baseline age and functional dependence.



Goto NA et al. CJASN 2019;14:1039-1047

Return From Transplant Failure

Increasing numbers: % 4-5% in US; 2-3% in Canada & Australia

High eGFR levels at re-start ?→worse outcome

inconsistent

confounded by acute indications for dialysis (e.g. AKI) & increased comorbidity

Decline in eGFR may be slower in failing kidney transplants than in native CKD

Transplant nephrologists may be so focused on keeping the graft working that they miss preparation for approaching ESKD

eGFR at Dialysis Initiation for Graft Failure

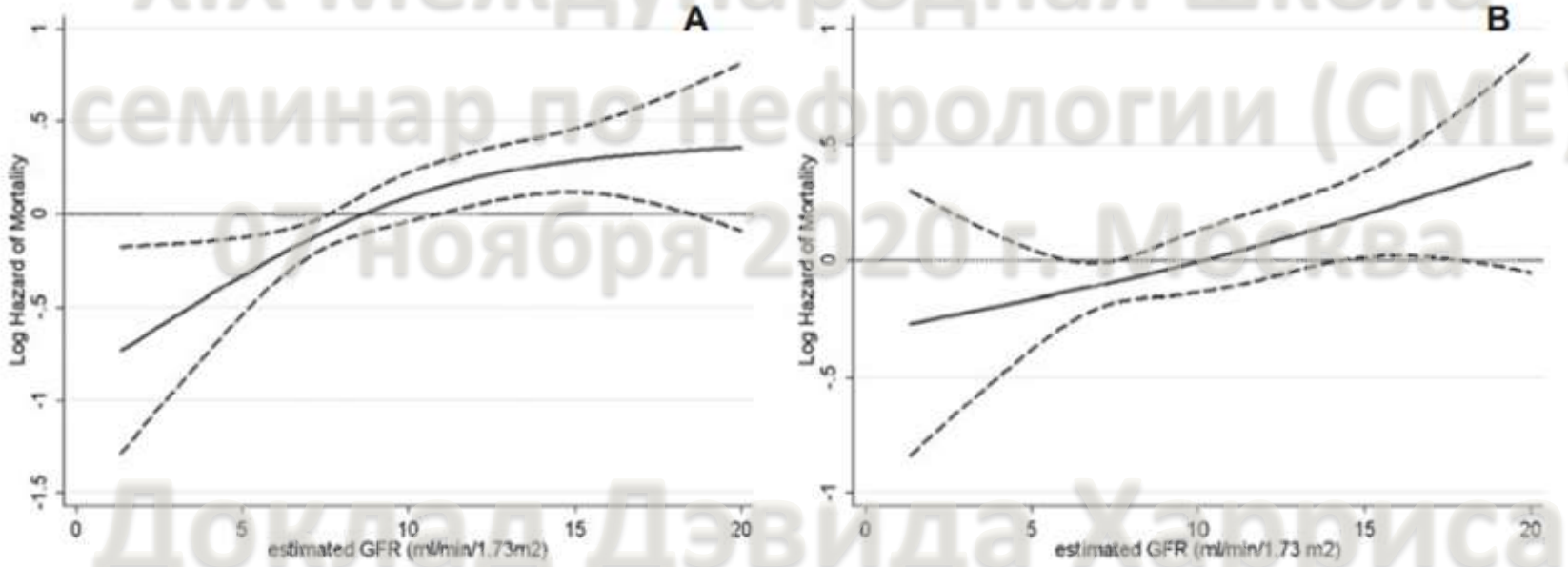
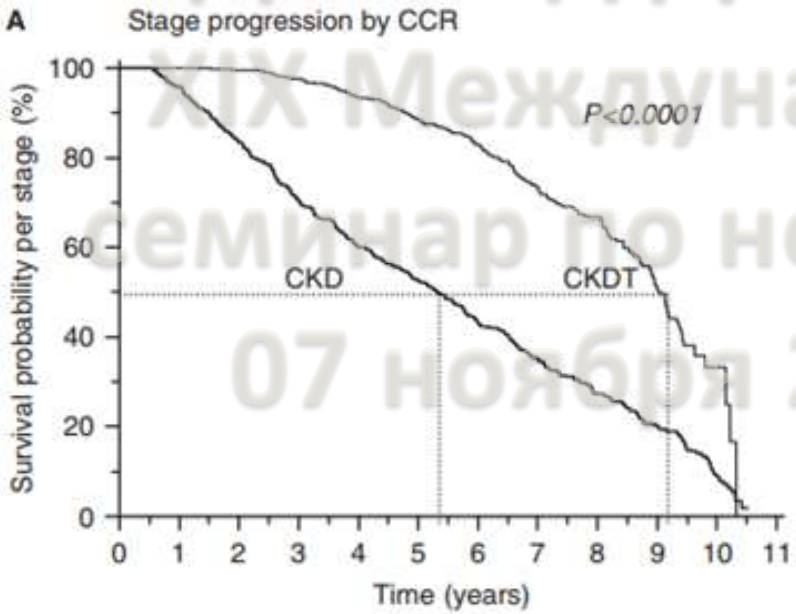
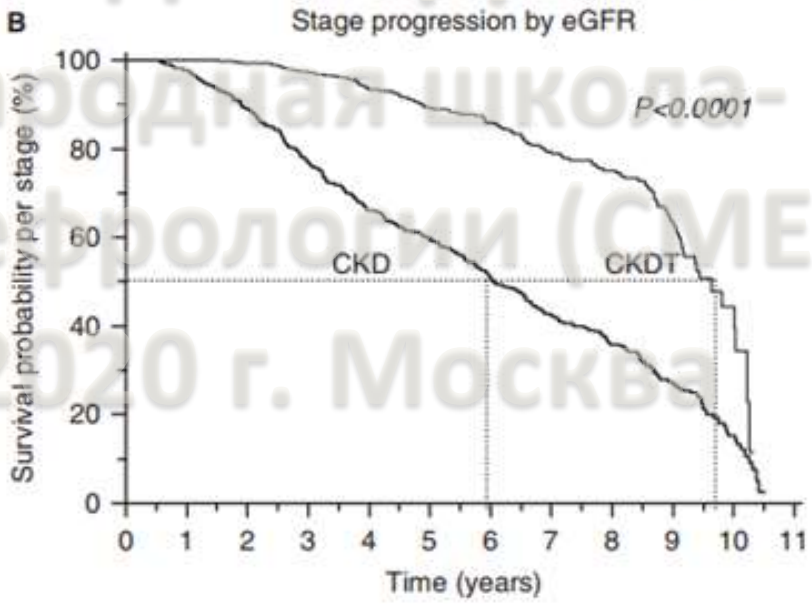


Fig 2. Hazard ratio (95% CIs) of death across the entire range (0–20 ml/min) of the eGFR level using unadjusted (A) and fully adjusted* (B) Cox regression analyses in 854 long-term failed transplant patients who restarted HD therapy*adjusted for: age, gender, diabetes, serum albumin, body mass index, and presence atherosclerotic heart disease.

Molnar et al. Sem Dial 2013





C

Stage ½ lives according to baseline CCR or eGFR

	CKD	CKD-T	P	HR	95% CI
Stage ½ life based on CCR (years)	5.4	9	<0.0001	2.9	2.4–3.4
Stage ½ life based on eGFR (years)	6	9.6	<0.0001	3.1	2.5–3.7

Fig. 1. Figure 1 displays the overall stage-to-stage progression rates according to baseline CCR and eGFR (CCR1 and eGFR1, respectively, panels **A** and **B**). Panel (**C**) shows kidney half-lives according to CCR1 and eGFR1. Briefly, the median time for 50% of kidney allografts to progress from one stage to the next was 9 years, compared to 5.4 years in the CKD group when kidney function was evaluated by CCR. Kidney half-lives were still significantly different between the two groups, when we used the MDRD eGFR estimation formula. In fact, half-lives were increased by an average of 7.2 months when eGFR was used compared to CCR. Best fit polynomial curve analyses revealed that the slopes were not parallel (data not shown).

Kukla A et al. NDT, 2008

Pediatric

Uncertainty about benefits of early vs late start

More likely to progress to ESKD than die, vs adults

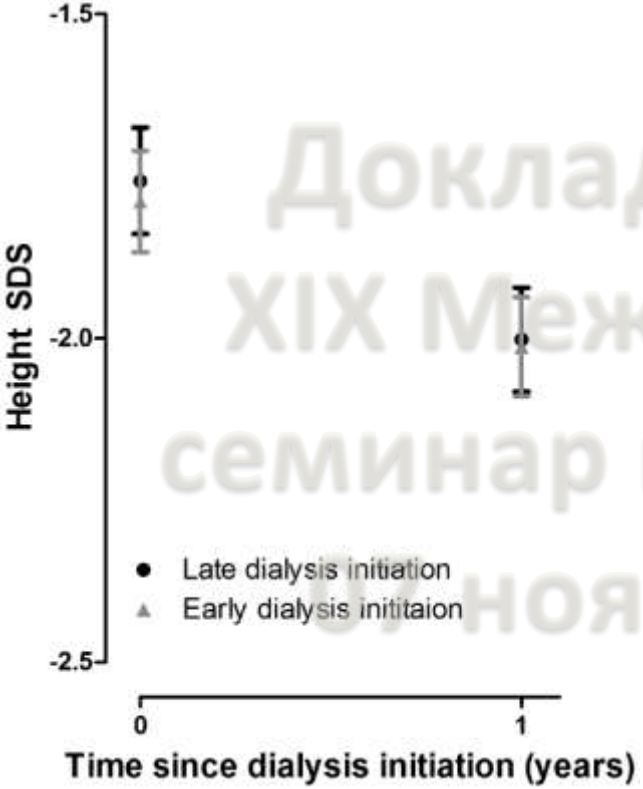
CKD progression slower with CAKUT

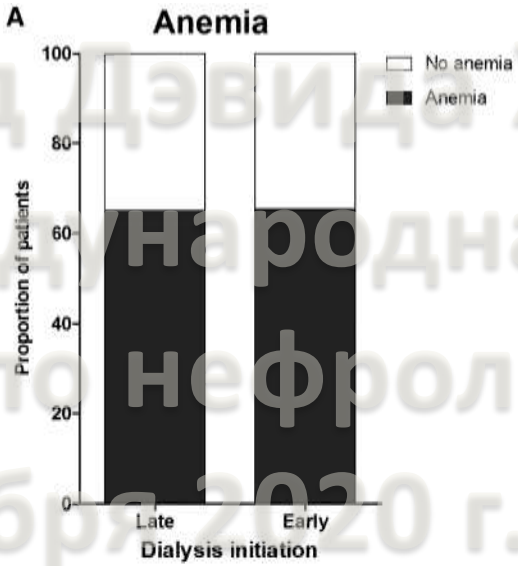
Complexity increased by growth, nutrition & cognitive/emotional maturation

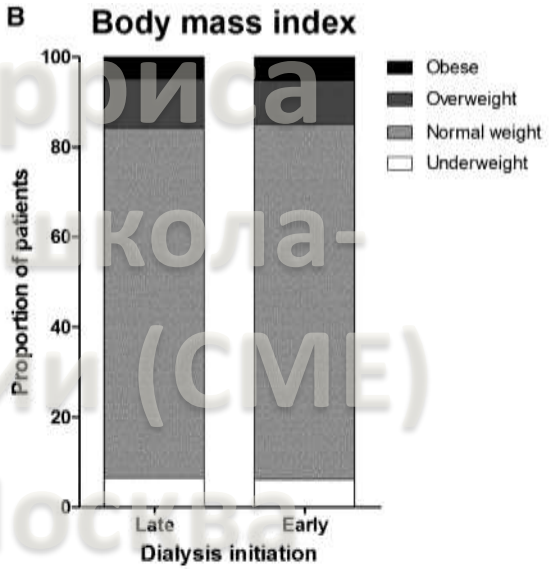
Think Twice before Postponing Chronic Dialysis in Children

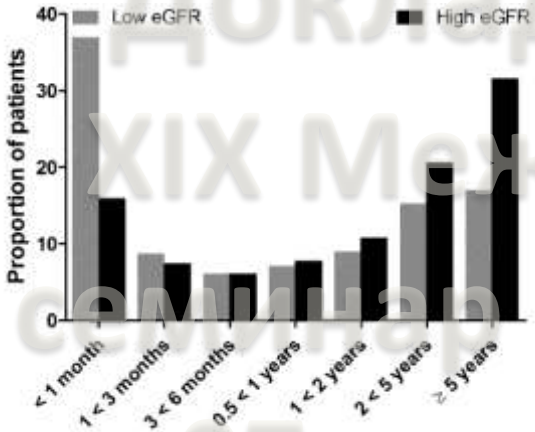
…. *“until a RCT is conducted in children.”*

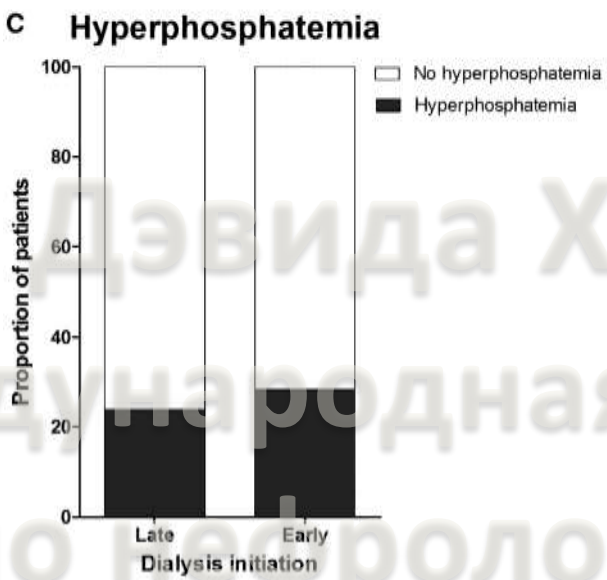
(Preka E et al. JASN 2019;30:2473-4)

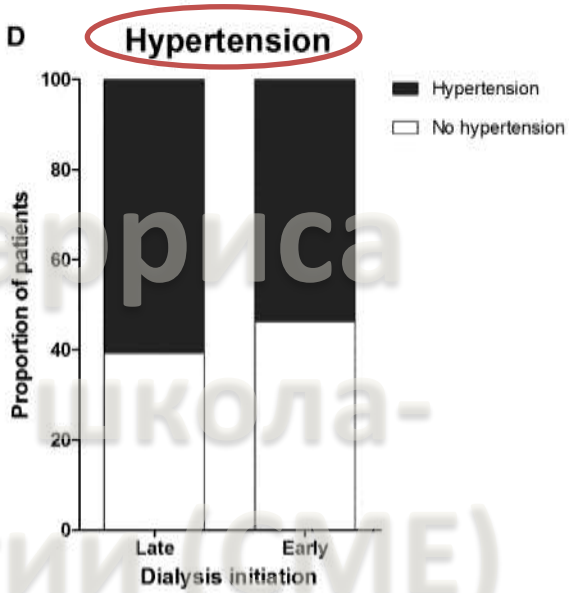












Preka E et al. NDT 2019;34:1932-40
children, n=2963

Pregnant

Effect of pregnant physiology on CKD

Maternal & foetal/neonatal outcomes

Indications to start dialysis:

eGFR (BUN<18mmol/L), + metabolic, fluid, electrolyte

Rivara MB & Mehrotra R. Sem Nephrol 2017;37:181–193

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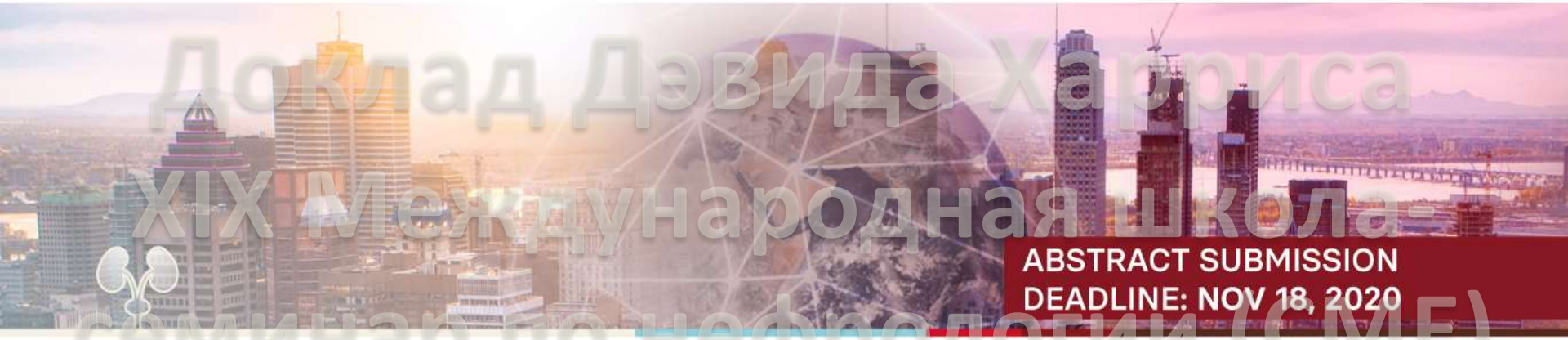

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