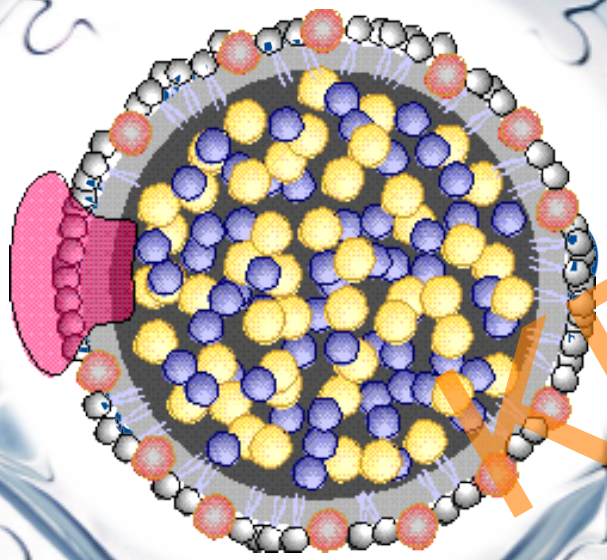


Dyslipidemia in DKD: Current & Future Lipid Lowering Strategies

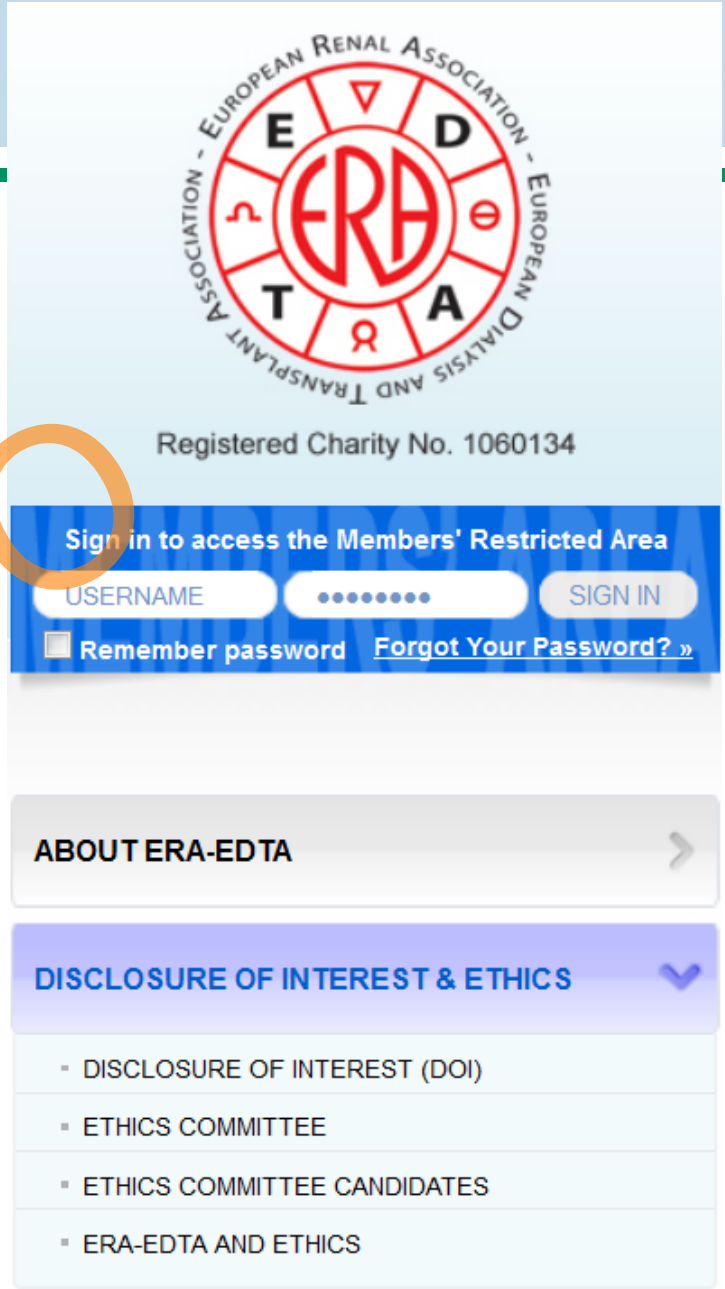
Christoph Wanner
Vancouver

February 5-8, 2015

Disclosure of Interests

KDIGO, NKF, ISRNM, KfH, Baxter, BöhringerIngelheim, Reata Mitsubishi, Noxxon, Keryx, Abbott, Astellas, Fresenius,MSD, Amgen, Sanofi, BMS, AstraZeneca, Genzyme, Roche, Vifor, AMAG

research grant to the institution, consultancy, honoraria, sponsored education,



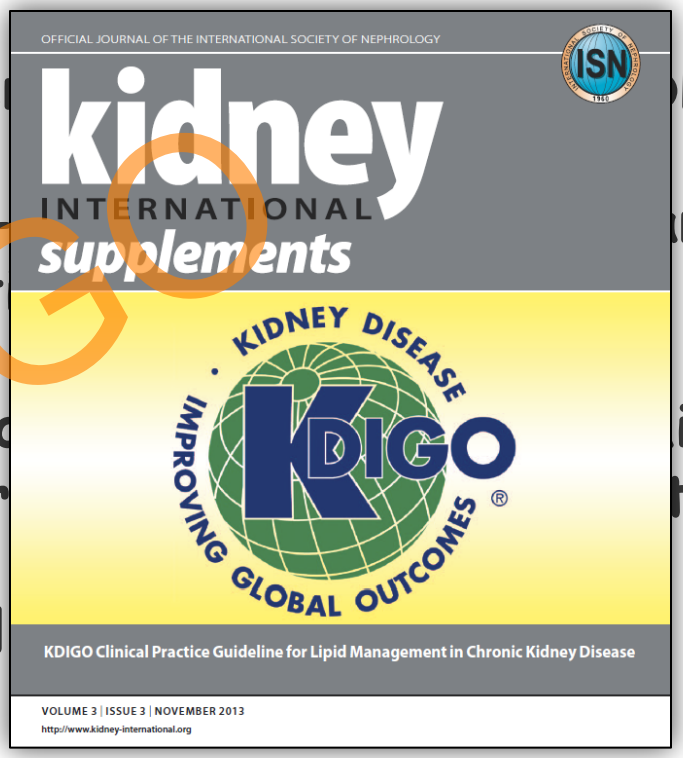
Objectives

Patte KD

Lipid- re all
stat

Role ising
ther tors

Novel
e.g.

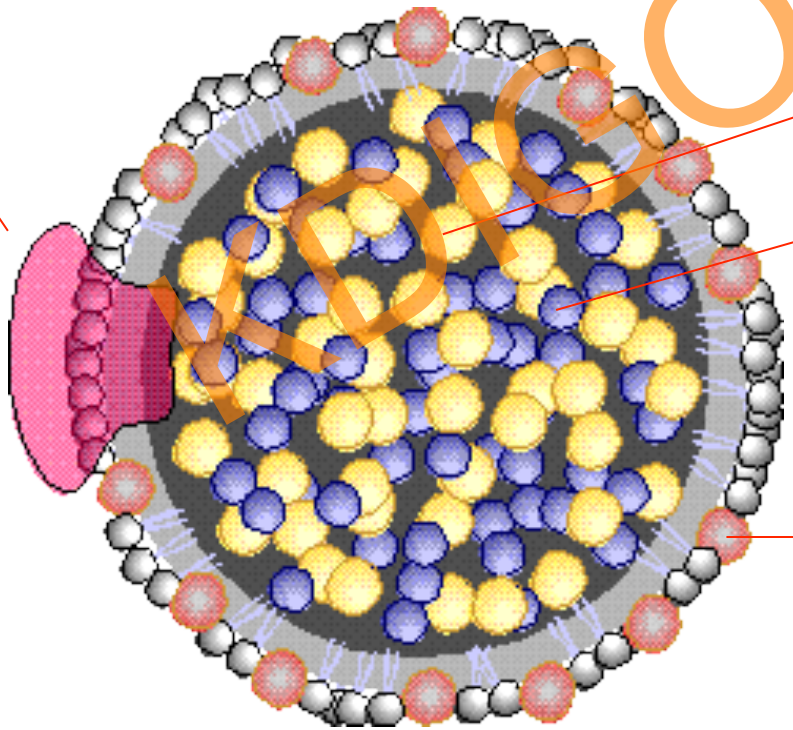


Dyslipidemia: 3 different languages

Apolipoproteins

A-I
A-II
B-100
C-I-III
E

Lipoprotein particles



Lipids

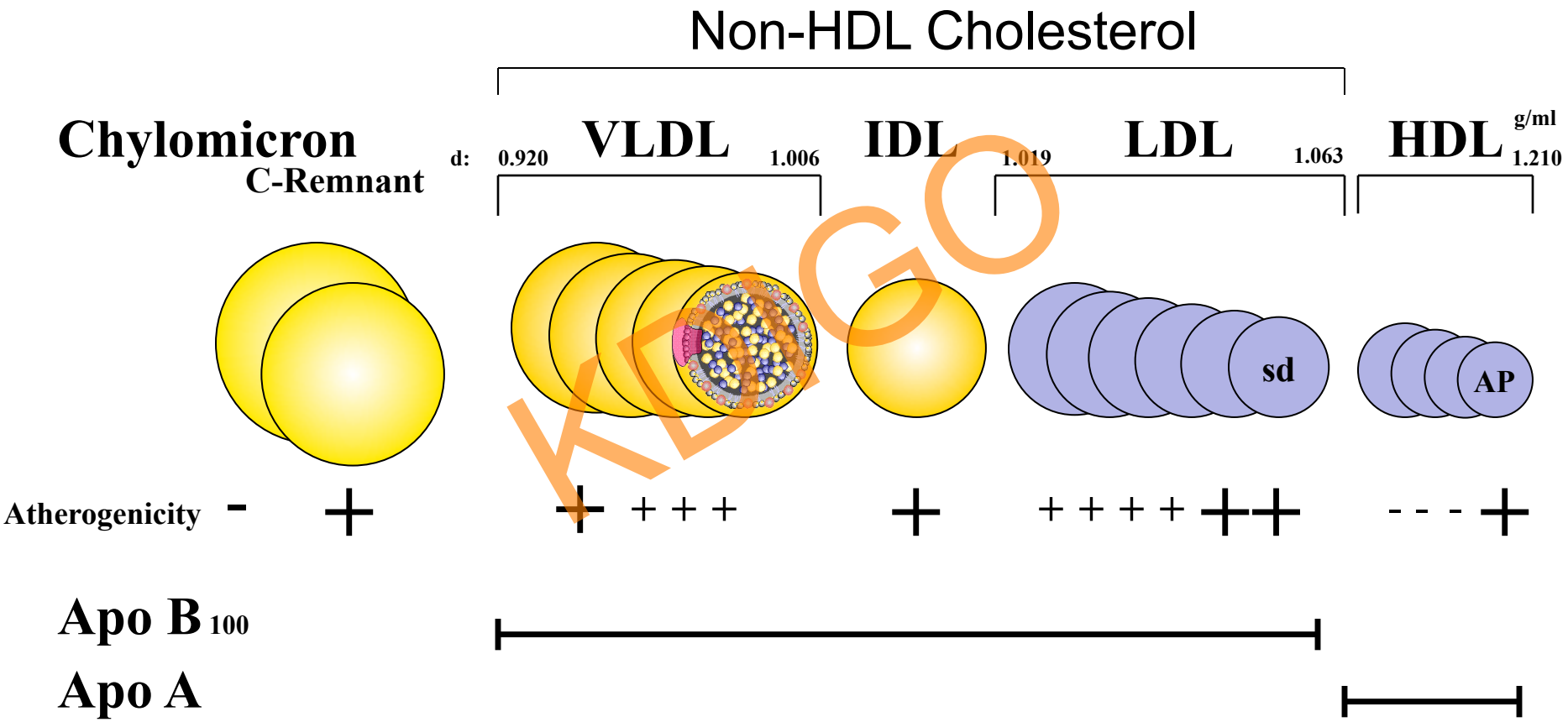
Triacylglyceride

Cholesterolester

Phospholipids

Non-esterified Cholesterol

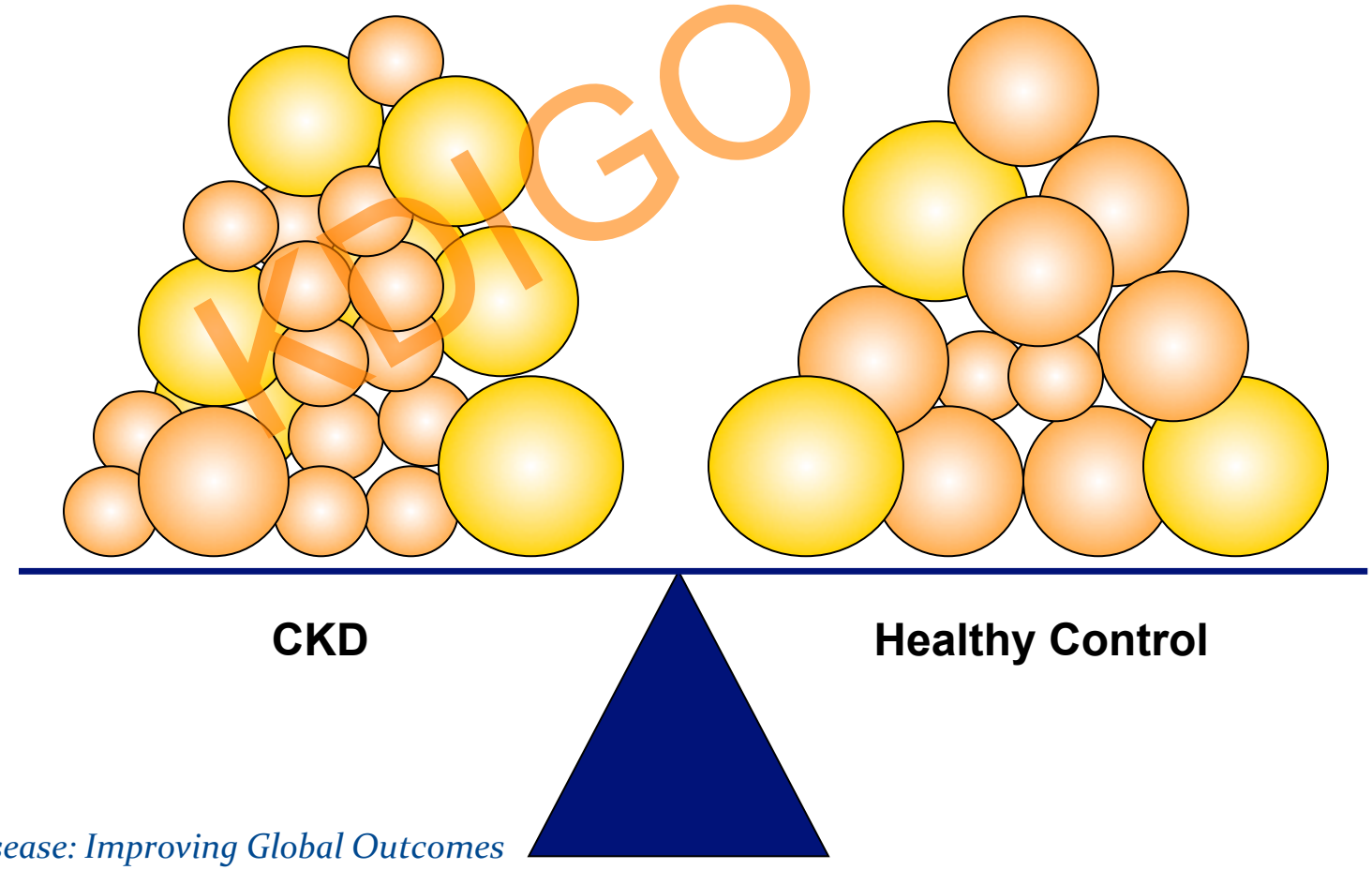
CKD: TG-rich ApoB containing Lp Particles



Otvos J. Clin Cardiol 1999; 22 (Suppl II): 21-27

Lipoprotein particles

Total Cholesterol	**200 mg/dl**	**200 mg/dl**
Triglycerides	**180 mg/dl**	**80 mg/dl**



Modulators of the lipid pattern

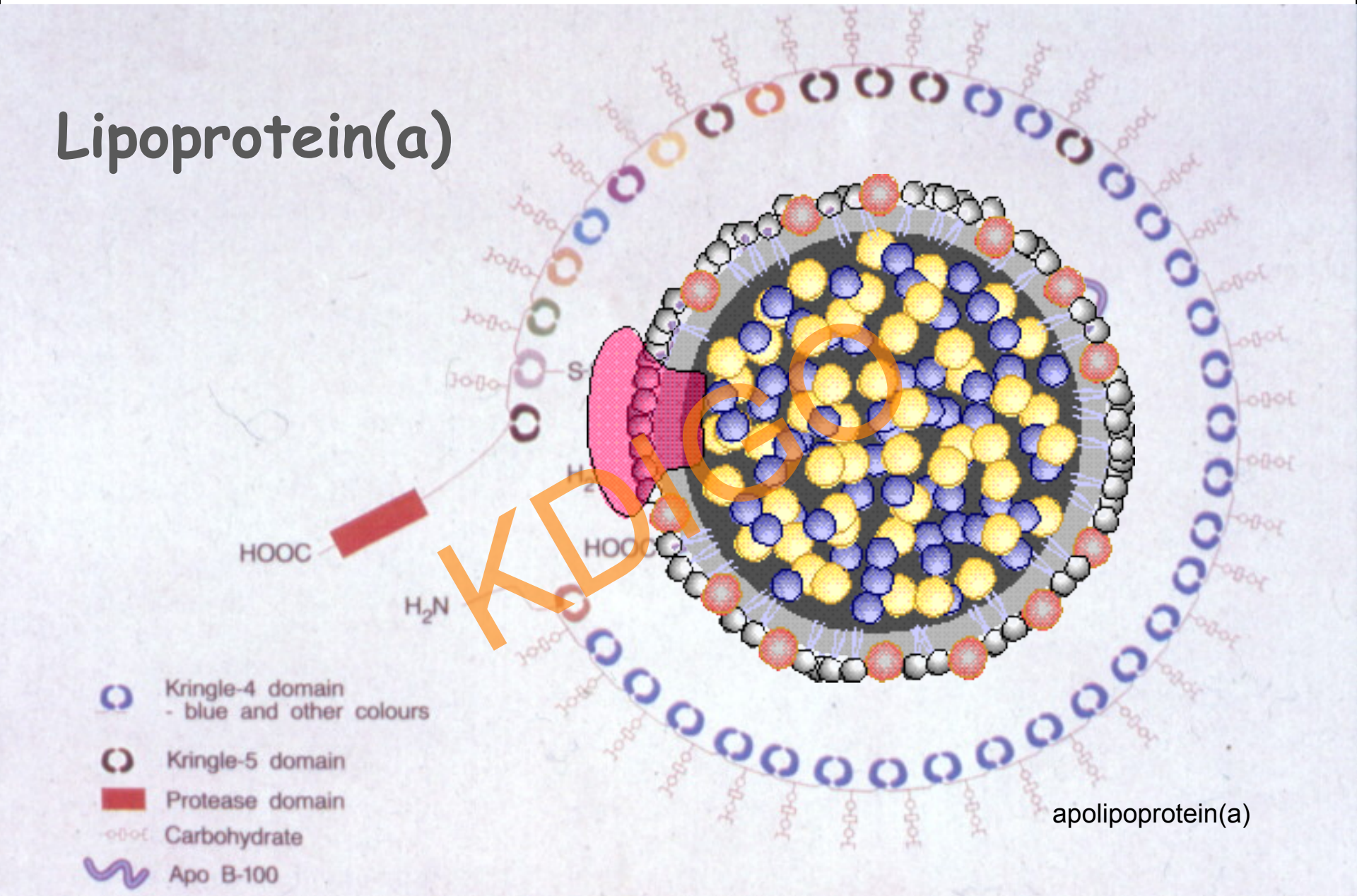
- **Proteinuria** & Nephrotic syndrome
- **Peritoneal dialysis** & uremic toxins & NS
- **Hemodialysis** & Heparin administration
- **Immunosuppression** & polypharmacy
- **sHPT** & LPL inhibitors
- **Insulin resistance**
- „method of determination of lipids"

Pattern of dyslipidemia

	TC	LCL-C	HDL-C	TG	Lp(a)
4D	216	125	34	224	32.6
AURORA	175	100	45	156	
SHARP	189	107	43	203	
ALERT	249	158	52	192	

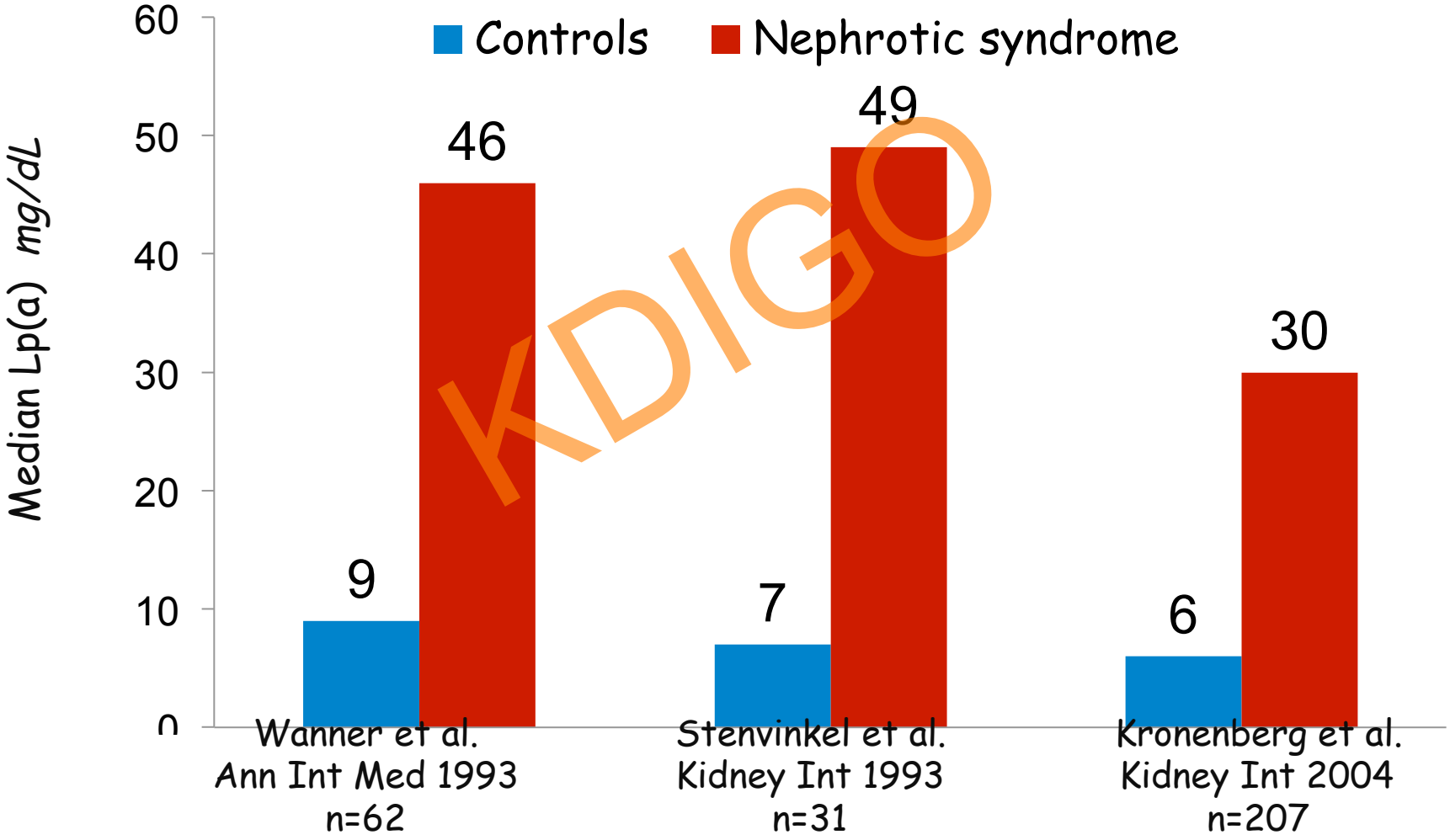
mg/dl

Lipoprotein(a)

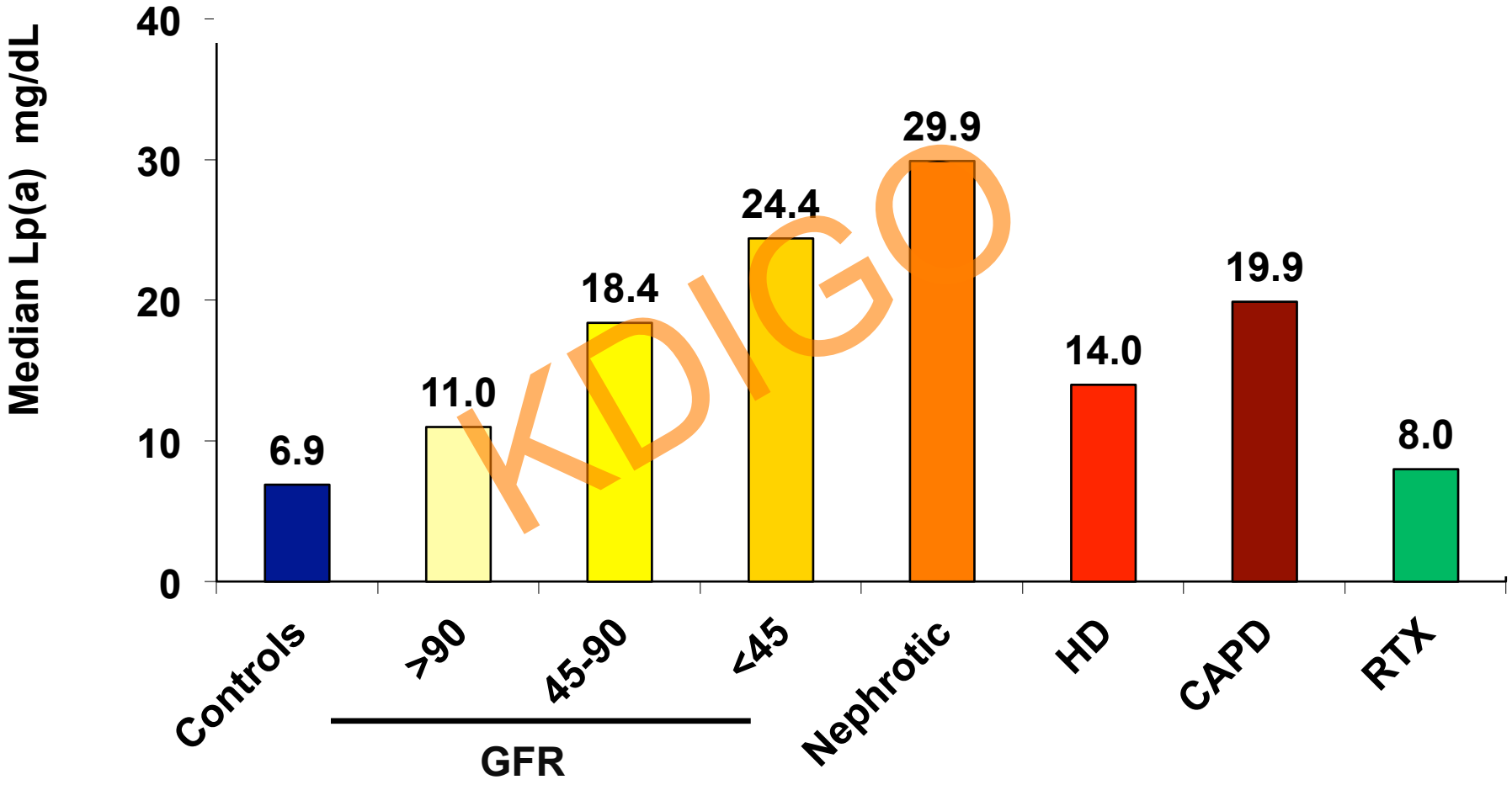


apolipoprotein(a)

Lp(a) concentrations in nephrotic syndrome



Lp(a) and kidney disease



J Clin Invest 91:397-401, 1993
Arterioscler Thromb 14:1399-1404, 1994
J Am Soc Nephrol 6:110-120, 1995

J Am Soc Nephrol 11:105-115, 2000
Kidney Int. 65: 606-612, 2004

Objectives

- Patterns of dyslipidemia in DKD
- Lipid-lowering medications: are all statins the same?
- Role of fibrates and HDL-raising therapies, e.g. CETP inhibitors
- Novel lipid-lowering agents, e.g. PSCK9 inhibitors

Lipid modifying agents

Lovastatin
Simvastatin
Atorvastatin
Rosuvastatin
Pravastatin
Fluvastatin
Pitavastatin

Niacin
Ezetimibe
Sevelamer
Colesevelam
Cholestyramine

Fenofibrate
Bezafibrate
Gemfibrozil

Combinations
Fish oil

PLANET I

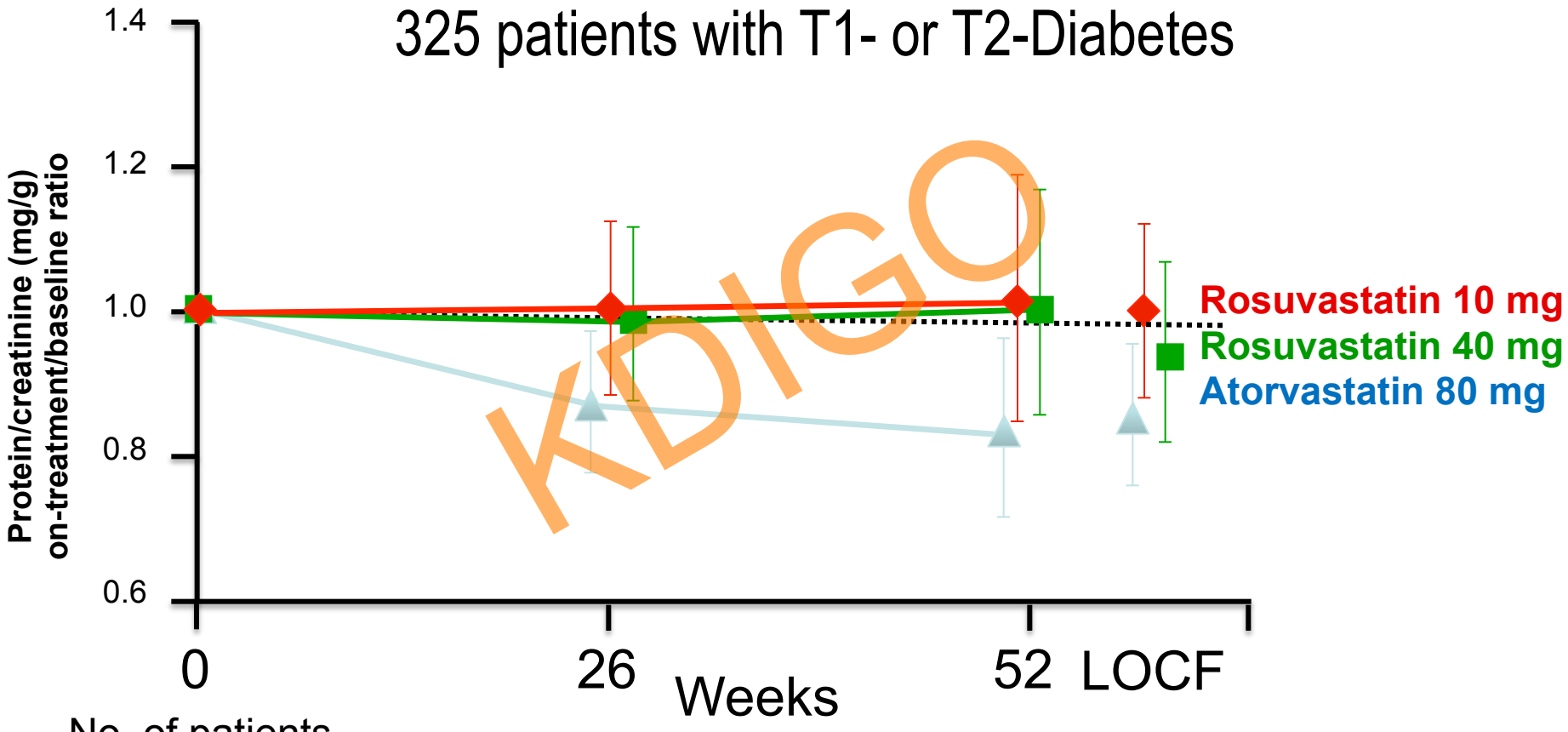
Prospective Eva**L**uation of Proteinuri**A** and Kid**N**ey Function in diabetic (PLANET I) and non-diab**ET**ic (PLANET II) Patients with progressive Kidney Disease

Renal effects of atorvastatin and rosuvastatin in patients with diabetes who have progressive renal disease (PLANET I): a randomised clinical trial

- *The Lancet Diabetes & Endocrinology*, *Available online 4 February 2015*,

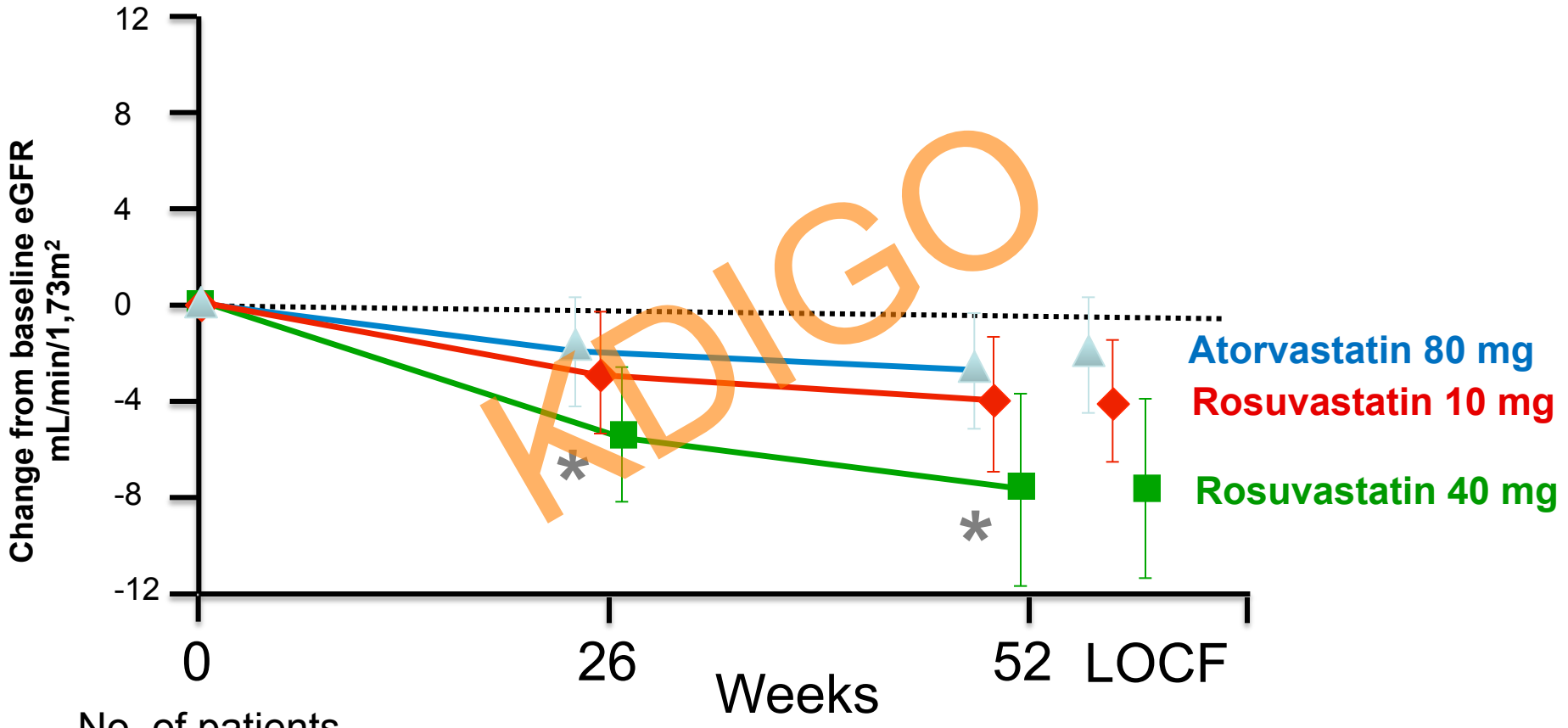
Dick de Zeeuw, Deborah A Anzalone, Valerie A Cain, Michael D Cressman, Hiddo J Lambers Heerspink, Bruce A Molitoris, John T Monyak, Hans-Henrik Parving, Giuseppe Remuzzi, James R Sowers, Donald G Vidt

Primary Endpoint: Proteinuria



No. of patients				
R10	107	98	91	107
R40	116	108	103	116
A80	102	92	81	102

Secondary Endpoint: Change in eGFR



No. of patients				
R10	107	100	93	107
R40	116	111	103	115
A80	102	92	84	101

Table 4 | Recommended doses (mg/d) of statins in adults with CKD

Statin	eGFR G1-G2	eGFR G3a-G5, including patients on dialysis or with a kidney transplant
Lovastatin	GP	nd
Fluvastatin	GP	80[1]
Atorvastatin	GP	20[2]
Rosuvastatin	GP	10[3]
Simvastatin/Ezetmibe	GP	20/10[4]
Pravastatin	GP	40
Simvastatin	GP	40
Pitavastatin	GP	2

Lower doses than those used in major trials of statins in CKD populations may be appropriate in Asian countries.
1 ALERT, 2 4D, 3 AURORA, 4 SHARP

Kidney inter., Suppl. 2013; 3: 259–305

Objectives

- Patterns of dyslipidemia in DKD
- Lipid-lowering medications: are all statins the same?
- Role of fibrates and HDL-raising therapies, e.g. CETP inhibitors
- Novel lipid-lowering agents, e.g. PSCK9 inhibitors

Fibrates: Risk Benefits and Role in Treating Dyslipidemias

25

Min Jun and Vlado Perkovic

Fibrate characteristics

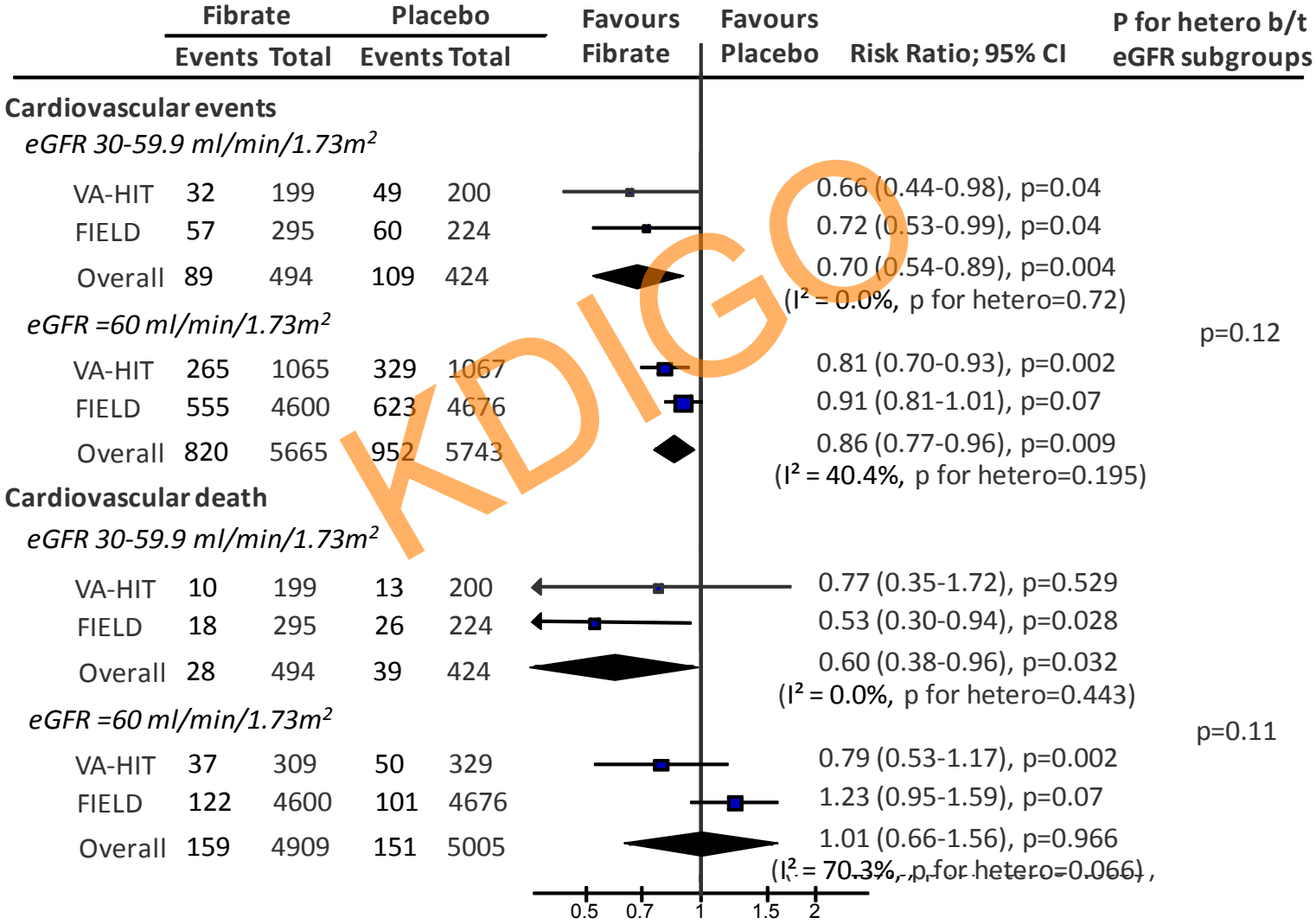
Fibrates effectively reduce triglycerides and elevate HDL-C targeting the residual CV risk

Jun et al. Lancet 2010;375:1875-84

Fibrates (most data with fenofibrate) raise serum creatinine (reversible process) and the mechanisms are still not settled (creatinine secretion, generation of vasodilatory prostaglandins, metabolic production). It does not translate to longer-term harm (FIELD and ACCORD trials) but potential benefits

Davis et al. Diabetologia 2010;54:280-90
Mychaleckyj et al. Diabetes Care 2012;35:1008-14

Fibrates in CKD



J Am Coll Cardiol. 2012;60:2061-71

Fibrate characteristics

Fibrates and metabolites accumulate with declining renal function. The risk of developing myopathy alone or in combination with statins (gemfibrocil>fenofibrate) increases.

Jones & Davidson AJ Cardiol 2005;95:120-2

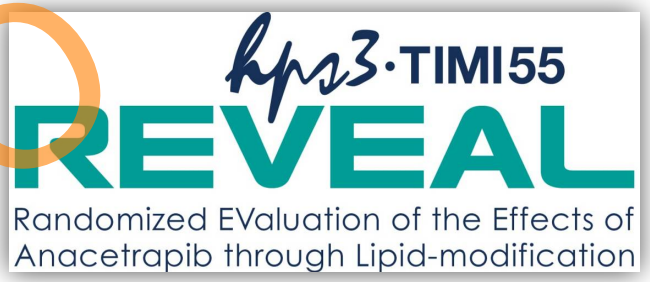
KDIGO 2013 (and KDOQI 2003) recommended that fibrate treatment be avoided in patients with an eGFR < 30 ml/min/ 1.73m2 and not used at all in combination with statins.

CETP Inhibition

Cholesterylester transfer protein normally transfers cholesterol from HDL to VLDL or LDL. Inhibition of this process results in higher HDL levels. LDL levels are reduced as well as Lp(a) by ~ 40%.

CETP Inhibition

Anacetrapib: REVEAL study ongoing (30.000 patients)



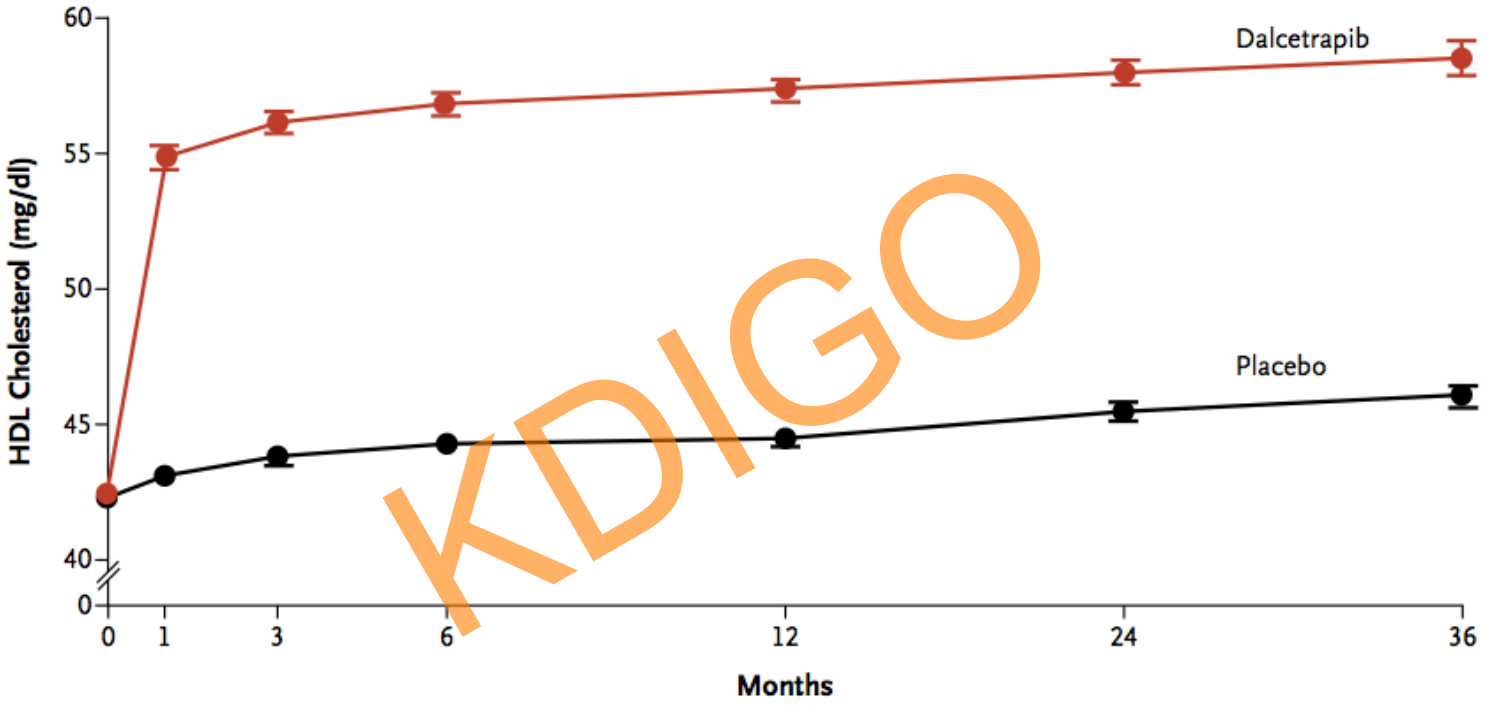
Studies have recently found low levels of anacetrapib in the blood of people who last took anacetrapib up to 4 years previously

Evacetrapib: ACCELERATE study ongoing (12.000 patients) started 10/2012 (4 P MACE) (S-creatinine < 2.2 mg/dl)

Changes in blood lipid and lipoprotein concentrations with CETP inhibitors

	Torcetrapib	Dalcetrapib	Anacetrapib	
	60 mg daily	600 mg daily	40 mg daily	150 mg daily
Total cholesterol	4%	n/a	1%	3%
LDL-cholesterol	-24%	-4%	-27%	-40%
Triglycerides	-9%	-3%	-11%	-11%
Apo B	-12%	n/a	-20%	-29%
HDL-cholesterol	61%	25%	86%	139%
Apo A1	25%	10%	32%	47%

HDL Targeting Therapies



No. at Risk

Placebo	7907	7685	7498	7272	6959	6436	3650
Dalcetrapib	7910	7663	7402	7196	6871	6333	3599

Schwartz et al. N Engl J Med 2012

Reasons for the dysfunctionality of HDL in CKD

CLINICAL RESEARCH www.jasn.org

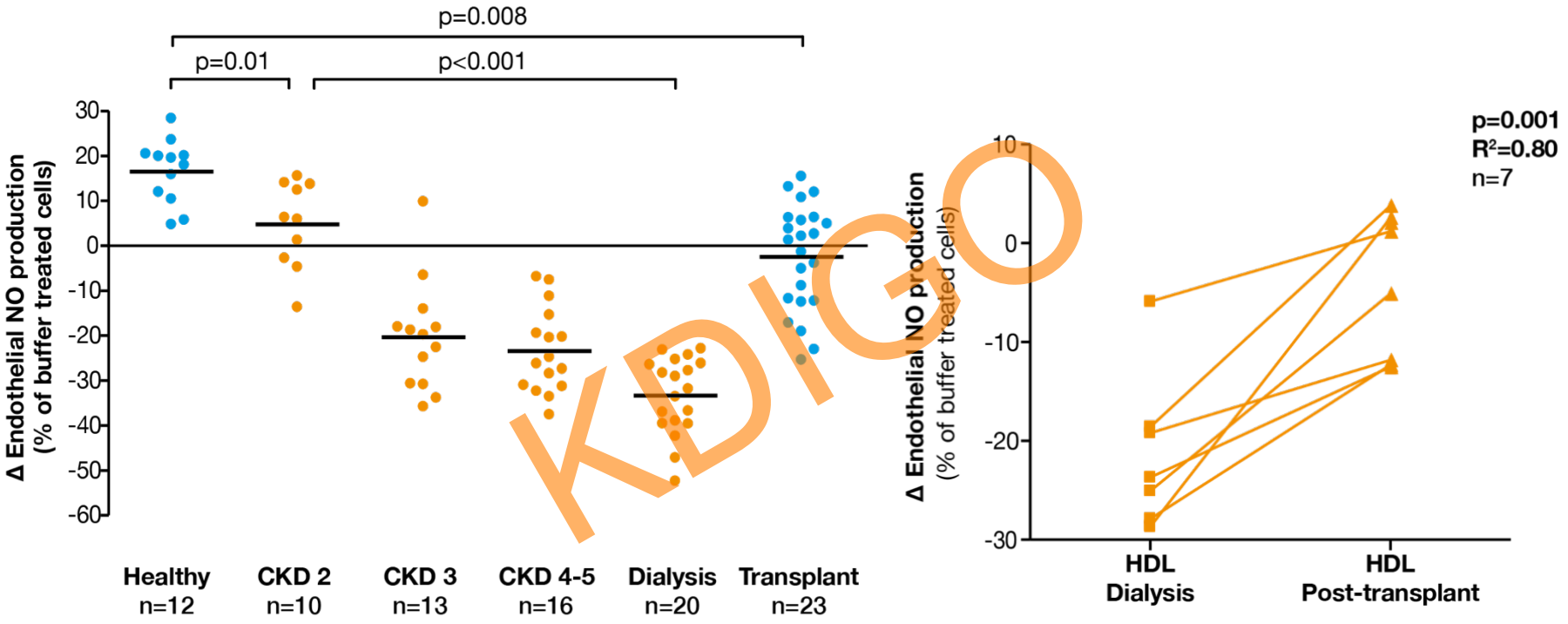
JASN 2012;23:934-947

Serum Amyloid A in Uremic HDL Promotes Inflammation

Thomas Weichhart,* Chantal Kopecky,* Markus Kubicek,† Michael Haidinger,* Dominik Döller,* Karl Katholnig,* Cacang Suarna,‡ Philipp Eller,§ Markus Tölle,‖ Christopher Gerner,¶ Gerhard J. Zlabinger,** Markus van der Giet,‖ Walter H. Hörl,* Roland Stocker,‡ and Marcus D. Säemann*

HDL isolated from healthy individuals inhibited the production of inflammatory cytokines by peripheral monocytes and HDL from HD patients did not show this anti-inflammatory property. Many HDL samples even promoted the production of inflammatory cytokines

HDL in children with CKD promotes endothelial dysfunction and an abnormal vascular phenotype



Shroff et al. JASN 2014 Nov;25:2658-68

Is HDL in CKD patients a toxic protein ?

CLINICAL EPIDEMIOLOGY www.jasn.org

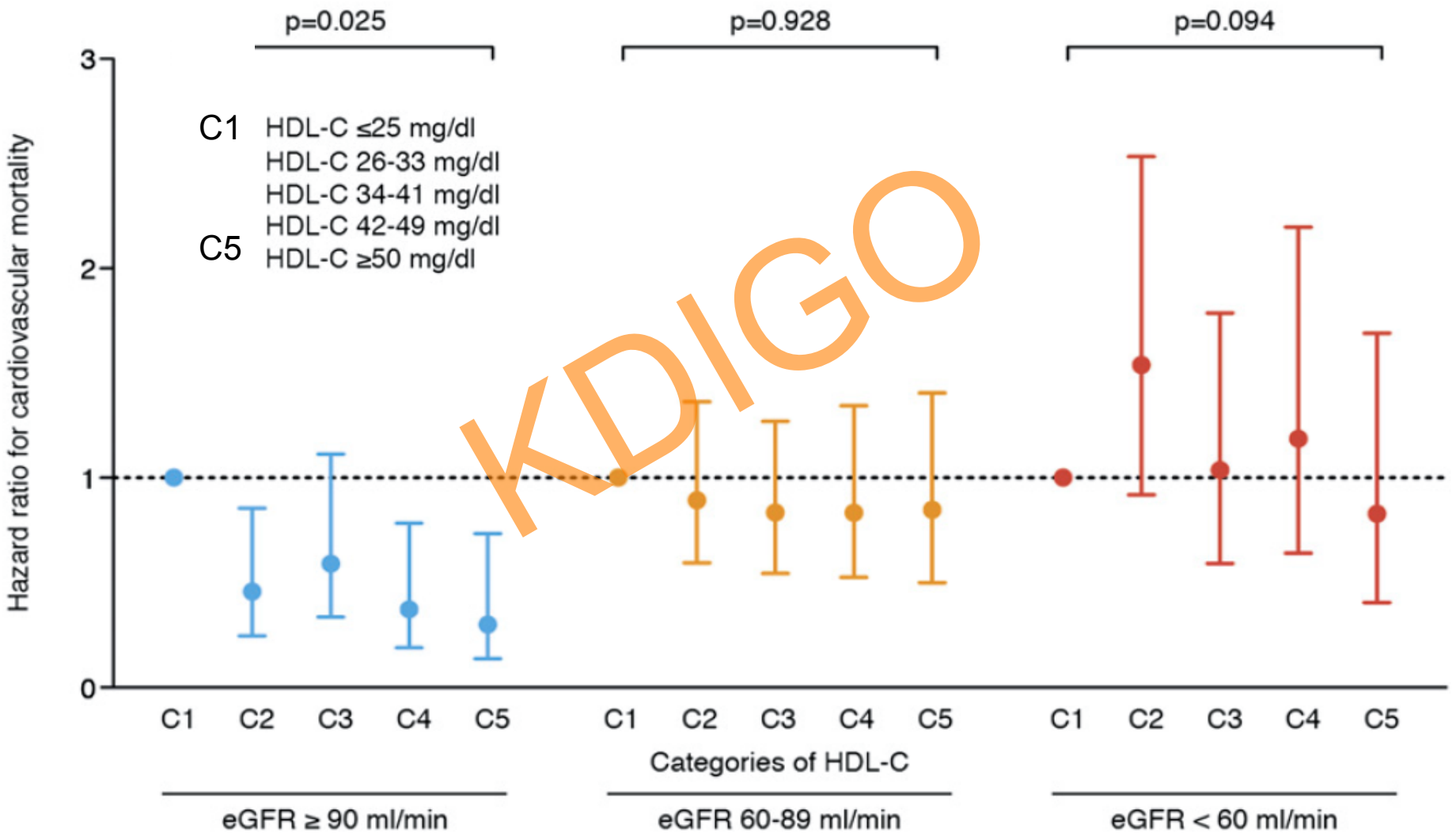
HDL Cholesterol Is Not Associated with Lower Mortality in Patients with Kidney Dysfunction

Stephen Zewinger,* Thimoteus Speer,* Marcus E. Kleber,† Hubert Scharnagl,‡ Rainer Woitas,§ Philipp M. Lepper,‖ Karolin Pfahler,* Sarah Seiler,* Gunnar H. Heine,* Winfried März,†‡¶ Günther Silbernagel,** and Danilo Fliser*

*Departments of Internal Medicine IV and ‖Internal Medicine V, Saarland University Hospital, Homburg/Saar, Germany; †Medical Faculty Mannheim, University of Heidelberg, Medical Clinic V (Nephrology, Hypertensiology, Endocrinology), Mannheim, Germany; ‡Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Graz, Austria; §Division of Nephrology, Department of Internal Medicine I, University of Bonn, Bonn, Germany; ¶Synlab Academy, Synlab Services LLC, Mannheim, Germany; and **Department of Angiology, Swiss

JASN 2014;25:1073-1082

HDL and cardiovascular events



Zewinger et al. JASN 2014

CLINICAL RESEARCH www.jasn.org

HDL Cholesterol, Apolipoproteins, and Cardiovascular Risk in Hemodialysis Patients

Günther Silbernagel,* Bernd Genser,†‡§ Christiane Drechsler,§‖ Hubert Scharnagl,¶ Tanja B. Grammer,† Tatjana Stojakovic,¶ Vera Krane,§‖ Eberhard Ritz,** Christoph Wanner,§‖ and Winfried März¶††‡‡

- 1255 HD patients with T2DM
- 66 years, BMI 28 Kg/m2
- FU 4 years, 49 % death rate, 31% CV events
- HDL-C, Apo A1 and Apo C3 were not related to outcomes
- Inverse association of ApoA2 with mortality (HR 0.63, 95% CI 0.40-0.89)

JASN 2015 Feb;26:484-492.

Objectives

- Patterns of dyslipidemia in DKD
- Lipid-lowering medications: are all statins the same?
- Role of fibrates and HDL-raising therapies, e.g. CETP inhibitors
- Novel lipid-lowering agents, e.g. PSCK9 inhibitors

Background: PCSK9 Inhibition

Alirocumab and Evolocumab are fully human monoclonal antibodies against PCSK9. They reduce LDL-C by up to 65% and are well tolerated in randomized, placebo-controlled, phase 2 clinical trials up to 1 year in over 3000 hypercholesterolemic patients.[1-7]

1. Lancet 2012;380:1995-2006.
2. Circulation 2012;126:2408-2417.
3. JAMA 2012;308:2497-2506.
4. Lancet 2012;380:2007-2017
5. J Am Coll Cardiol 2012;59:2344-53
6. N Engl J Med 2012;367:1891-900
7. Lancet 2012;380:29-36.

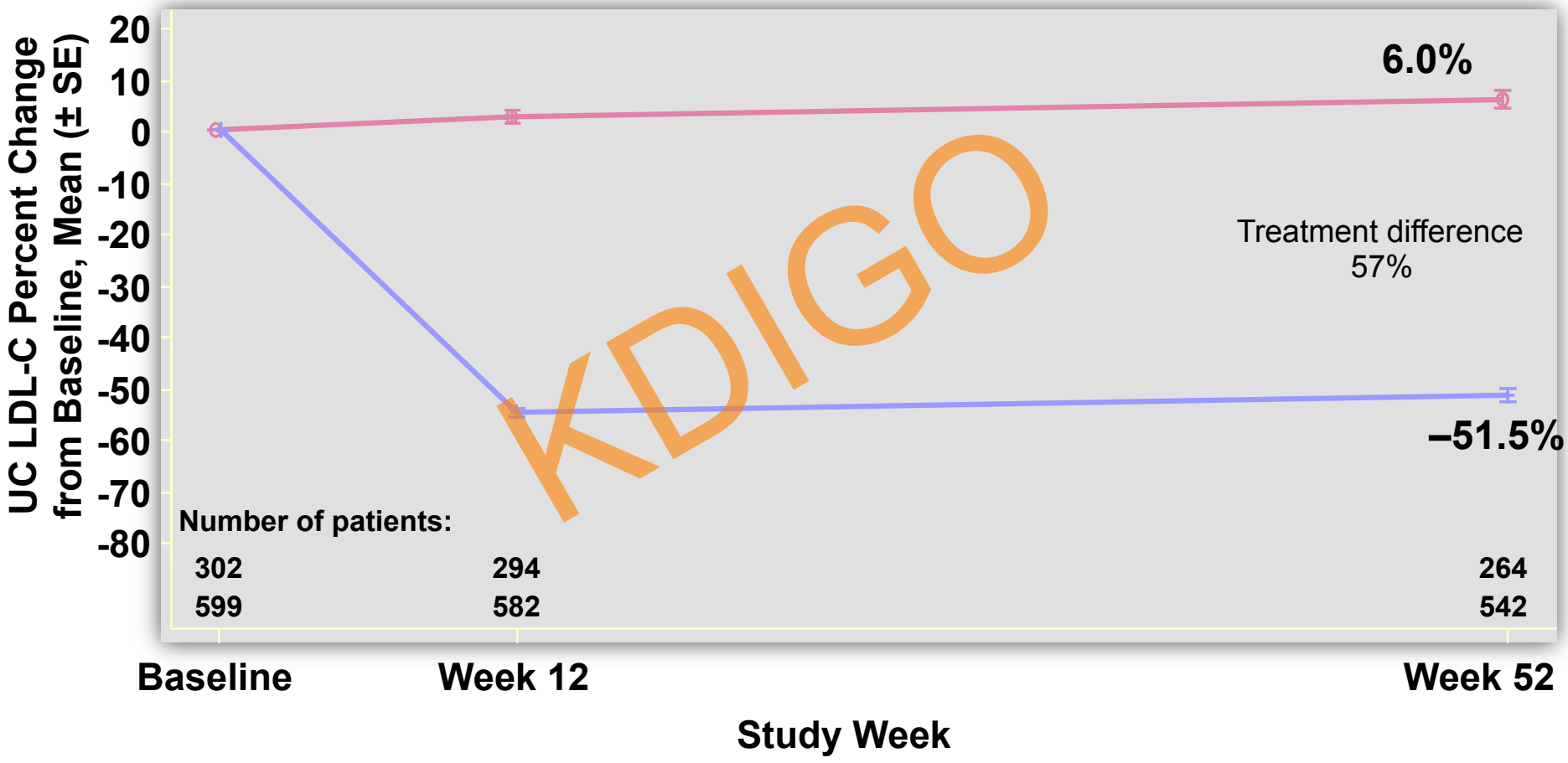
ORIGINAL ARTICLE

A 52-Week Placebo-Controlled Trial of Evolocumab in Hyperlipidemia

Dirk J. Blom, M.D., Ph.D., Tomas Hala, M.D., Michael Bolognese, M.D., Michael J. Lillestol, M.D., Phillip D. Toth, M.D., Lesley Burgess, M.B., B.Ch., M.Med., Ph.D., Richard Ceska, M.D., Ph.D., Eli Roth, M.D., Michael J. Koren, M.D., Christie M. Ballantyne, M.D., Maria Laura Monsalvo, M.D., Kate Tsirtsonis, M.Sc., Jae B. Kim, M.D., Rob Scott, M.D., Scott M. Wasserman, M.D., and Evan A. Stein, M.D., Ph.D., for the DESCARTES Investigators*

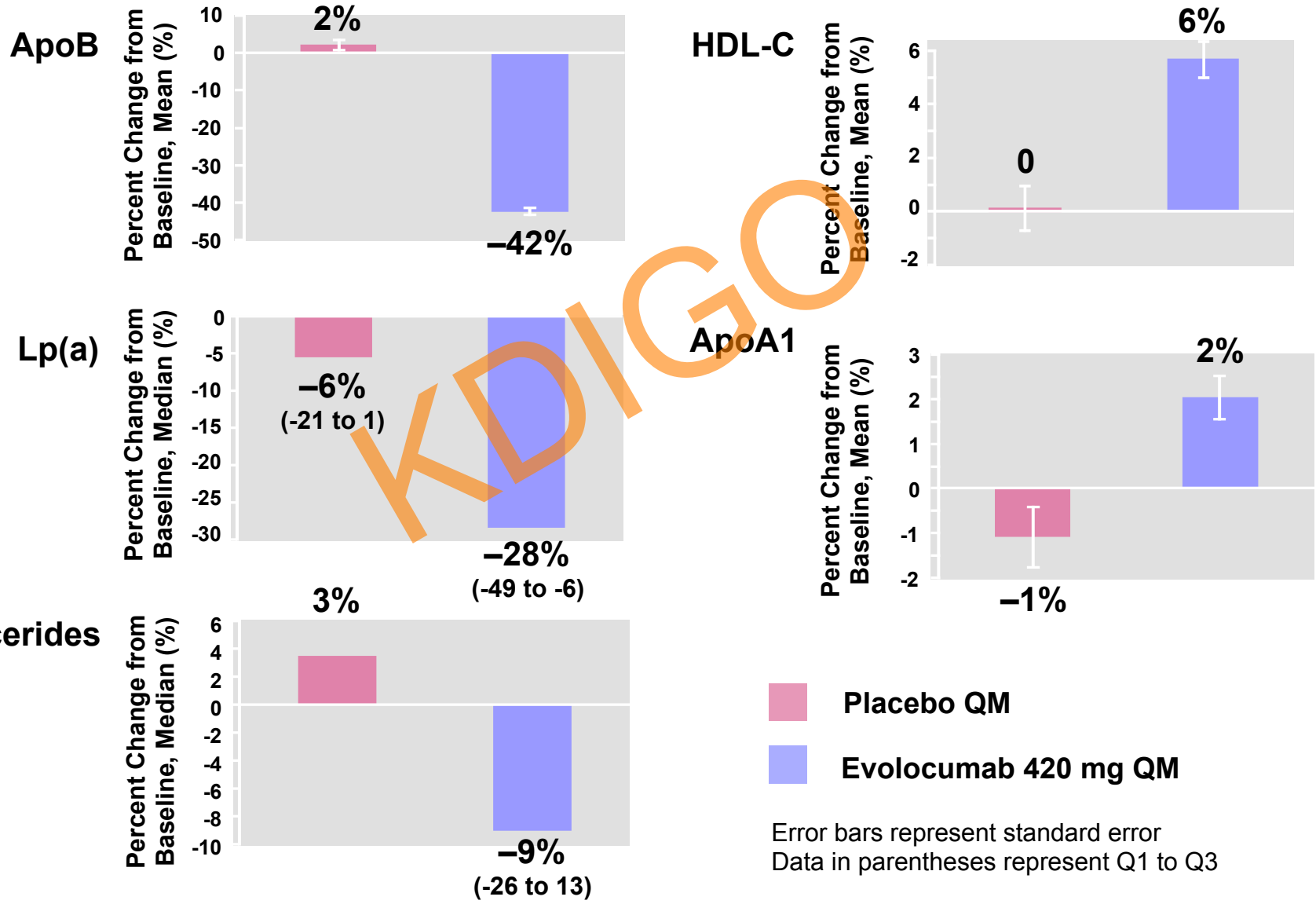
This article was published on March 29 2014, at NEJM.org.

% Change LDL-C From Baseline



Full analysis set, LDL by Ultracentrifugation

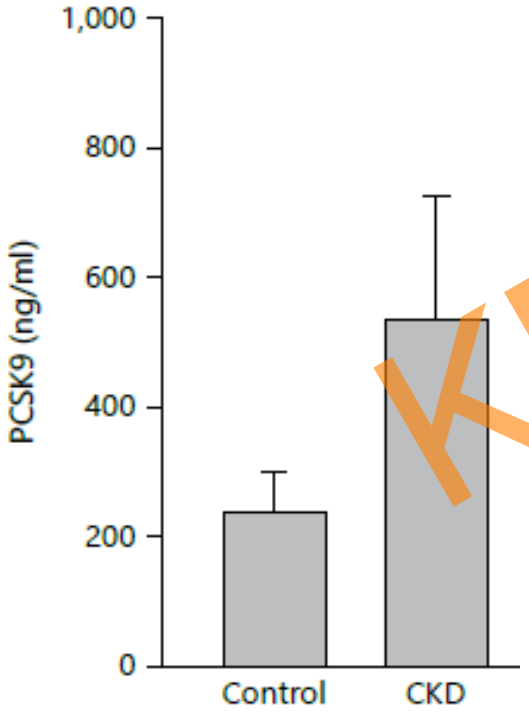
Other Lipids at Week 52



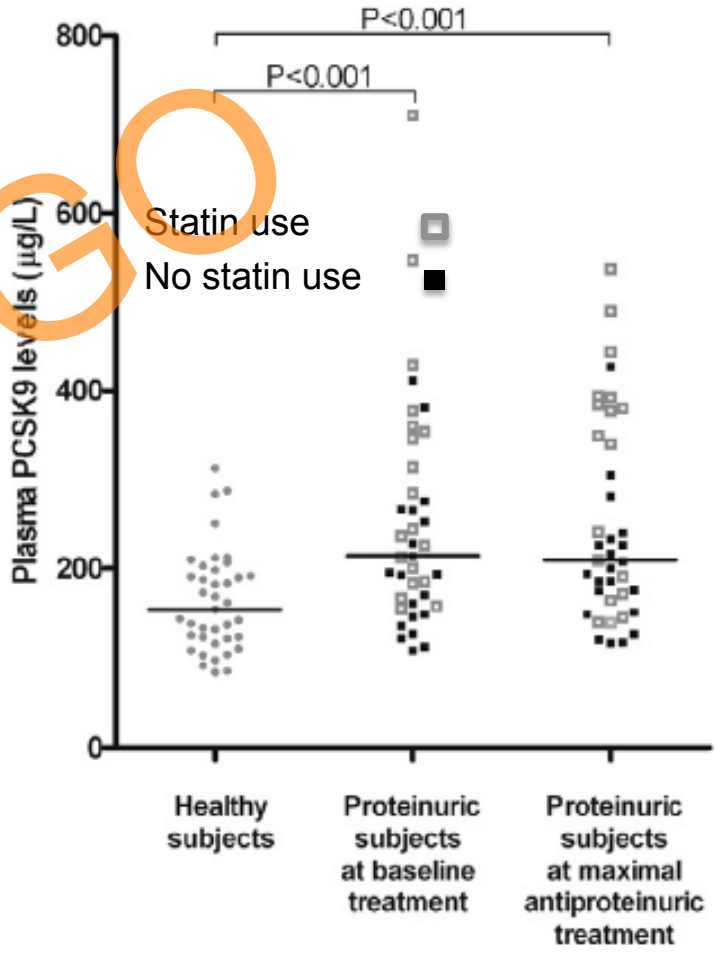
Error bars represent standard error
Data in parentheses represent Q1 to Q3

PCSK9 is elevated in CKD and proteinuria

Konarzewski M et al. Am J Nephrol 2014;40:157–63



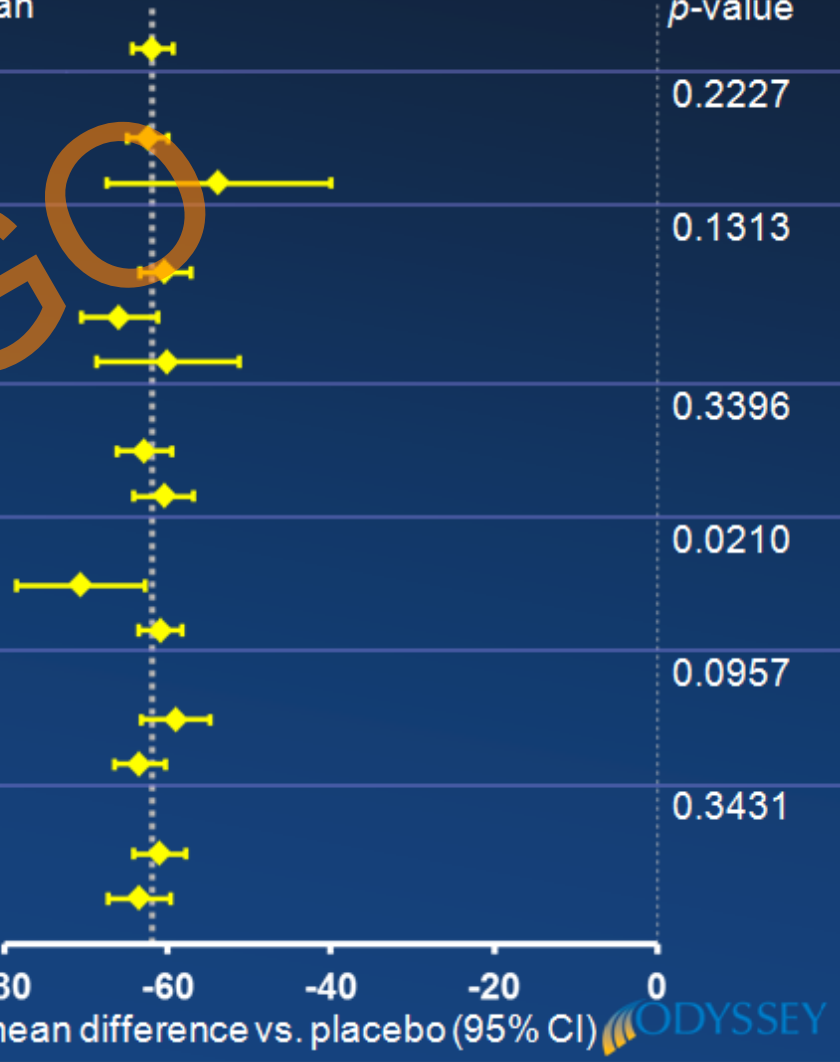
Kwakernaak AJ et al. Atherosclerosis 2013;226:459–65



ODYSSEY LONG TERM

Difference (alirocumab vs. placebo) in LDL-C % Change from Baseline to W24

Subgroup	Alirocumab n	Alirocumab LS mean	Placebo n	Placebo LS mean	Interaction *p*-value
Overall	1530	-61.0	780	0.8	
Race					0.2227
White	1419	-61.6	722	0.8	
Black/African American	53	-49.5	24	4.3	
Age					0.1313
<65	963	-60.4	498	-0.1	
65 to <75	442	-62.9	221	3.0	
≥75	125	-59.5	61	0.5	
BMI					0.3396
<30	852	-61.5	406	1.3	
≥30	674	-60.3	371	0.1	
Moderate CKD					0.0210
Yes	73	-62.0	174	8.7	
No	1356	-60.9	707	0.0	
Diabetes					0.0957
Yes	545	-60.0	273	-1.0	
No	985	-61.6	507	1.8	
Baseline fasting TGs, mg/dL					0.3431
<150	928	-58.8	450	2.2	
≥150	602	-64.5	329	-1.1	



All patients on background of maximally tolerated statin ± other lipid-lowering therapy

ODYSSEY

Controversy & Summary

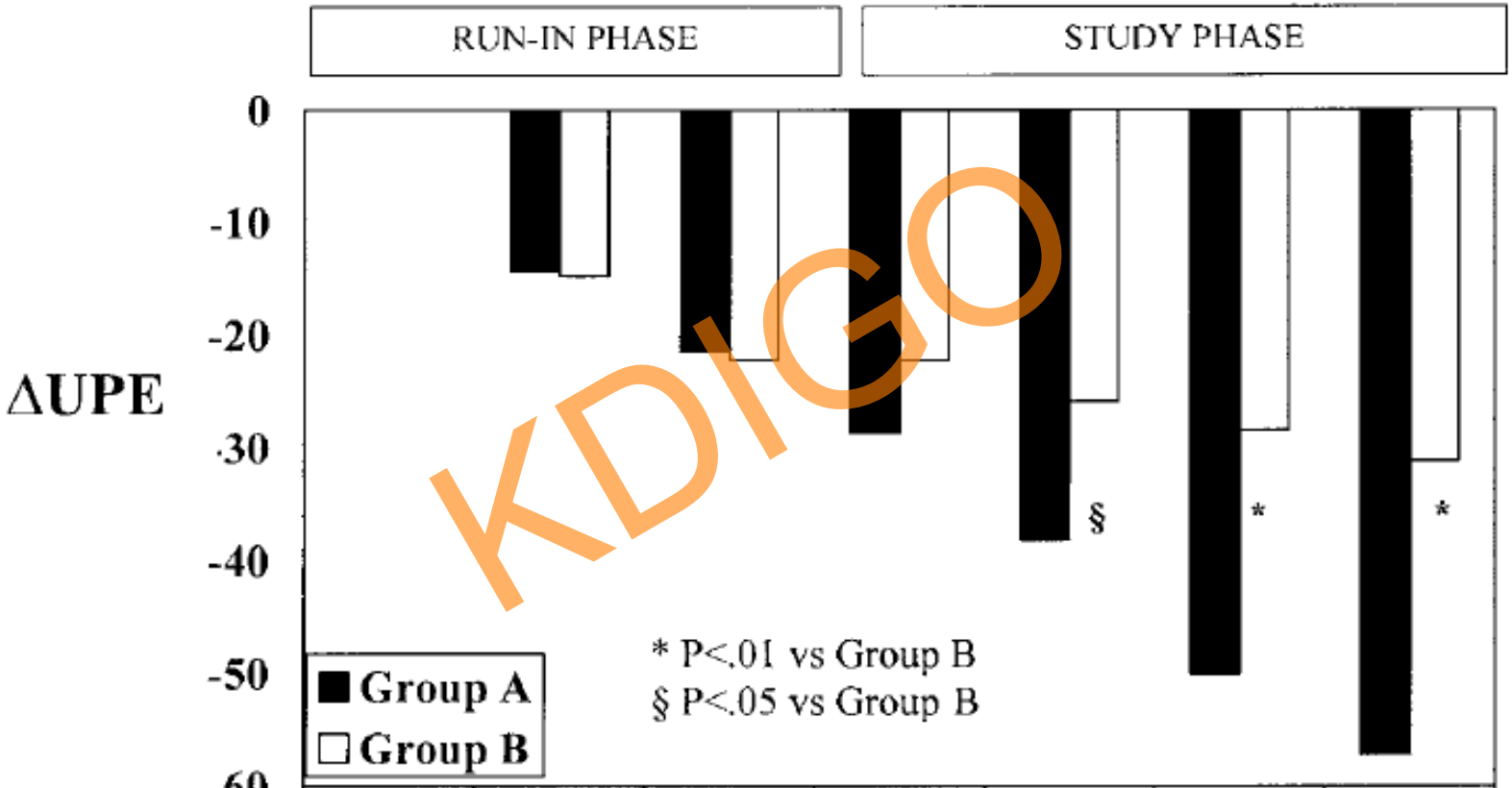
- Outcomes of the CKD patients within the CETP inhibitor trials are of interest
- Subcategories of CKD patients may show an unmet need for fibrates and PCSK9 inhibitors or a combination of these drugs
- Lipoprotein(a) may become a new target in CKD patients, especially in proteinuric or nephrotic syndrome patients

Thank you

A Controlled, Prospective Study of the Effects of Atorvastatin on Proteinuria and Progression of Kidney Disease

Stefano Bianchi, MD, Roberto Bigazzi, MD, Alberto Caiazza, MD, and Vito M. Campese, MD

Am J Kidney Dis 2003



	-12	-6-	0	3	6	9	12
Group A	0	-14,3	-21,4	-28,6	-38,2	-50	-57,2
Group B	0	-14,8	-22,3	-22,3	-25,9	-28,5	-31,2

Months

	Start of Run-In Phase	Start of Study Phase
No. of patients (M/F)	56 (38/18)	—
Age	55.6 ± 1	—
BMI (w/h^2)	27.6 ± 0.26	—
Hypertension (yes/no)	27/29	—
Office systolic BP (mm Hg)	144.3 ± 2.4	133.0 ± 1.0
Office diastolic BP (mm Hg)	93.3 ± 1.8	84.8 ± 0.8
CrCl (mL/min)	55.5 ± 1.4	50.4 ± 1.3
UPE (g/24 h)	2.7 ± 0.1	2.2 ± 0.1
Total cholesterol (mg/dL)	320.4 ± 4.7	310.6 ± 3.3
LDL cholesterol (mg/dL)	189 ± 5	198 ± 4.1
HDL cholesterol (mg/dL)	36.2 ± 0.7	36.1 ± 0.6
Serum albumin (g/dL)	3.35 ± 0.06	3.30 ± 0.06

Controversy & Summary

- Do new treatments provide the opportunity to go from moderate intensity to high intensity LDL lowering in CKD patients?
- Acute fibrate-induced creatinine elevation in T2DM with relatively preserved renal function may confer longer-term renoprotective effects.
- The correction of the abnormal HDL composition and the improvement of its vasoprotective properties remains to be shown.