CTRR
Centre for Transplant and Renal Research

The Westmead Institute FOR MEDICAL RESEARCH

University of Sydney

What is new in CKD treatment?

DAVID HARRIS

7/11/20

Westmead Hospital

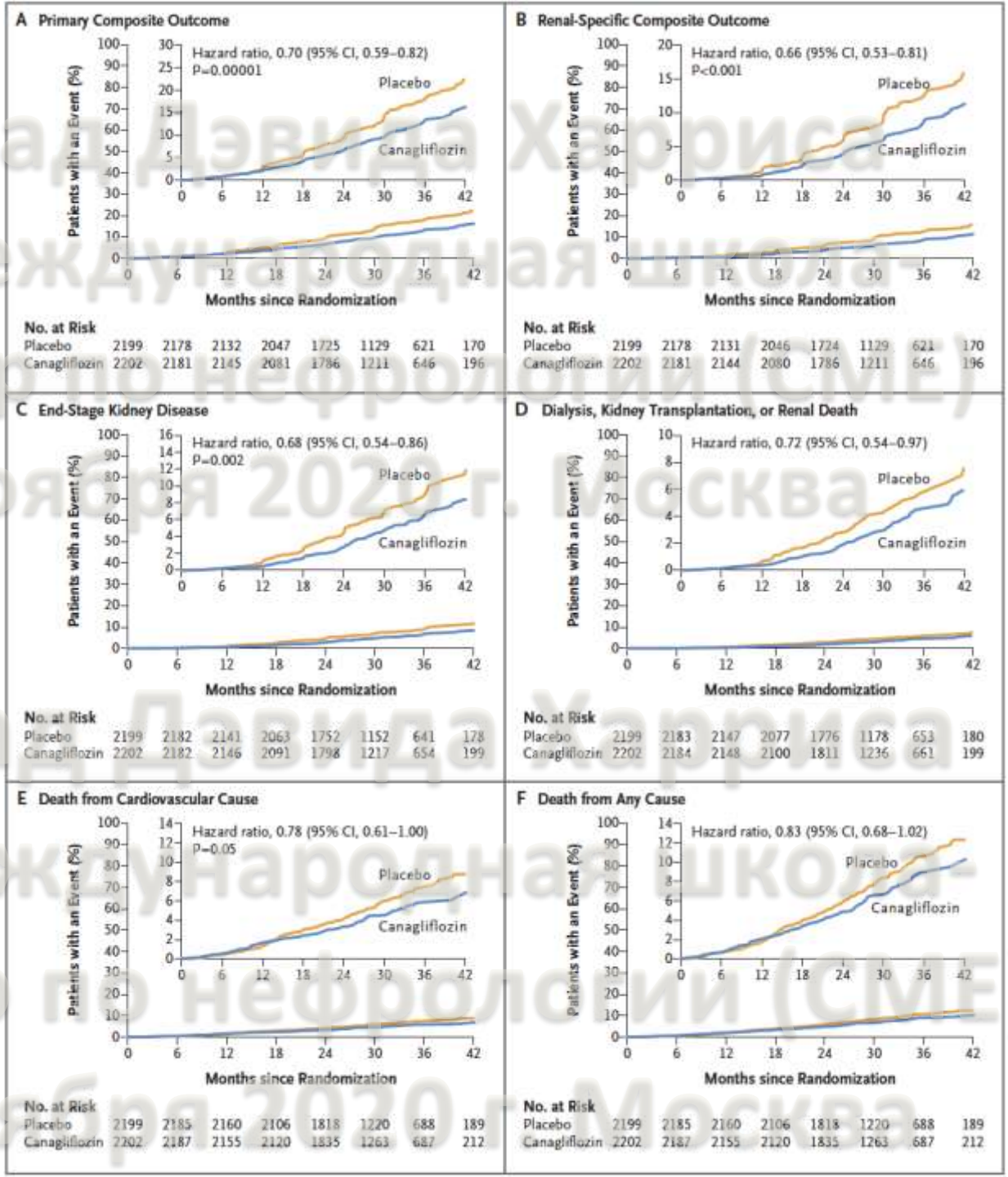
Post-ACEi doldrums….

Treat to help slow decline in kidney function and reduce hypertension risk*

- Lifestyle changes
  - Smoking cessation
  - Dietary salt restriction
  - Moderate alcohol consumption
  - Maintain BMI between 18.5 and 24.9 kg/m^2 through diet and exercise
  - Avoid more than two caffeinated drinks per day
- Blood pressure: assess and maintain blood pressure <130/80 mmHg with ACE inhibitor or ARB
- Cholesterol: maintain total cholesterol level <4.0 mmol/L with diet and statin
- Blood glucose (for patients with concurrent diabetes): aim for HbA_{1c} <7.0%
- Avoid nephrotoxic drugs and episodes of acute kidney injury

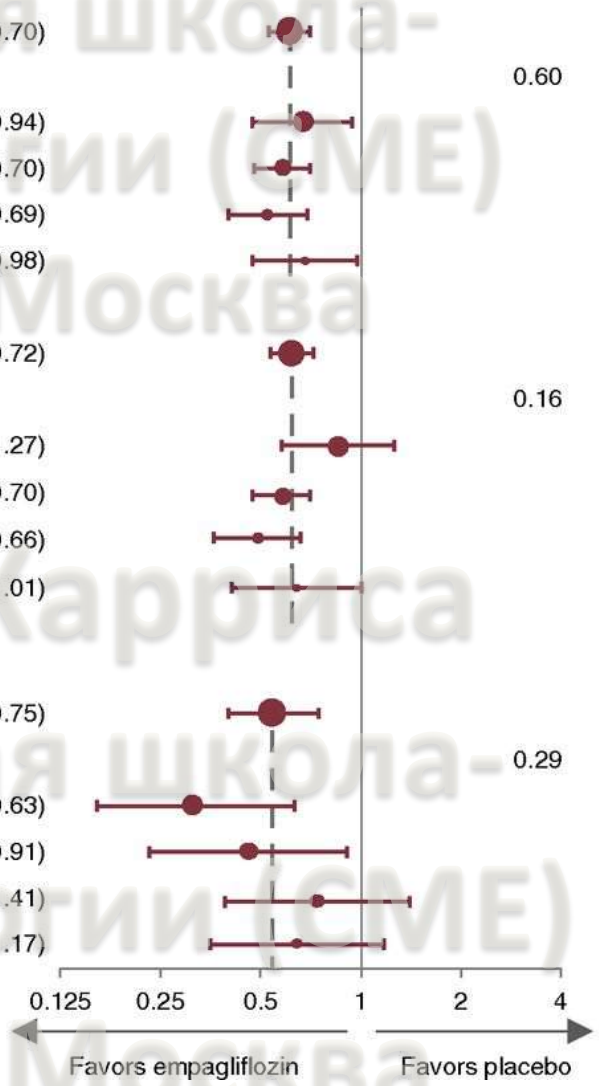
Cadnapaphornchai CJASN 2014;9:889

CREDENCE
NEJM 2019



Forest plot showing that the risk reduction of kidney outcomes with empagliflozin versus placebo is consistent across KDIGO risk categories.

	Empagliflozin	Placebo	Hazard ratio (95% CI)	Hazard ratio (95% CI)	*P*-value for interaction
	n with event/*N* analyzed (%)				
Incident or worsening nephropathy					
All patients	525/4124 (12.7)	388/2061 (18.8)	0.61 (0.53, 0.70)		
KDIGO risk categories*					0.60
Low risk	78/2180 (3.6)	56/1086 (5.2)	0.67 (0.47, 0.94)		
Moderately increased risk	254/1323 (19.2)	187/655 (28.5)	0.58 (0.48, 0.70)		
High risk	117/430 (27.2)	89/219 (40.6)	0.52 (0.40, 0.69)		
Very high risk	66/148 (44.6)	52/88 (59.1)	0.68 (0.47, 0.98)		
Progression to macroalbuminuria					
All patients	459/4091 (11.2)	330/2033 (16.2)	0.62 (0.54, 0.72)		
KDIGO risk categories*					0.16
Low risk	69/2180 (3.2)	39/1086 (3.6)	0.86 (0.58, 1.27)		
Moderately increased risk	244/1323 (18.4)	179/655 (27.3)	0.58 (0.47, 0.70)		
High risk	94/415 (22.7)	75/209 (35.9)	0.49 (0.36, 0.66)		
Very high risk	45/130 (34.6)	33/70 (47.1)	0.64 (0.41, 1.01)		
Doubling of serum creatinine,† initiation of kidney replacement therapy, or death from kidney					
All patients	81/4645 (1.7)	71/2323 (3.1)	0.54 (0.40, 0.75)		
KDIGO risk categories*					0.29
Low risk	13/2205 (0.6)	20/1094 (1.8)	0.31 (0.16, 0.63)		
Moderately increased risk	16/1334 (1.2)	17/671 (2.5)	0.46 (0.23, 0.91)		
High risk	25/704 (3.6)	15/356 (4.2)	0.74 (0.39, 1.41)		
Very high risk	24/352 (6.8)	19/186 (10.2)	0.64 (0.35, 1.17)		



Levin A et al. CJASN 2020
doi:10.2215/CJN.14901219

Primary Outcome According to Prespecified Subgroups at Baseline

Subgroup	Dapagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of participants/total no.		
All participants	197/2152	312/2152	0.61 (0.51–0.72)
Age			
≤65 yr	122/1247	191/1239	0.64 (0.51–0.80)
>65 yr	75/905	121/913	0.58 (0.43–0.77)
Sex			
Male	126/1443	209/1436	0.57 (0.46–0.72)
Female	71/709	103/716	0.65 (0.48–0.88)
Race			
White	110/1124	174/1166	0.62 (0.49–0.79)
Black	7/104	14/87	0.33 (0.13–0.81)
Asian	53/749	77/718	0.66 (0.46–0.93)
Other	27/175	47/181	0.54 (0.33–0.86)
Geographic region			
Asia	50/692	69/654	0.70 (0.48–1.00)
Europe	57/610	89/623	0.60 (0.43–0.85)
North America	35/401	69/412	0.51 (0.34–0.76)
Latin America	55/449	85/463	0.61 (0.43–0.86)
Type 2 diabetes			
Yes	152/1455	229/1451	0.64 (0.52–0.79)
No	45/697	83/701	0.50 (0.35–0.72)
Estimated GFR			
<45 ml/min/1.73 m²	152/1272	217/1250	0.63 (0.51–0.78)
≥45 ml/min/1.73 m²	45/880	95/902	0.49 (0.34–0.69)
Urinary albumin-to-creatinine ratio			
≤1000	44/1104	84/1121	0.54 (0.37–0.77)
>1000	153/1048	228/1031	0.62 (0.50–0.76)
Systolic blood pressure			
≤130 mm Hg	46/793	96/749	0.44 (0.31–0.63)
>130 mm Hg	151/1359	216/1403	0.68 (0.56–0.84)

HJ Heerspink et al. N Engl J Med 2020. DOI: 10.1056/NEJMoa2024816

Ongoing renal and cardiovascular outcome trials in Type 2 Diabetes

Trial Name	Treatment	Number of participants	Primary Outcome	Planned completion date
VERTIS CV	Ertugliflozin	8000	Cardiovascular	2019
Dapa HF	Dapagliflozin	4744	Heart Failure	2019
FIDELIO-DKD	Finerinone	5734	**Renal**	2020
Dapa_CKD	Dapagliflozin	4000	**Renal**	2020
EMPOROR	Empagliflozin	8850	Heart Failure	2020
DELIVER	Dapagliflozin	4700	Heart Failure	2021
FIGARO	Finerinone	7437	Cardiovascular	2021
SCORED	Sotagliflozin	10,500	Cardiovascular	2022
EMPA-Kidney	Empagliflozin	5000	**Renal**	2022
SOUL	Semaglutide	9642	Cardiovascular	2024
FLOW	Semaglutide	3160	**Renal**	2024

Perkovic V. ASN Kidney News 2019

MECHANISMS (not just lowering BSL)

SGLT2i: decr hyperfiltration (+ TGF), decr "tubular stress", natriuresis, lower BP

GLP-1ra: anti-oxidant, anti-inflammation, anti-fibrotic

INDICATIONS (DM2)

First-line: metformin + lifestyle

Second-line: + GLP-1ra or SGLT2i if CV disease

+ SGLT2i if CHF

RENOPROTECTION

SGLT2i: 30% ESKD RR (with/without RASi)

DPP4i: some reduction in albuminuria

GLP-1ra: some reports

CV-PROTECTION

SGLT2i >metformin, GLP-1ra, DPP4i

PRECAUTIONS/ADVERSE EVENTS

Contraindicated if eGFR<30: metformin, SGLT2i

Adjust dose if eGFR <30: DPP4i (except linagliptin)

No hypoglycaemia or incr BWt (unlike insulin, sulphonylureas, thiazolodinediones)

IMPLEMENTATION FAILURE

Recommendations for SGLT2i vs GLP-1 RA on the basis of kidney failure risk stratification

eGFR	UACR <30 mg/g	UACR 30–299 mg/g	UACR ≥300 mg/g
>60 ml/min per 1.73 m²	SGLT2i or GLP-1 RA[a]	SGLT2i is preferred. GLP-1 RA as an alternative if SGLT2i is contraindicated or not tolerated, and as an add-on for uncontrolled metabolic risk[b]	SGLT2i should be initiated. GLP-1 RA as an add-on for uncontrolled metabolic risk[c]
30–60 ml/min per 1.73 m²	SGLT2i is preferred. GLP-1 RA as an alternative if SGLT2i is contraindicated or not tolerated, and as an add-on for uncontrolled metabolic risk[b]		SGLT2i should be initiated. GLP-1 RA as an add-on for uncontrolled metabolic risk[c]
15–29 ml/min per 1.73 m²	GLP-1 RA (dulaglutide) is preferred. Initiation of SGLT2i is currently contraindicated[d]		

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

Li J et al. CJASN 2020;15

SGLT2i, sodium glucose co-transporter 2 inhibitor; GLP-1 RA, glucagon-like peptide 1 receptor agonist; UACR, urinary albumin-to-creatinine ratio.
[a]In patients with low kidney failure risk, SGLT2i and GLP1-RA are similar in preventing worsening albuminuria. Consider SGLT2i if patients have a high risk for heart failure hospitalization. Consider GLP-1 RA if patients have uncontrolled metabolic risks.
[b]In patients with moderate kidney failure risk and adequate eGFR >30 ml/min per 1.73 m², SGLT2i is preferred. Consider adding GLP-1 RA for uncontrolled metabolic risks.
[c]In patients with high kidney failure risk and adequate eGFR >30 ml/min per 1.73 m², SGLT2i is preferred. Consider adding GLP-1 RA for uncontrolled metabolic risks.
[d]In patients with high kidney failure risk but eGFR is <30 ml/min per 1.73 m², GLP-1 RA (dulaglutide) is recommended for safer glycemic control and potential kidney protection. Currently, the data to support the use of SGLT2i for kidney failure prevention in eGFR <30 ml/min per 1.73 m² is lacking.

Table 3. Strategies to mitigate the adverse effects of SGLT2i and GLP1-RA

Adverse Effects	Frequency	Severity	Mitigating Strategies
SGLT2i			
Genital fungal infection	[a]	Low	Keep genital area dry and clean. Prophylactic topical treatment for fungal infection in high-risk patients
Volume depletion	[a]	Low	Proactive dose reduction of diuretics in euvolemic patients. Hold SGLT2i when patients have nausea, vomiting, or diarrhea. Implement "Sick day protocol"
UTI	[b]	Low	Use with caution. Avoid in patients at high risk of recurrent UTI (*e.g.*, indwelling foley catheter or self-catheterization)
DKA	[c]	High	Patient education on early recognition and implement "STOP DKA" protocol (stop SGLT2i, test for ketones, maintain intake of fluid and carbohydrates, and use maintenance and supplemental insulin)
Amputation	[b]	High	Encourage self-examination by patients or caregivers. Foot examination by health care provider at clinic visits. Temporarily hold SGLT2i when having an open wound or infection of the foot
Bone fracture	[b]	High	Caution in patients with risk of fall. Monitor PTH and vitamin D
GLP-1 RA			
Nausea/vomiting/diarrhea	[a]	Low	Patient education on symptom recognition. Start at low dose and slowly uptitrate over 2–4 wk
Cholelithiasis and cholecystitis	[b]	High	Patient education on recognition of symptoms
Acute pancreatitis	[d]	High	Caution in patients with history of pancreatitis

SGLT2i, sodium glucose co-transporter 2 inhibitor; GLP-1 RA, glucagon-like peptide 1 receptor agonist; UTI, urinary tract infection; DKA, diabetic ketoacidosis; PTH, parathyroid hormone.
[a]Commonly reported in multiple, large clinical trials.
[b]Increased risk reported in a single, large clinical trial.
[c]Increased risk reported in meta-analysis of clinical trials.
[d]Reported in small clinical trials or case series.

Li J et al. CJASN 2020;15

PROGRESSION OF POLYCYSTIC DISEASE
Current/recent trials

mTOR inhibitors (sirolimus, everolimus)

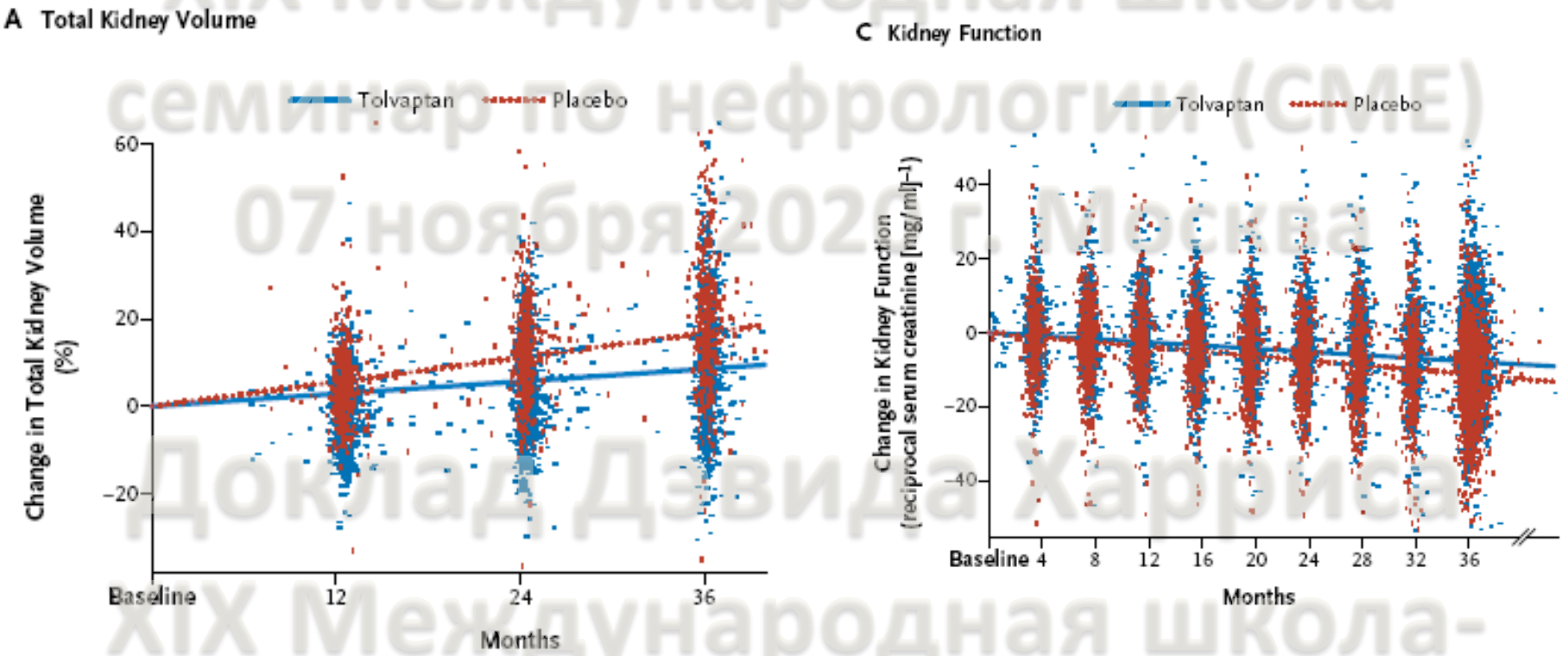
somatostatin analogues (octreotide)

V2 antagonists (tolvaptan)

(statins)

(ACEi & ARBs)

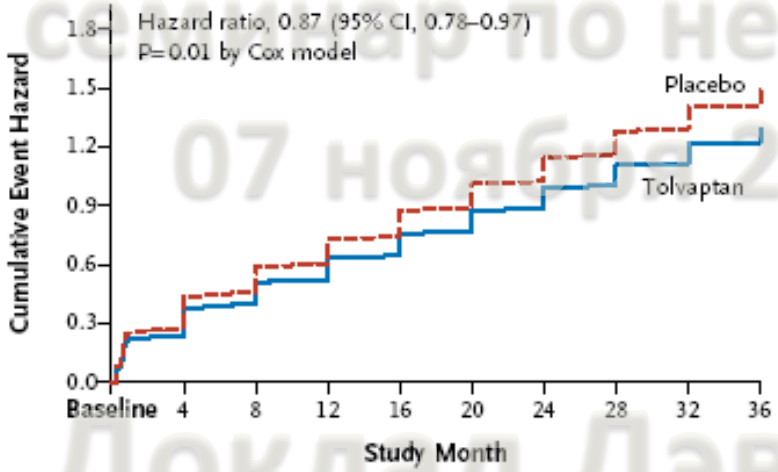
Vasopressin receptor antagonist (tolvaptan) attenuates early-stage ADPKD



Torres et al. N Engl J Med 2012

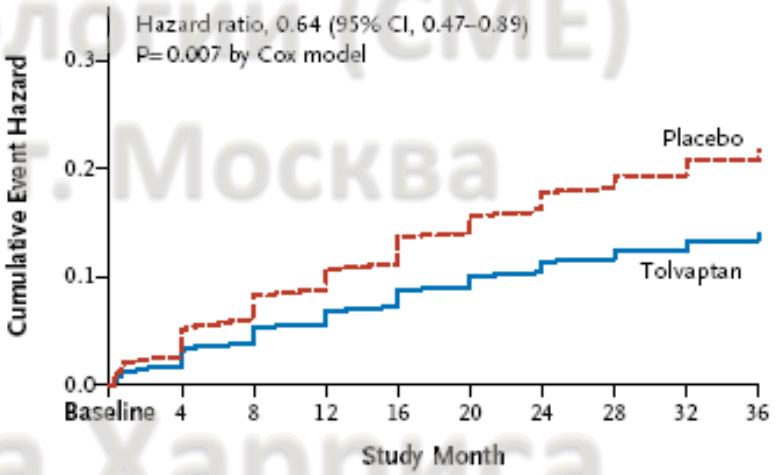
Vasopressin receptor antagonist (tolvaptan) attenuates early-stage human ADPKD (Vicente Torres and TEMPO investigators)

B Risk of ADPKD-Related Composite Events



No. at Risk										
Tolvaptan	961	870	835	811	792	776	763	752	744	642
Placebo	483	472	463	454	446	438	428	422	418	359

D Risk of Clinically Significant Kidney Pain



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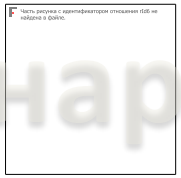
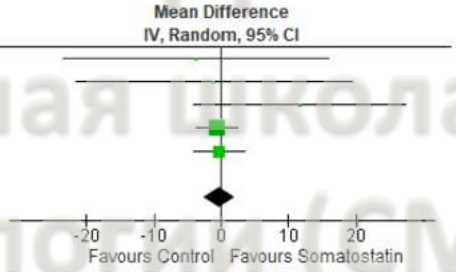


Somatostatin reduces TLV, not eGFR or TKV

A eGFR

Study or Subgroup	Somatostatin Analogue Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Ruggenenti	54	23.6	12	57.7	25.7	12	1.4%	-3.70 [-23.44, 16.04]	2005
Hogan	64.6	25.66	21	65.7	26.4	9	1.3%	-1.10 [-21.54, 19.34]	2010
ALADIN	76.33	27.96	36	64.64	36.25	31	2.1%	11.69 [-4.00, 27.38]	2013
DIPAK-1	42.6	12.8	146	43.2	13.7	144	56.6%	-0.60 [-3.65, 2.45]	2018
ALADIN 2	19.6	6.3	35	19.9	9.2	35	38.6%	-0.30 [-3.99, 3.39]	2019
Total (95% CI)			**250**			**231**	**100.0%**	**-0.27 [-2.57, 2.03]**	

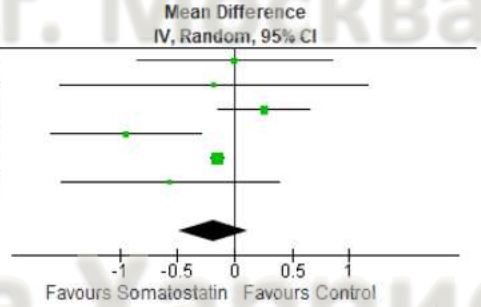
Heterogeneity: Tau² = 0.00; Chi² = 2.40, df = 4 (P = 0.66); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)



B TKV

Study or Subgroup	Somatostatin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Ruggenenti	2.622	1.111	12	2.623	1.021	12	9.9%	-0.00 [-0.85, 0.85]	2005
LOCKCYST	0.983	1.173	12	1.17	2.66	20	4.7%	-0.19 [-1.53, 1.15]	2009
Hogan	1.128	0.796	21	0.873	0.306	8	23.8%	0.25 [-0.15, 0.66]	2010
ALADIN	1.672	1.195	35	2.621	1.603	35	14.1%	-0.95 [-1.61, -0.29]	2013
DIPAK-1	0.118	0.227	134	0.272	0.265	138	39.2%	-0.15 [-0.21, -0.10]	2018
ALADIN 2	3.043	2.32	35	3.613	1.69	35	8.3%	-0.57 [-1.52, 0.38]	2019
Total (95% CI)			**249**			**248**	**100.0%**	**-0.19 [-0.50, 0.12]**	

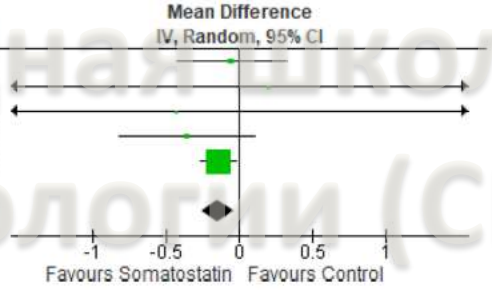
Heterogeneity: Tau² = 0.06; Chi² = 10.39, df = 5 (P = 0.07); I² = 52%
Test for overall effect: Z = 1.20 (P = 0.23)



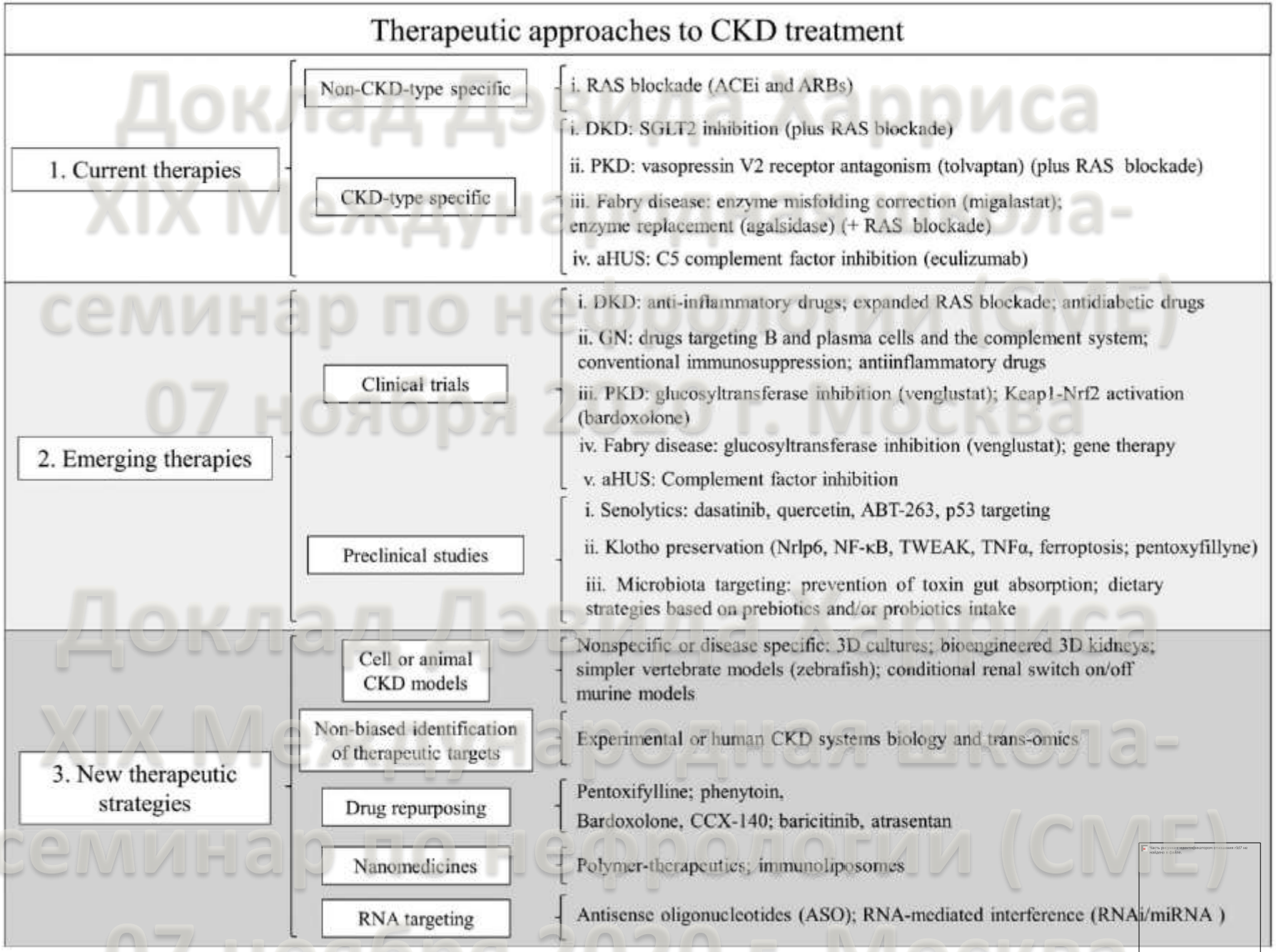
C TLV

Study or Subgroup	Somatostatin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Caroli	1.524	0.453	12	1.58	0.48	12	8.9%	-0.06 [-0.43, 0.32]
Hogan	5.557	2.659	28	5.36	3.33	14	0.3%	0.20 [-1.81, 2.20]
LOCKCYST	4.471	10.417	27	4.896	10.804	26	0.0%	-0.42 [-6.14, 5.29]
Pisani	1.479	0.47	14	1.837	0.748	14	5.8%	-0.36 [-0.82, 0.10]
Van Aerts	-0.052	0.388	83	0.089	0.382	74	85.0%	-0.14 [-0.26, -0.02]
Total (95% CI)			**164**			**140**	**100.0%**	**-0.15 [-0.26, -0.03]**

Heterogeneity: Tau² = 0.00; Chi² = 1.16, df = 4 (P = 0.89); I² = 0%
Test for overall effect: Z = 2.56 (P = 0.01)

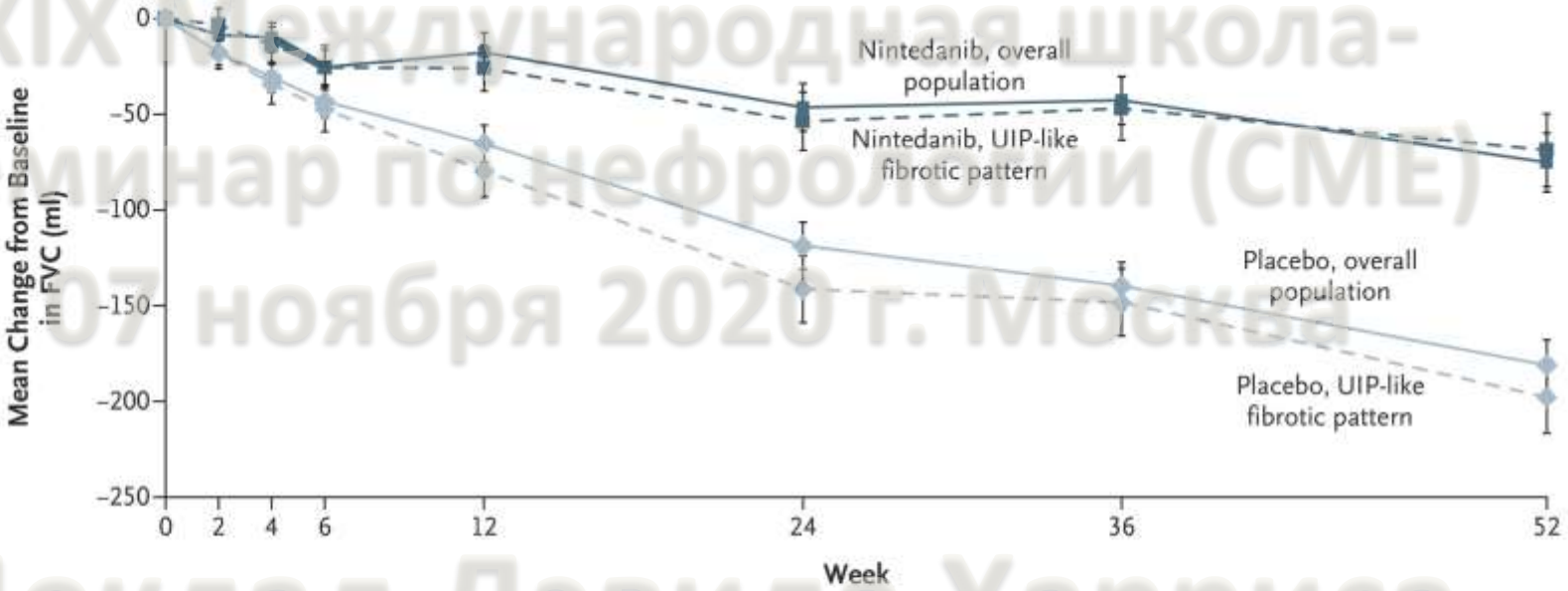


Griffiths J. BMJ Open 2020;10 (Systematic review & metanalysis)



Ramos AM. Expert Opinion Drug Discovery 2020;15:101–115

Nintedanib for interstitial lung disease



No. of Patients								
Overall population								
Nintedanib	332	326	320	322	314	298	285	265
Placebo	331	325	326	325	320	311	296	274
Patients with UIP-like fibrotic pattern								
Nintedanib	206	203	200	199	193	180	171	160
Placebo	206	202	202	201	197	190	176	162

IC inhibitor of tyrosine kinases

Flaherty KR. NEJM 2019;381:1718-1727

Some novel therapies in human CKD

Pirfenidone: study withdrawn

Nox1/4 inhibitor – negative trial

Anti-CTGF antibodies FG3019: studies terminated

SSAO/ VAP1 inhibitors: phase 1 clinical trial concluded, not reported

Curcumin – phase 3 trial completed, not reported

Tranilast and analogues FT011: in phase 1b clinical trial

Alpha-lipolic acid: recruiting

Tie2 Rec activator - angiopoietin receptor, tyrosine kinase inhibitor: in development

JAK-STAT inhibitors: in development

LOX inhibitors: in development

Anti TGF-β Ab (LY2382770) – negative trial

Novel anti-fibrotic drugs tested in clinical trials, prematurely interrupted

Phase	Group	Drug	Target	RAAS blockade association	Kidney disease	Status and adverse effects	Effects	Reference
Priming phase	NFkB blockers	Bindarit	MCP-1		DKD, CKD	Discontinuation of clinical development of the drug		29
	Chemokine antagonists	MLN1202	CCR2		DKD, CKD	Prematurely stopped for unknown reasons		NCT02410499
		BMS-813160	CCR2/CCR5		DKD	Discontinuation of clinical development of the drug		NCT01752985
		Bardoxolone	Nrf2	Yes	DKD, CKD	Prematurely terminated for high rate of cardiovascular events	Did not reduce the risk of ESRD or death	89
		Gevokizumab	IL-1β		DKD	Prematurely terminated		[211]
Activation and execution phase	Endothelin receptor antagonists	Atrasentan	ET-1	Yes	DKD, CKD		Prematurely stopped due to lack of efficacy	NCT01858532
		Avosentan	ET-1	Yes	DKD	Trial stopped because of fluid retention	Reduced albuminuria	97
	Integrin blockers	STX-100	αvβ6 integrin		Renal transplant	Prematurely stopped for unknown reasons		NCT00878761
	TGF-β blockers	LY2382770	TGF-β		DKD, CKD		Prematurely stopped due to lack of efficacy	111
	CTGF blockers	FG-3019	CTGF		FSGS	Prematurely stopped for unknown reasons		NCT00782561
		FG-3019	CTGF	yes	DKD, CKD	Prematurely stopped for suboptimal study design		NCT00913393
Progression phase	Galectin-3 antagonist	GCS-100	galectin-3		DKD	Discontinuation of clinical development of the drug because the Company was required to conduct additional chemical characterization	Mild increase of GFR	154

ACTIVATORS

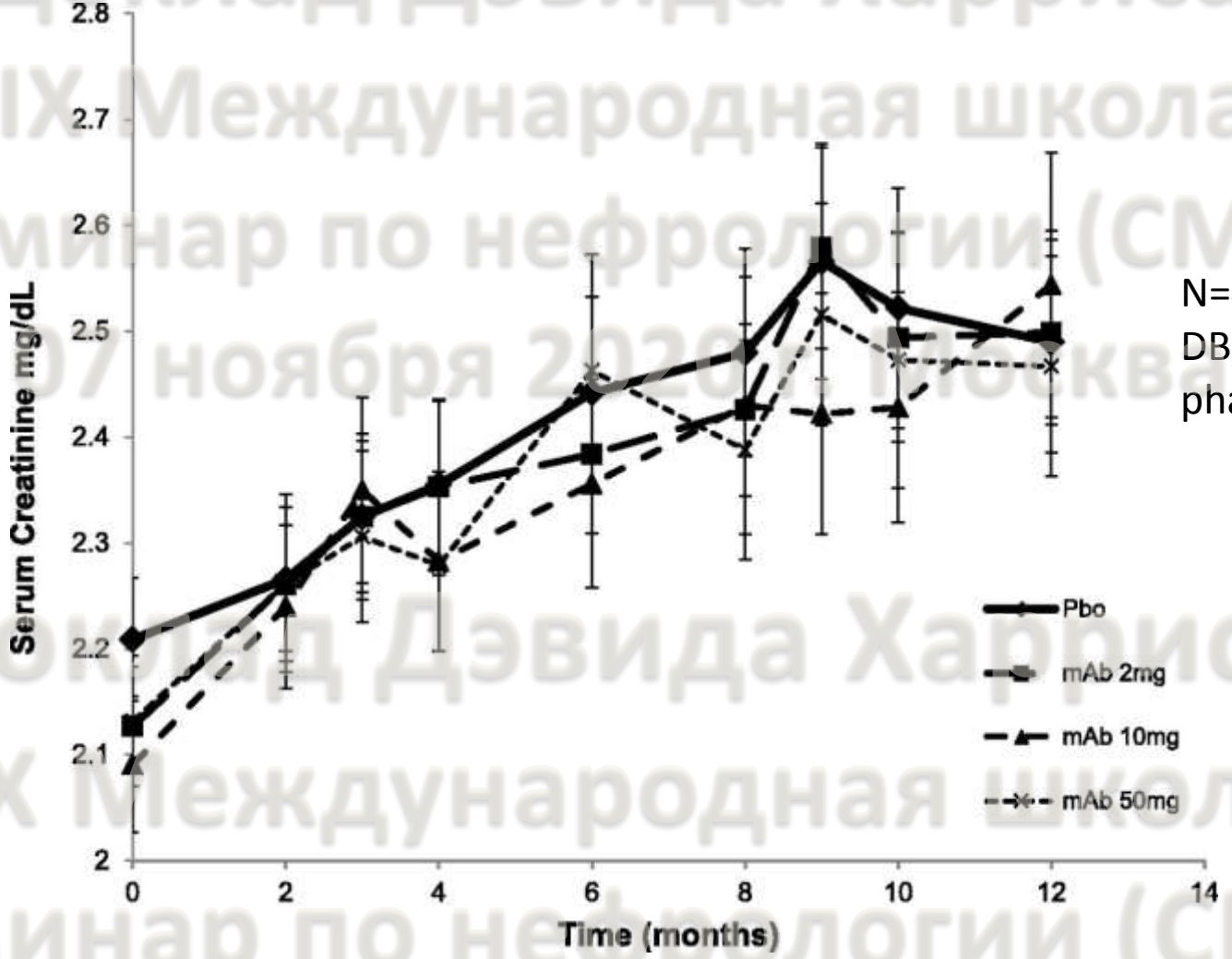
Nrf2

INHIBITORS

NFκB
chemokines
IL-1β
endothelin receptor
integrin
TGF-β
CTGF
galectin-3

Allinovi M et al. Matrix Biol 2018

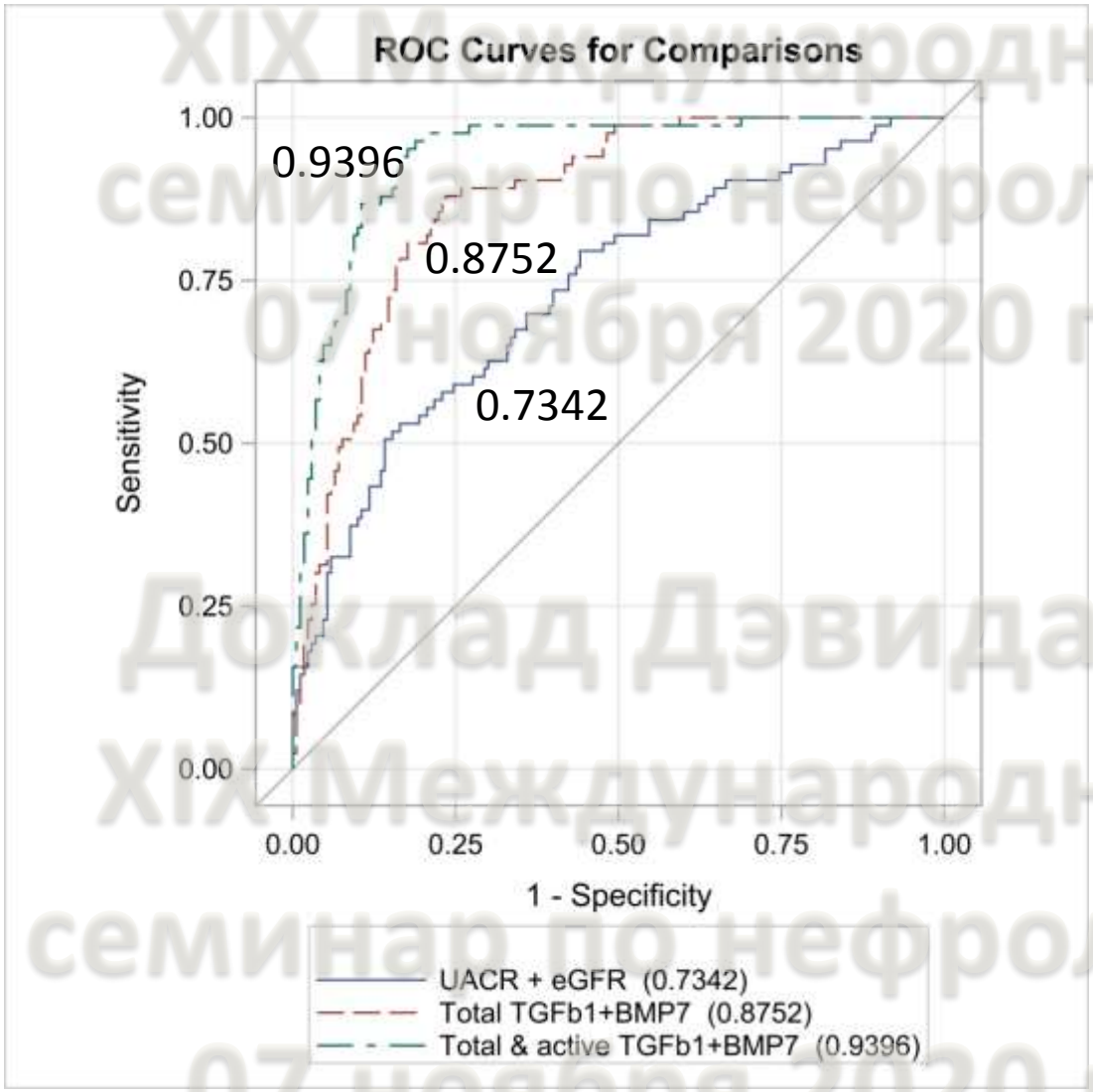
TGF-β1 mAb for DN trial terminated



N=416
DB, randomised
phase 2

Voelker J et al. JASN 2017;28:953-962

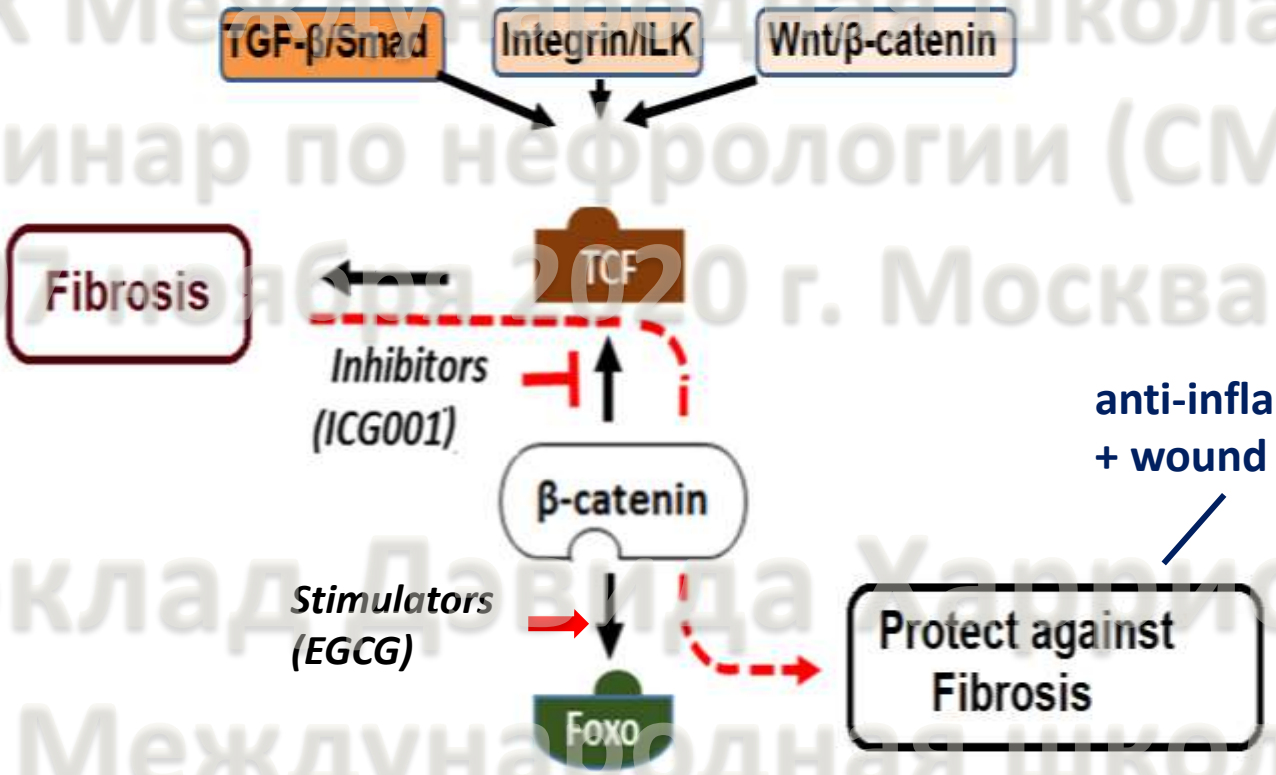
BMP7 and TGFβ1 are better predictors of major renal endpoints than eGFR+UACR



baseline serum
TREAT participants (n=1000)

Wong et al. KI 2013

TGF-β causes tissue fibrosis through three major Signaling Pathways



Hypothesis: β-catenin/Foxo is the key target to dissociate profibrotic from anti-inflammatory and wound-healing effects of TGF-β

Therapeutic targeting β-catenin/Foxo by inhibition of β-catenin/TCF……

reduces

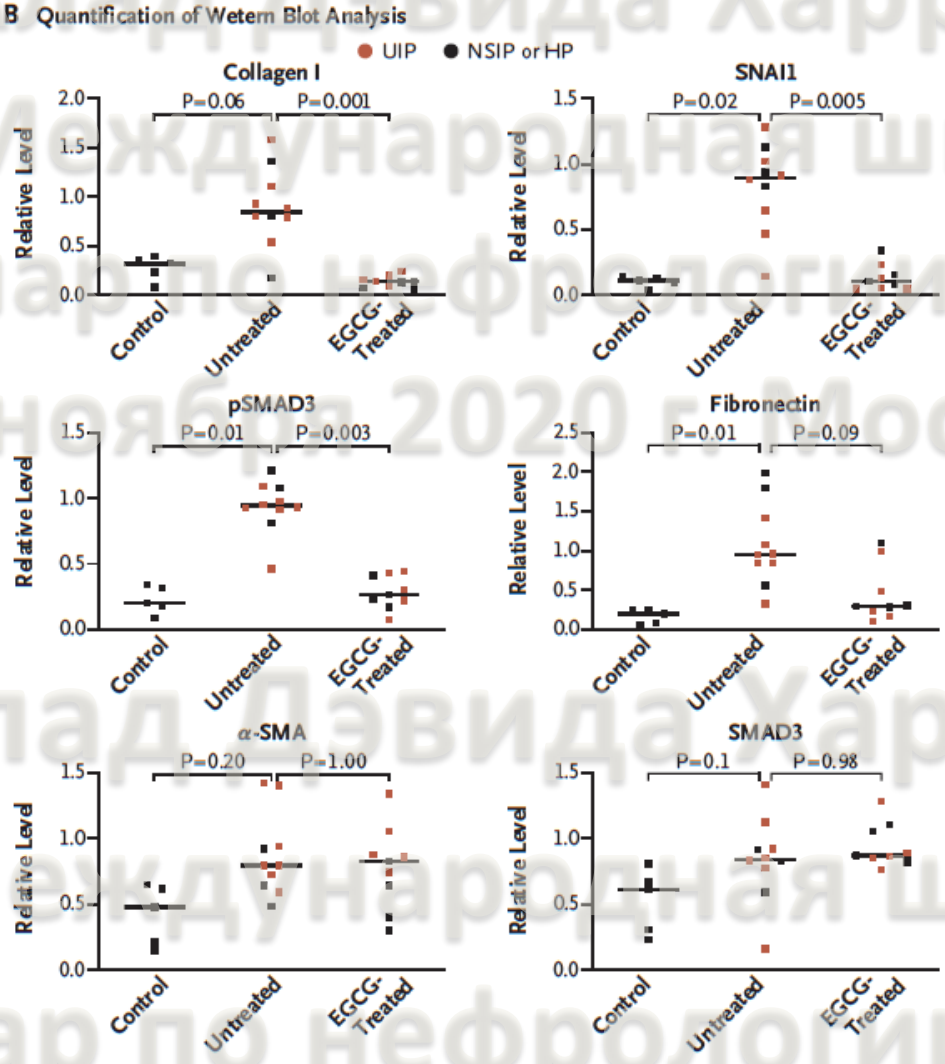
fibrosis (kidney, lung, liver)

infiltration of lymphocytes & macrophages,
(Treg-dependent)

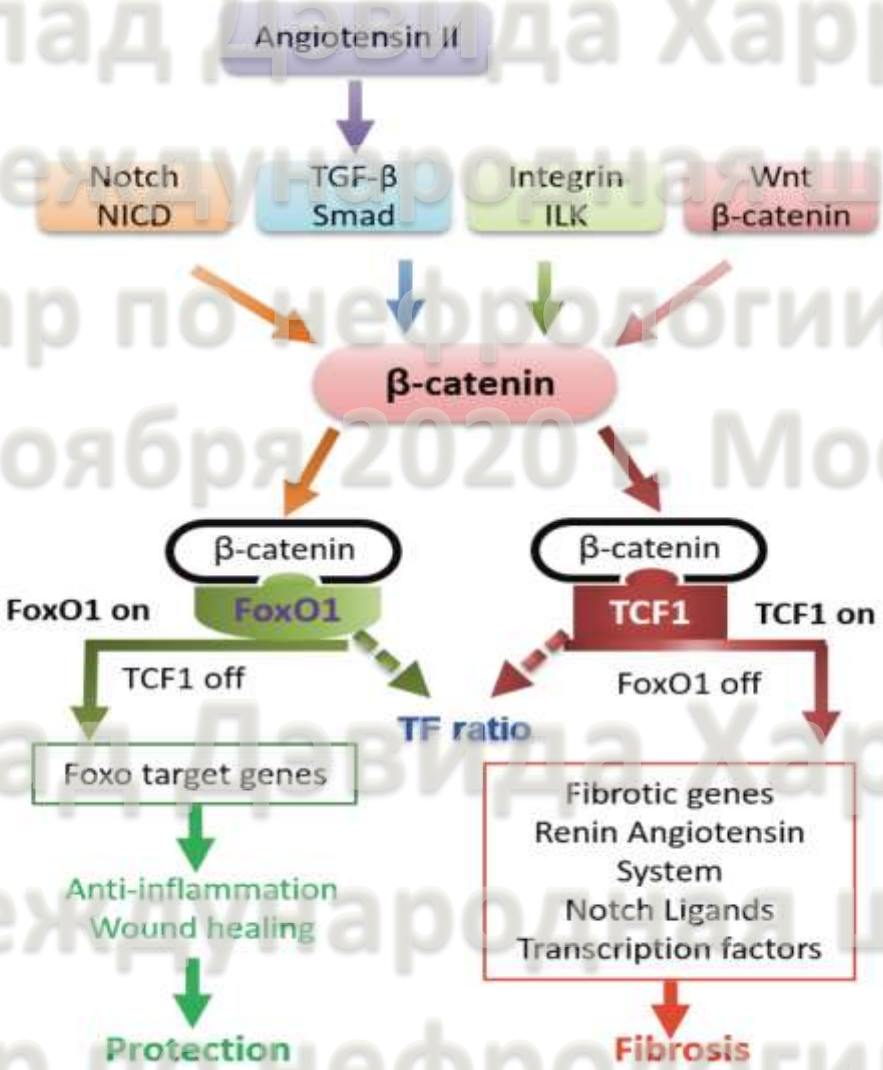
increases

non-fibrotic wound healing

Reversal of TGFβ1-Driven Profibrotic State in Patients with Pulmonary Fibrosis



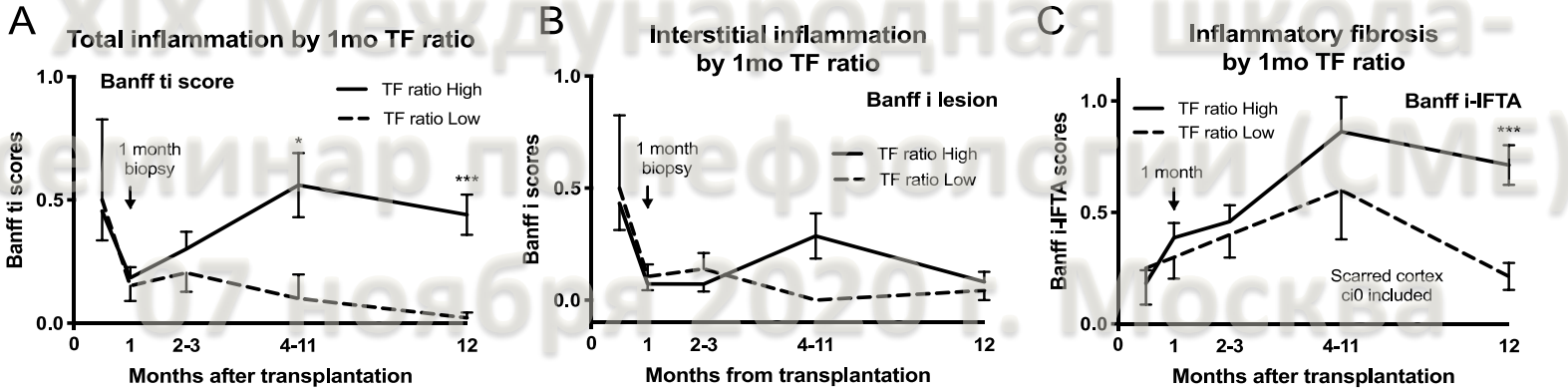
Chapman HA, Wei Y. NEJM 2020;382:1068-70



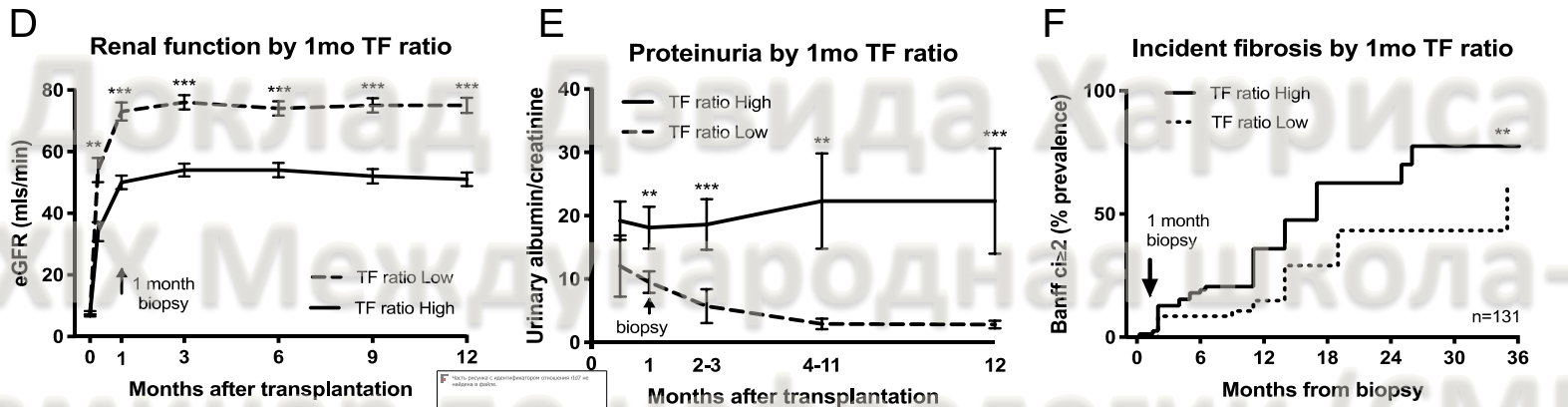
Доклад Дэвида Харриса
XIX Международная школа-семинар по нефрологии (CME)
07 ноября 2020 г. Москва

Yang Y, Nankivell B, Zheng G, Harris DC. Am J Transpl 2020

1-month biopsy TF ratio and subsequent cortical inflammation

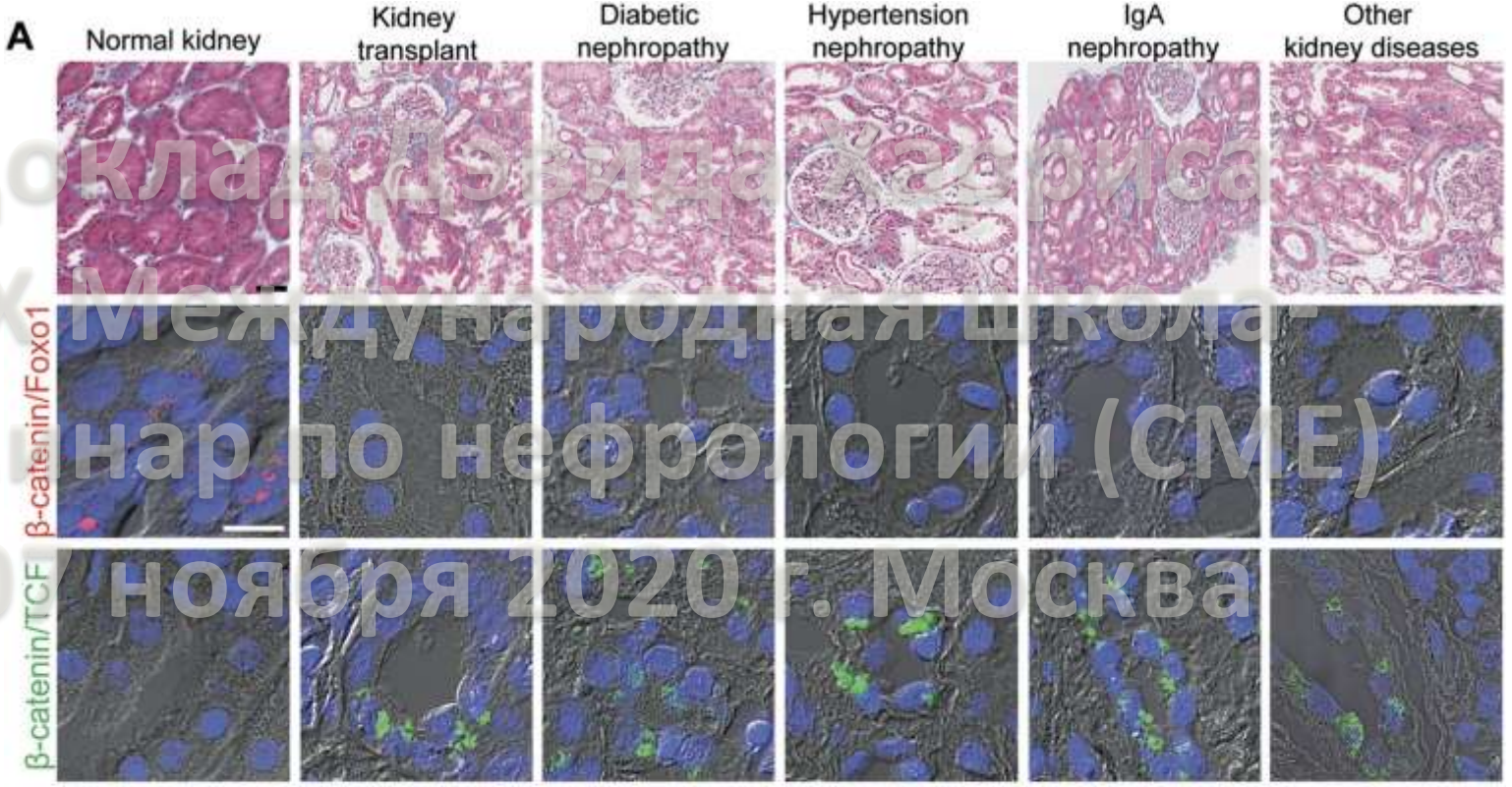


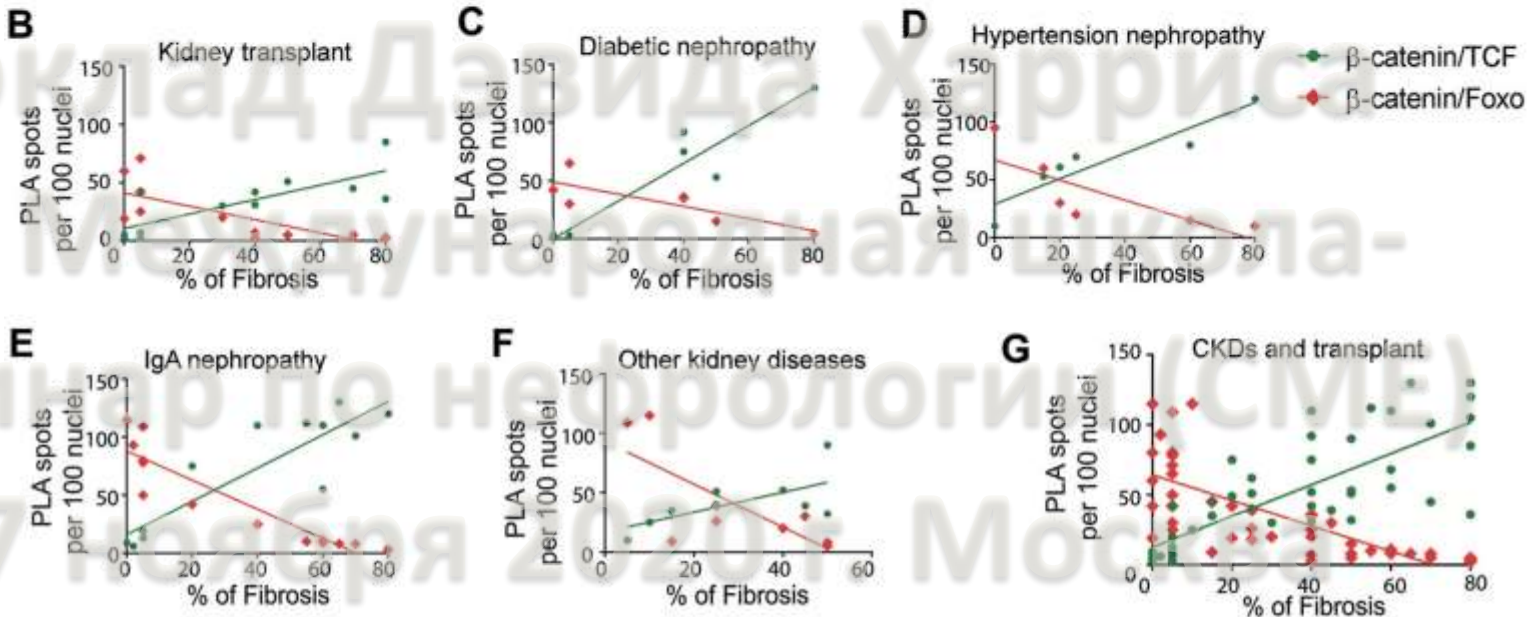
1-month biopsy TF ratio and later clinical outcomes



Yang Y, Nankivell B, Zheng G, Harris DC. Am J Transpl 2020

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





Rao P
Lab Inv 2019

NOVEL METHODS FOR DETECTING FIBROSIS & PREDICTING PROGRESSION

MR elastography[1]

Convolutional neural network[2]

Quantum Cascade Laser (QCL)-based infrared spectroscopic (IR) imaging[3]

Anti-collagen1-conjugated gold nanoparticles[4]

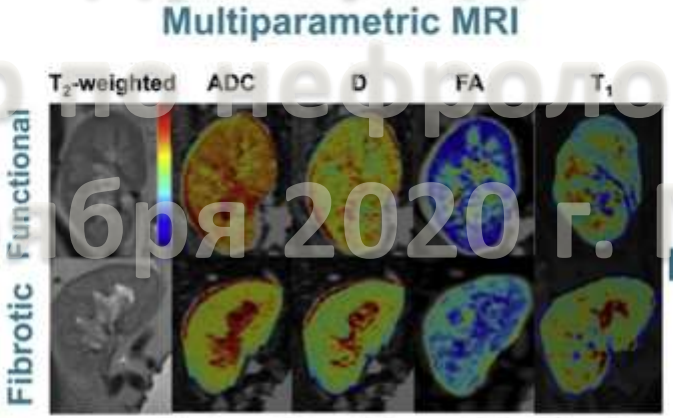
Functional MRI[5]

Fluorescence lifetime imaging (FLIM)[6]

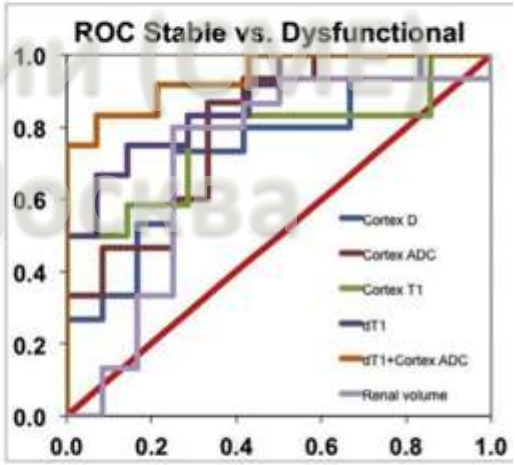
1. Morrell GR. JASN 2017;28:2564. Kirpalani A. CJASN 2017;12:1671. Sun Q. Sci Transl Med 2019: 11
2. Kolachalama VB. KI Reports 2018;3:464-75
3. Varma VK. Scientific Reports 2018;8:686
4. Zhu XY. Invest Radiol 2018;53:623-8
5. Wang W. CJASN 2019;14:1372. Feng Y-Z Br J Radiol 2020
6. Ranjit S. Kid Int 2020

Multiparametric magnetic resonance imaging shows promising results to assess renal transplant dysfunction with fibrosis.

Stable function allografts	Chronic dysfunction allografts
12 patients	15 patients
2 indication biopsies	15 biopsies confirming fibrosis



Apparent diffusion coefficient ADC range: 0-3 x 10^{-3} mm^2/s
True diffusion coefficient D range: 0-3 x 10^{-3} mm^2/s
Fractional anisotropy FA range: 0-1
Longitudinal relaxation time T_1 range: 0-2500 ms



CONCLUSION:

The combination of cortical apparent diffusion coefficient (ADC) and longitudinal relaxation time (T_1) measurements show promising results for the non-invasive assessment of chronic renal allograft dysfunction with fibrosis.

ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Bane et al., 2019

Cortical T1→ Banff IFTA

Cortical T1 & ADC →chronic dysfunction + fibrosis + GFR decline at 18 months

TARGETING INFLAMMATION

DNA VACCINATION

chemokines/receptors: CCL2, CCL5, CX3CR1
costimulatory molecules: CD40

INHIBITING EFFECTOR CELLS

REGULATORY CELLS

(mesenchymal stem cells)
protective macrophages: M2a, M2c, Mreg
tolerogenic dendritic cells
regulatory lymphocytes
regulatory innate lymphoid cells: ILC2, ILCreg

CAR & CSSR

Factors affecting efficacy

cell type (MSC, mac, DCs, Treg)

autologous vs allogeneic (donor vs 3rd party)

origin (blood, marrow, cord, liver, adipose, peritoneum)

preparation (trophic factors etc)

modification (genetic, cytokine, antigen-pulse)

number

route

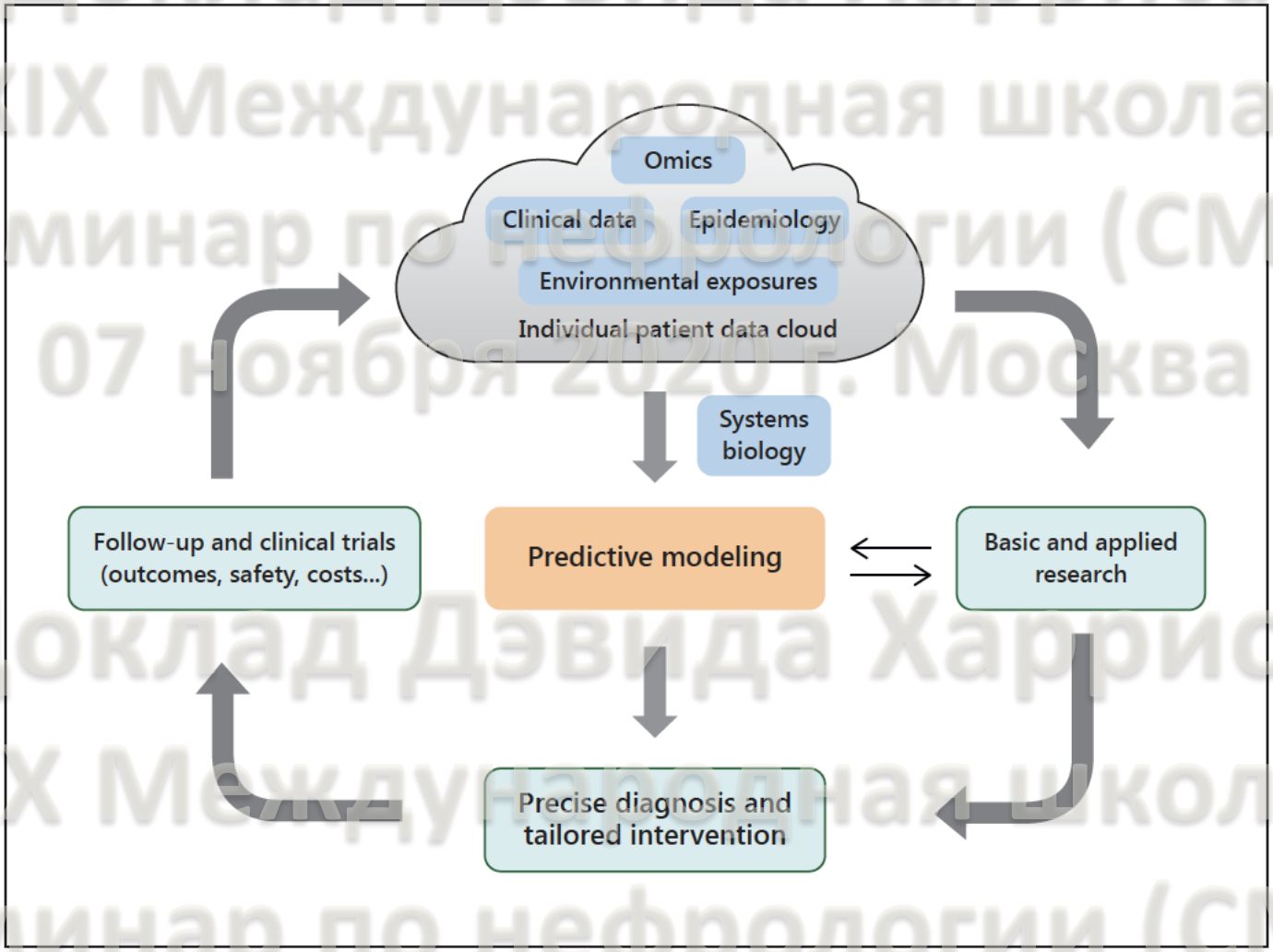
timing

sequestration
elimination
proliferation
phenotype drift/switch
immune response

Potential adverse events

transient pro-inflammatory effects
auto- & allo-immunity
oncogenicity
maldifferentiation (teratoma)
opportunistic infection
(myocardial) microcalcification
(pulmonary) fibrosis

Precision Medicine & CKD



Sun L. Med Princ Pract 2017;26:101-7

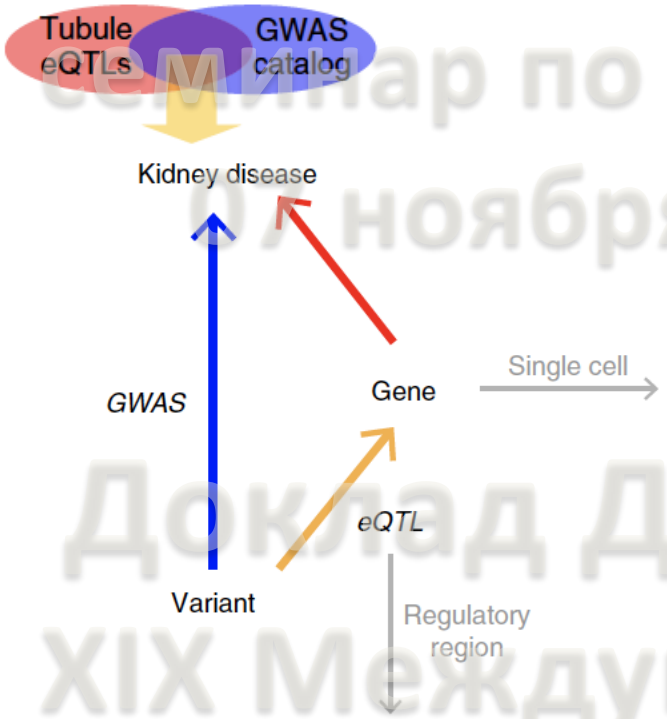
Renal fibrosis & -omics

Field	Positive correlation	Negative correlation
Genomics	IL-18 (+137 GG, –607CC); TGF-β_1 (–509 TT); AS (int 2 CC); UMOD (rs12917707; rs12446492); ELMO1 gene; Nox2 gene	TGF-β_1 (+869 TT); UMOD (rs13333226, rs12917707); Sirt1 gene
Epigenomics	DNA methylation (e.g., Klotho promoter); histone modifications (e.g., profibrotic and ER stress-related genes)	apelin-13, KLF4
Transcriptomics	miR-192, miR-29, miR-21, miR-150, mRNA (e.g., APE1, AT1R, CXCR4, THBS1, TRIB1)	miR-93, miR-217, miR-200a, miR-26a, mRNA (e.g., BMP7, CD2AP)
Proteomics	TGF-β_1, α-SMA, NGAL, KIM-1, CD147, CXCL1, annexin A1, HE4, NGAL, MBL, MMP-7, MMP-9, CTGF, uVDBP, periostin, CKD273 peptides	HO-1, E-cadherin
Metabolomics	cystatin C, lipids (e.g., ectopic, oxidized), glycolysis, acetoacetate, phosphorylcholine/choline, H-1 NMR-based metabonomics	pyruvate, glycine, L-carnitine

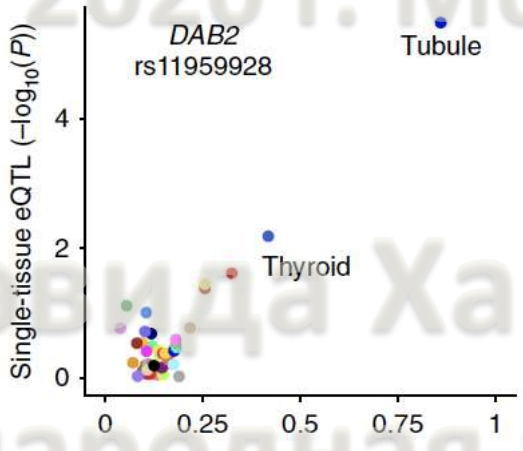
Sun L. Med Princ Pract 2017;26:101-7

Renal compartment–specific genetic variation analyses to identify new CKD pathways

CKD GWAS
+ human glomerular & tubular (eQTL) atlas
+single-cell RNA sequencing & regulatory region maps
+ proximal tubule endolysosomal enrichment



→ **DAB2, (TGF-β adaptor protein)**



reduce tubular DAB2
→ protect from murine CKD

eQTL = expression quantitative trait loci

Qiu CX et al. Nat Med 2018;24:1721-31

ISN Programs in Russia since 2015

Continuing Medical Education

- 13 meetings organized in Russia.
- Main training topics: CKD, General Nephrology, Glomerular Diseases.

Educational Ambassadors

- 4 Educational Ambassadors visits to Russia.
- Main training topics: AKI, CKD, Clinical Nephrology.

Sister Centers (SRC/STC)

2 graduated pairs:

- SRC Russia-Russia (graduated in 2018), between *Irkutsk Regional Clinical Hospital* and *Moscow Clinical City Hospital*.
- SRC Russia-Finland (graduated in 2020), between *National Medical Research Center for Children's Health* and *University of Helsinki*.

Sister Centers (SRC/STC)

2 active links:

- SRC Russia-Belgium (Level A), between *Pirogov Russian National Research Medical University* and *University Hospitals Leuven*.
- SRC Uzbekistan-Russia-Finland (Level C), between *Tashkent Pediatric Medical Institute*, *National Medical Research Center for Children's Health* and *University of Helsinki*.

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ISN 60 years
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