Ruolo emergente delle HDL e nuovi farmaci: quali prospettive per il rene?

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Lipids and lipoproteins in CKD

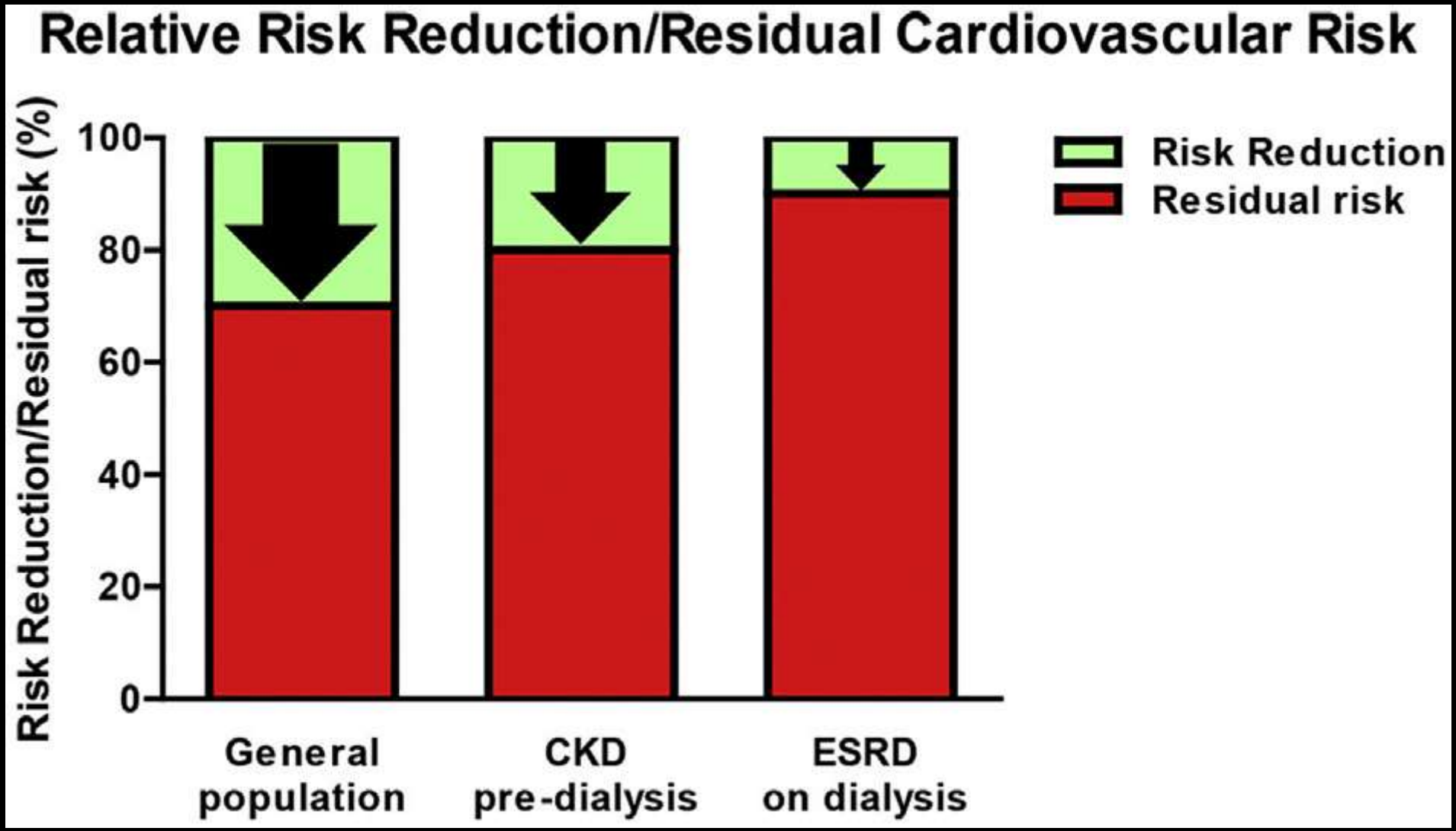
Table 1. Lipid and apolipoprotein profile across CKD

	Pre-dialysis CKD	Nephrotic syndrome	Hemodialysis	Peritoneal dialysis
Total cholesterol	→↑	↑↑	→↓	↑
LDL cholesterol	→↑	↑↑	→↓	↑
Small dense LDL	↑	↑	↑	↑
ApoB	→	↑↑	↓→↑	↑
HDL	↓	→↓	↓	↓
Triglyceride	↑	↑	↑	↑↑
Lp(a)	→↑	↑↑	↑	↑↑
ApoA-I	→↓	→↑	↓	↓

CKD, chronic kidney disease; LDL, low-density lipoprotein.

Kon et al, Arch. Med. Res. 2015

CKD and cardiovascular risk



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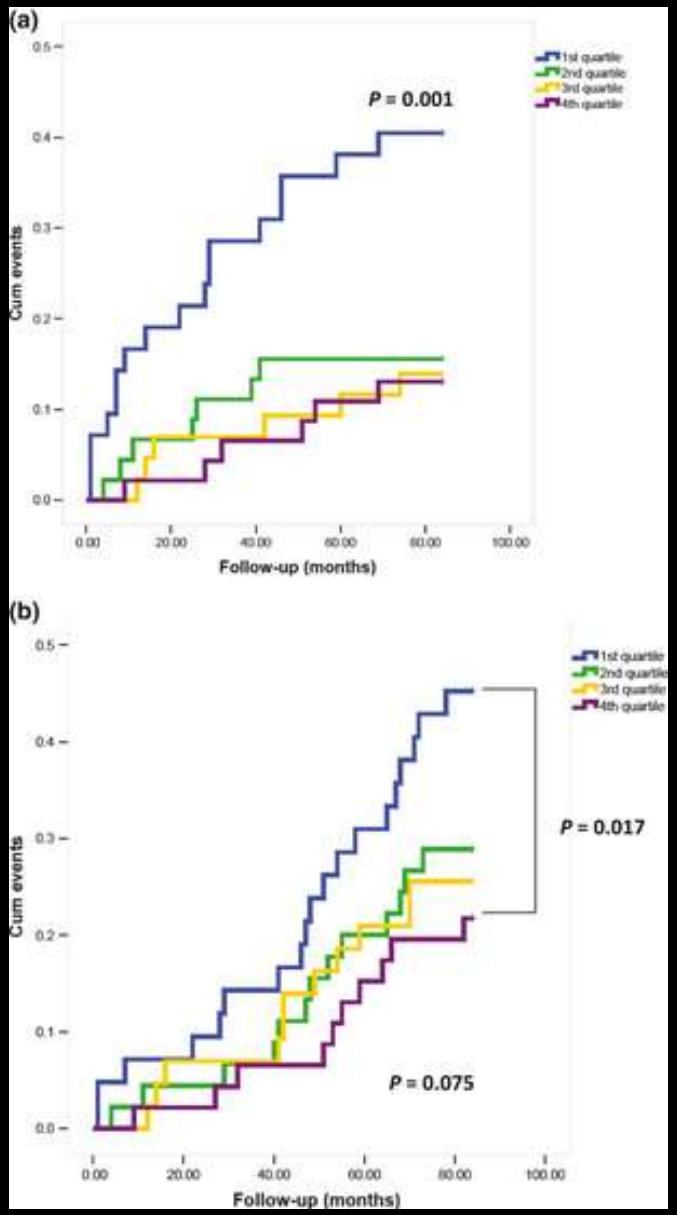
HDL-C levels are an independent predictor of the progression of chronic kidney disease

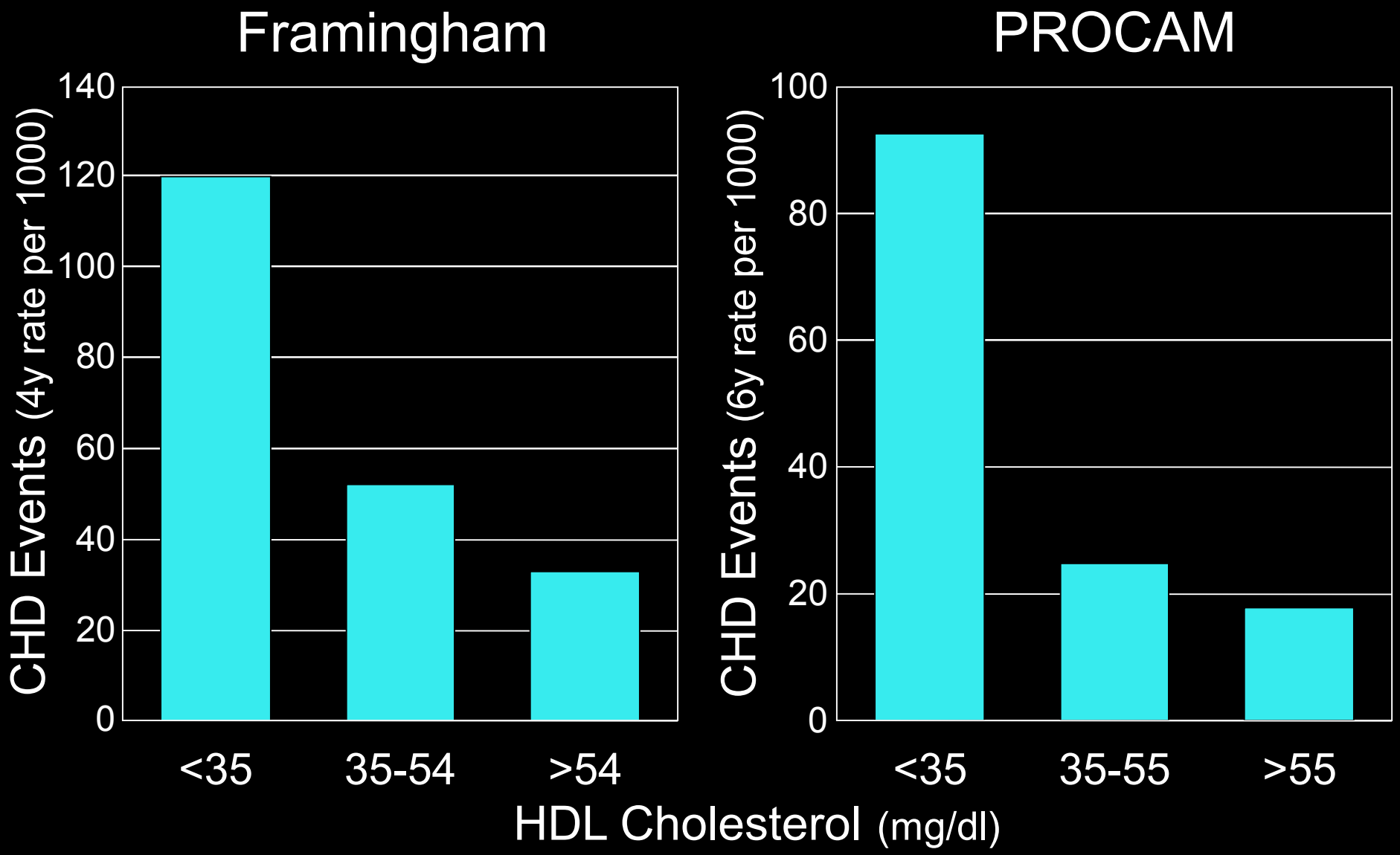
1st quartile: <40 mg/dl
2nd quartile: 40-48 mg/dl
3rd quartile: 48-60 mg/dl
4th quartile: ≥60 mg/dl



The events considered were for panel (a) doubling of creatinine levels and/or entry on dialysis; and for panel (b) GFR reduction by at least 50% and/or entry on dialysis.

Baragetti et al, J Intern Med 2013; 274: 252

HDL and Coronary Heart Disease



Gordon et al, Am.J.Med. 62:707,1977

Assmann et al, Atherosclerosis 124:S11, 1996

HDL Biologic Activities

- Reverse Cholesterol Transport

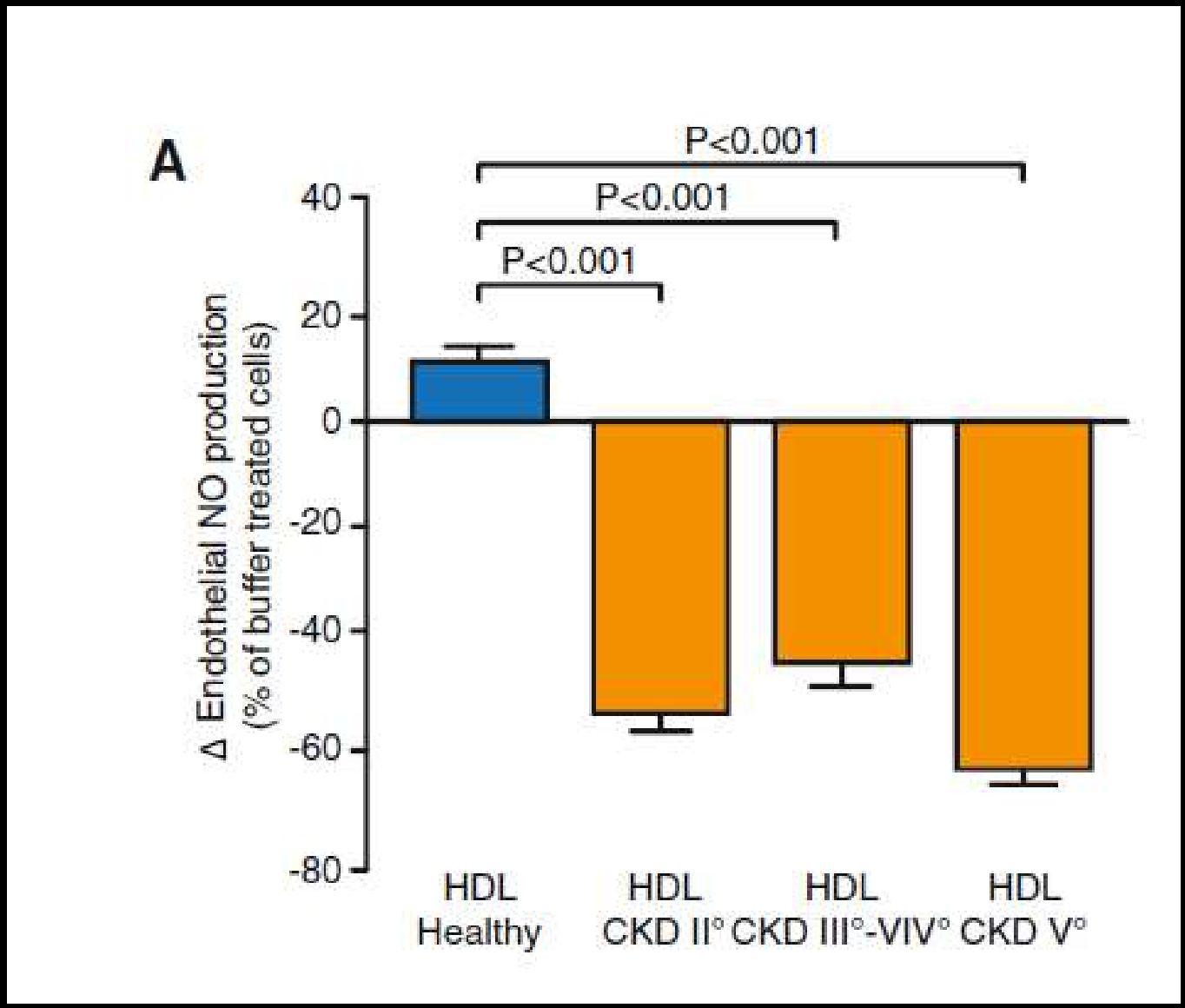
  Arterial cholesterol efflux
  Hepatic cholesterol uptake

- Endothelial Protection

  Cell adhesion
  Cytokines
  Vascular tone

- Antioxidant

HDL dysfunction in CKD



Speer et al Immunity 38:754, 2013

Plasma lipids in CKD

	CKD-HD	CKD	Controls	*P*
n	198	50	40	
Sex, M/F	124/74	33/17	24/16	0.906
Age, y	67.0±13.3	68.5±13.7	60.6±6.1	0.006
BMI, Kg/m^2	22.8±4.2	23.9±3.4	24.7±2.8	0.006
Smoking status, %				0.100
Never	59	65	50	
Former	19	31	38	
Current	22	4	12	
Hypertension, %	71	92	23	<0.0001
Diabetes, %	15	14	0	0.005

Data are Means±SD

Calabresi et al. J Intern Med 2015; 277:552

Plasma lipids in CKD

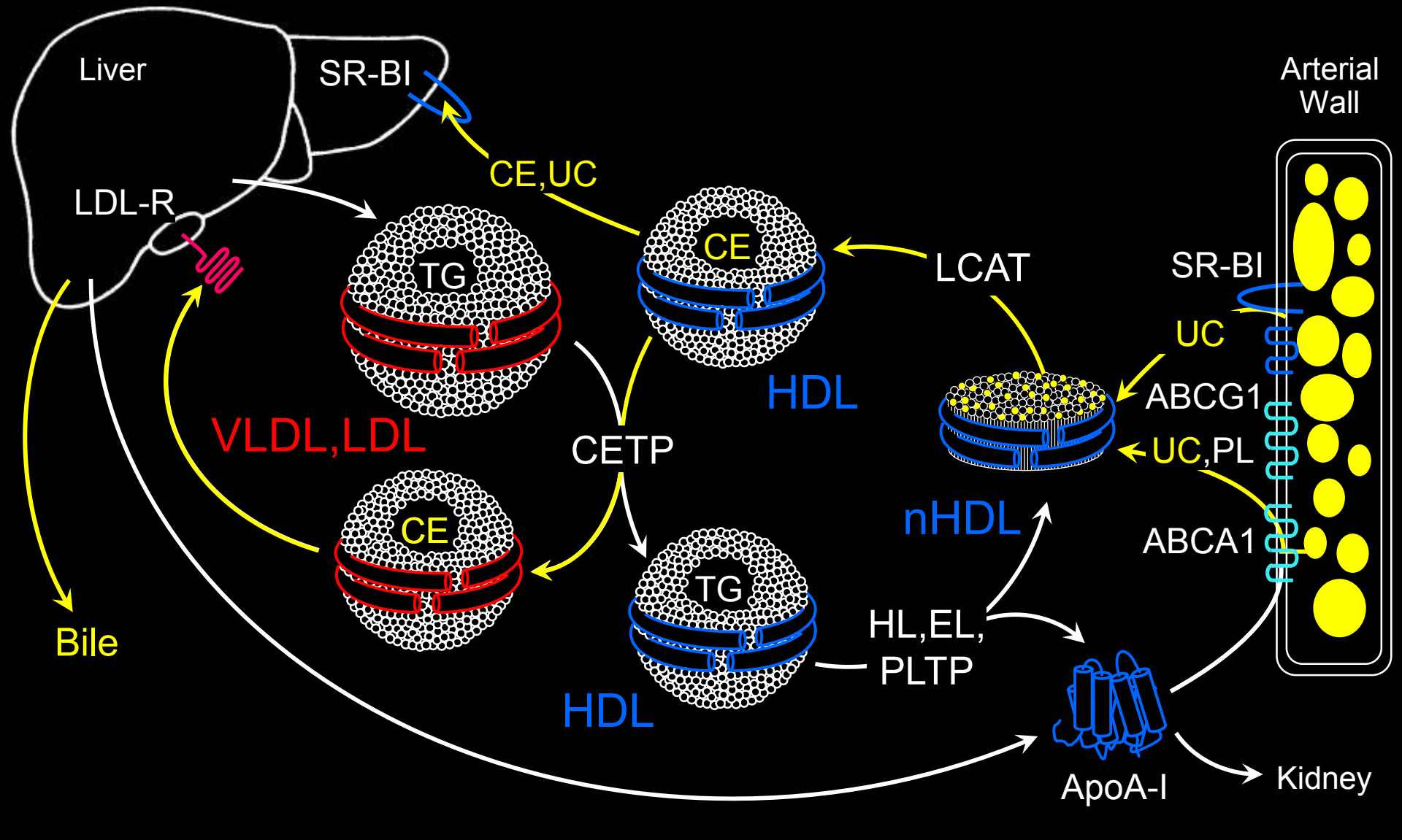
	CKD-HD	CKD	Controls	*P**
Total cholesterol, mg/dL	156.8±43.9	180.5±39.6	211.5±38.3	<0.0001
LDL cholesterol, mg/dL	85.5±37.4	99.7±34.0	131.5±33.2	<0.0001
HDL cholesterol, mg/dL	41.3±13.2	50.2±12.3	59.2±11.8	<0.0001
ApoA-I, mg/dL	92.3±20.5	119.2±18.0	134.7±17.5	<0.0001
ApoA-II, mg/dL	20.3±5.4	22.8±4.2	26.4±3.7	<0.0001
ApoB, mg/dL	79.6±28.9	100.7±27.4	119.4±32.7	<0.0001
Triglycerides, mg/dL	150.7±83.1	153.4±71.0	103.5±44.4	0.001

Data are Means±SD.

**P* values, assessed by one way ANOVA or Chi-square test, adjusted for sex, age, BMI, smoking status, hypertension, diabetes, and assumption of lipid-modifying agents.

Calabresi et al. J Intern Med 2015; 277:552

HDL Metabolism
and Antiatherogenic Cholesterol Transport



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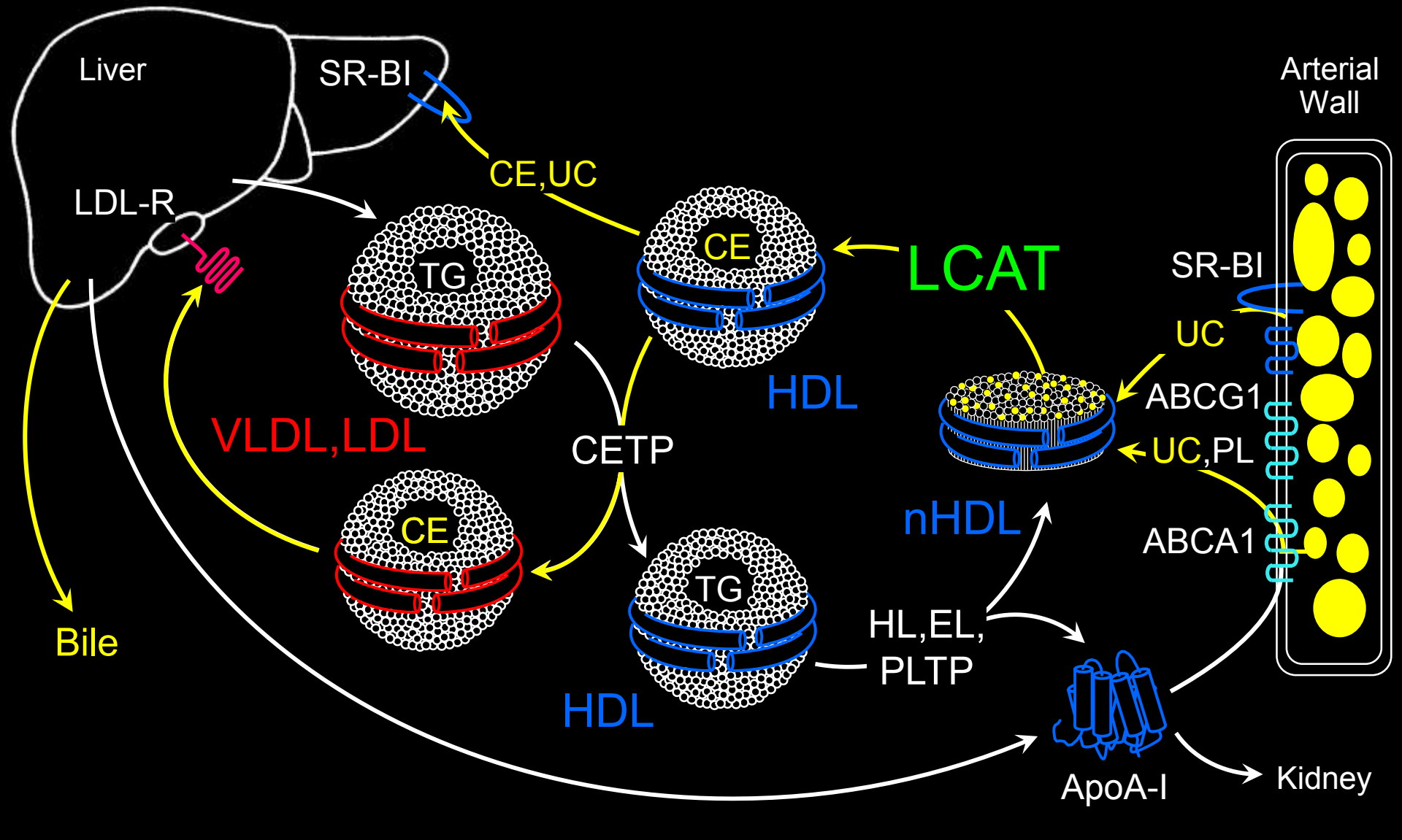


Lecithin:Cholesterol Acyltransferase

- 63-65 kD monomeric glycoprotein
- gene mapped to chromosome 16q22
- consists of 6 exons encoding a protein of 440 residues
- mature plasma protein: 416 aa
- 6 cysteines, Cys^{31} and Cys^{184} are free
- 4 N-glycosylation and 2 O-glycosylation sites

- synthesized in the liver (and brain, testes)
- circulates in plasma reversibly bound to HDL (and LDL)
- average plasma levels: ~5 μg/ml

- esterifies cholesterol in biological fluids

Familial LCAT Deficiency

Biochemical Phenotype

- Low HDL-C
- High Triglycerides
- Normal LDL-C

Santamarina-Fojo S, Hoeg JM, Assmann G, Brewer HBJr
The Metabolic & Molecular Bases of Inherited Diseases
McGraw-Hill, 2001: 2817-2833.

Genetic LCAT Deficiency in Italy

Plasma Lipids/lipoproteins

Number of mutant *LCAT* alleles	Two (n=18)	One (n=63)	Zero (n=39)	Trend *P**
TC (mg/dl)	160.7 ±20.8	162.4 ±7.2	196.7 ±9.2	0.344
UC (mg/dl)	125.1 ±17.5	49.3 ±2.2	50.4 ±4.1	<0.001
LDL-C (mg/dl)	102.9 ±16.5	97.2 ±6.6	114.6 ±8.5	0.578
HDL-C (mg/dl)	10.4 ±1.6	40.0 ±2.0	51.4 ±2.9	<0.001
TG (mg/dl)	242.4 ±37.5	125.1 ±8.6	118.8 ±30.3	<0.001
ApoA-I (mg/dl)	47.4 ±4.7	105.3 ±3.4	131.4 ±5.0	<0.001
ApoA-II (mg/dl)	10.4 ±1.4	28.9 ±0.8	34.3 ±1.6	<0.001
ApoB (mg/dl)	60.7 ±11.7	90.0 ±4.2	93.9 ±6.1	0.004

Calabresi et al, Atherosclerosis 222:299; 2012

Mean ±SEM, *adjusted for age, sex and family

Familial LCAT Deficiency

Biochemical Phenotype

Low HDL-C

High Triglycerides

Normal LDL-C

Clinical Phenotype

Corneal opacity

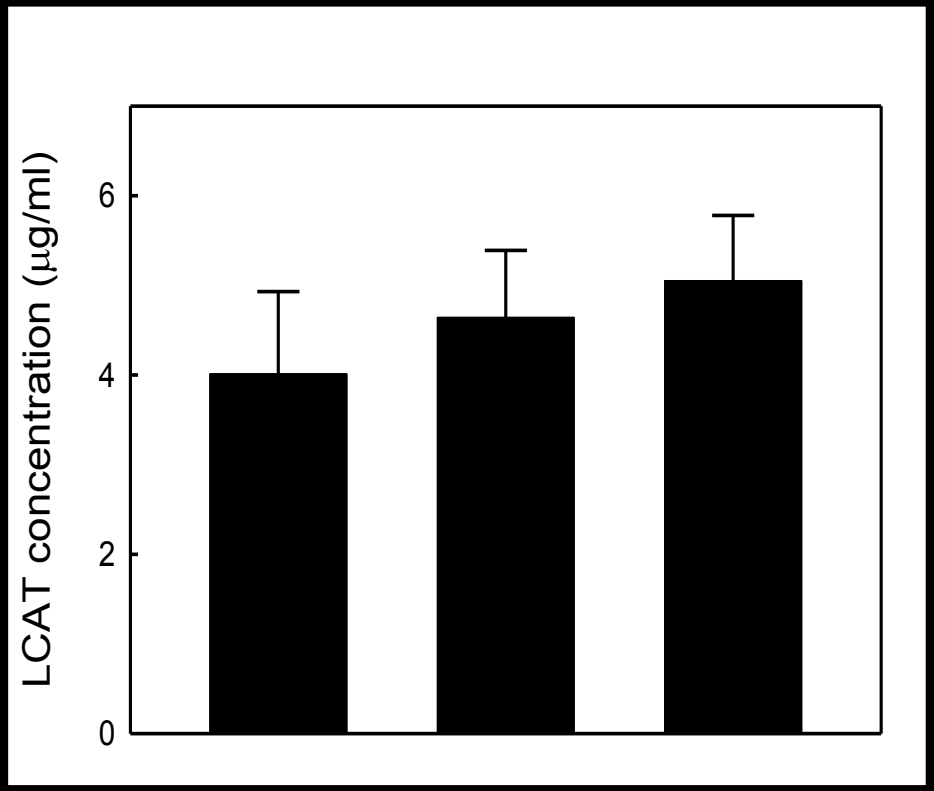
Anemia

Renal disease

Santamarina-Fojo S, Hoeg JM, Assmann G, Brewer HBJr
The Metabolic & Molecular Bases of Inherited Diseases
McGraw-Hill, 2001: 2817-2833.

LCAT concentration and activity in CKD

P<0.0001



Calabresi et al. J Intern Med 2015; 277:552

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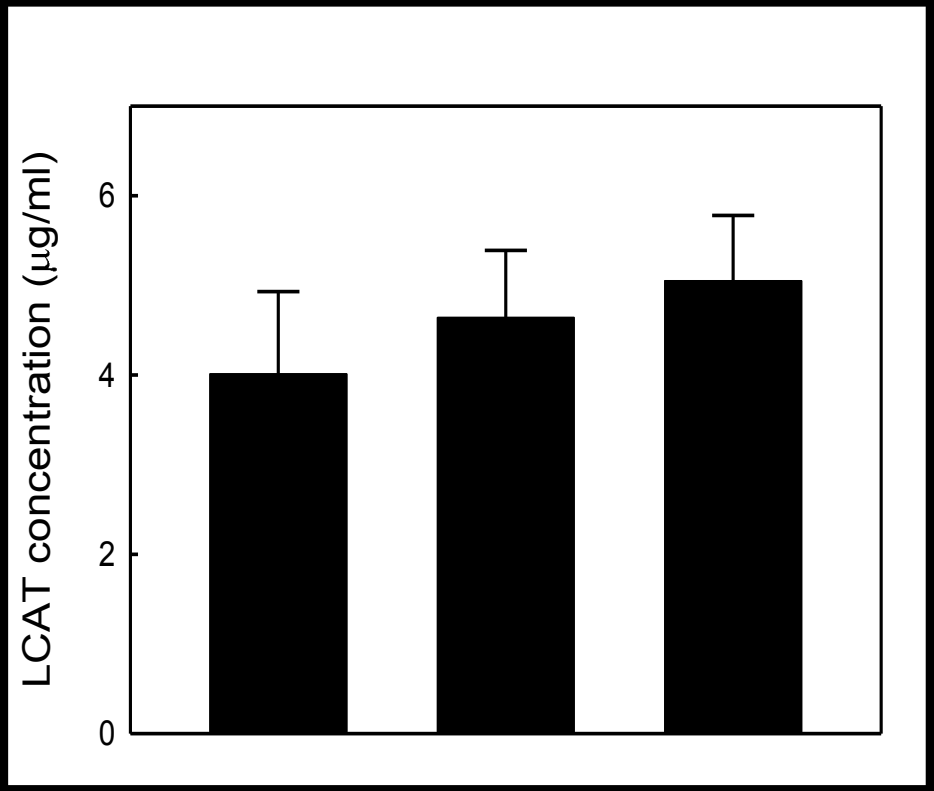
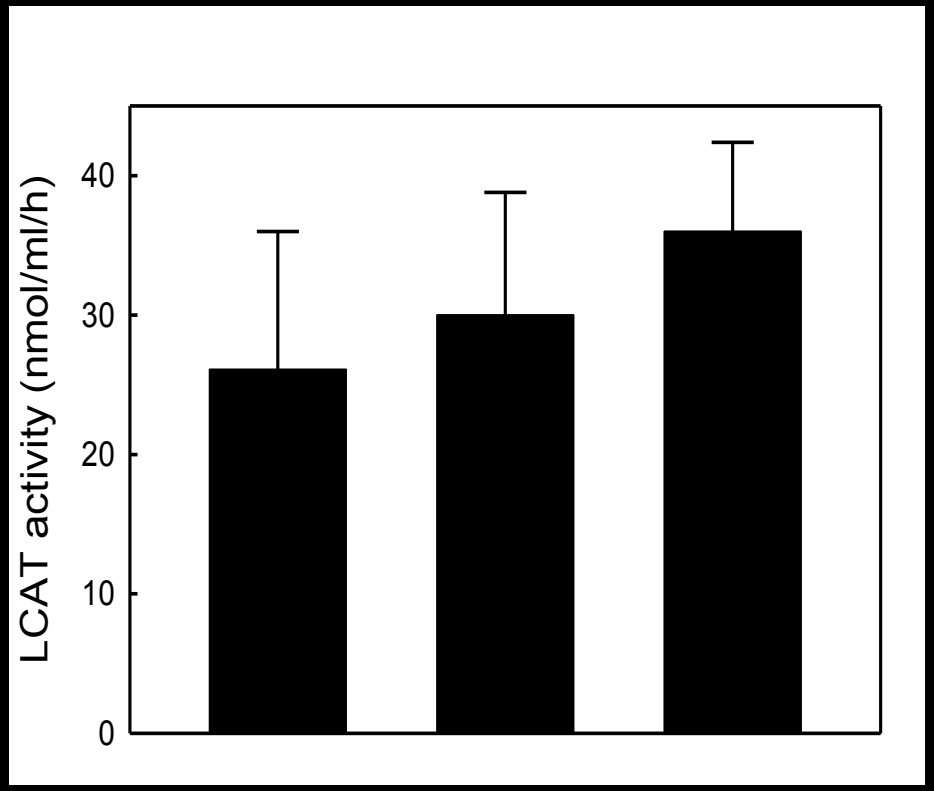


P<0.0001



Calabresi et al. J Intern Med 2015; 277:552

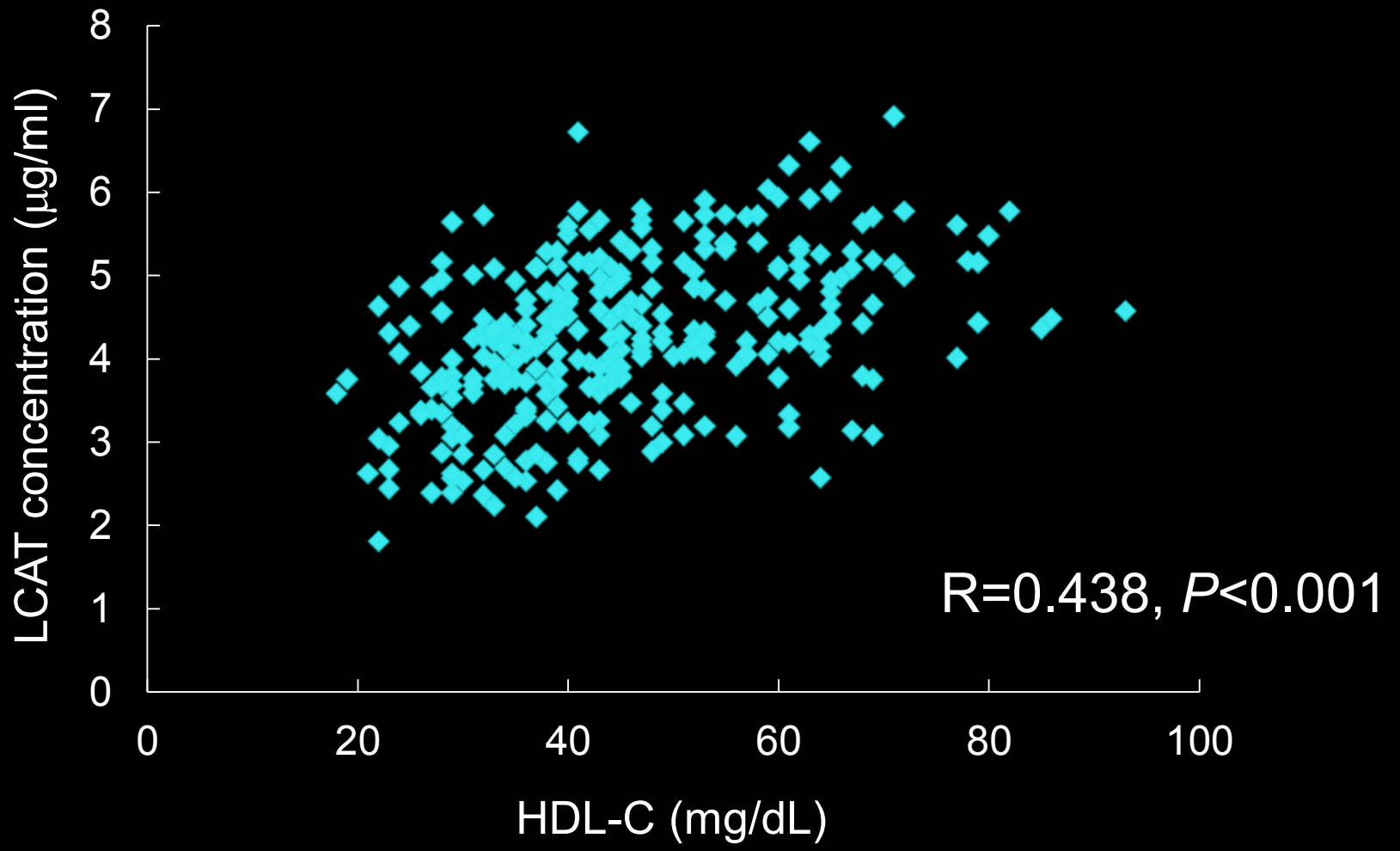
Cholesterol esterification in CKD

	CKD-HD	CKD	Controls	*P**
Unesterified/total cholesterol	0.34±0.05	0.29±0.04	0.27±0.02	<0.0001
CER, nmol/ml/h	30.2±11.2	28.9±10.7	38.5±8.5	0.0001
LCAT activity, nmol/ml/h	26.1±9.9	30.0±8.8	36.0±6.4	<0.0001
LCAT concentration, µg/mL	4.01±0.92	4.64±0.75	5.05±0.73	<0.0001

Data are Means±SD.
**P* values, assessed by one way ANOVA or Chi-square test, adjusted for sex, age, BMI, smoking status, hypertension, diabetes, and assumption of lipid-modifying agents.

Calabresi et al. J Intern Med 2015; 277:552

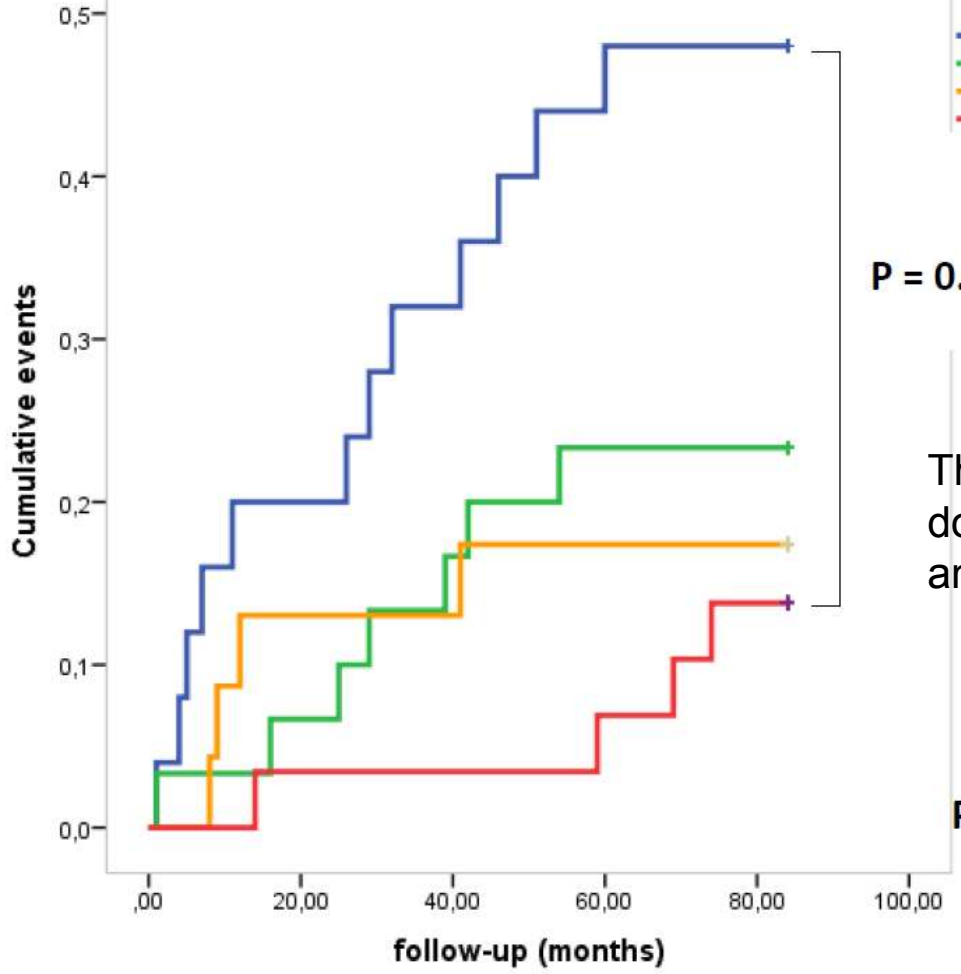
Cholesterol esterification in CKD



Calabresi et al. J Intern Med 2015; 277:552

LCAT quartiles and CKD progression

NephroPLIC Study



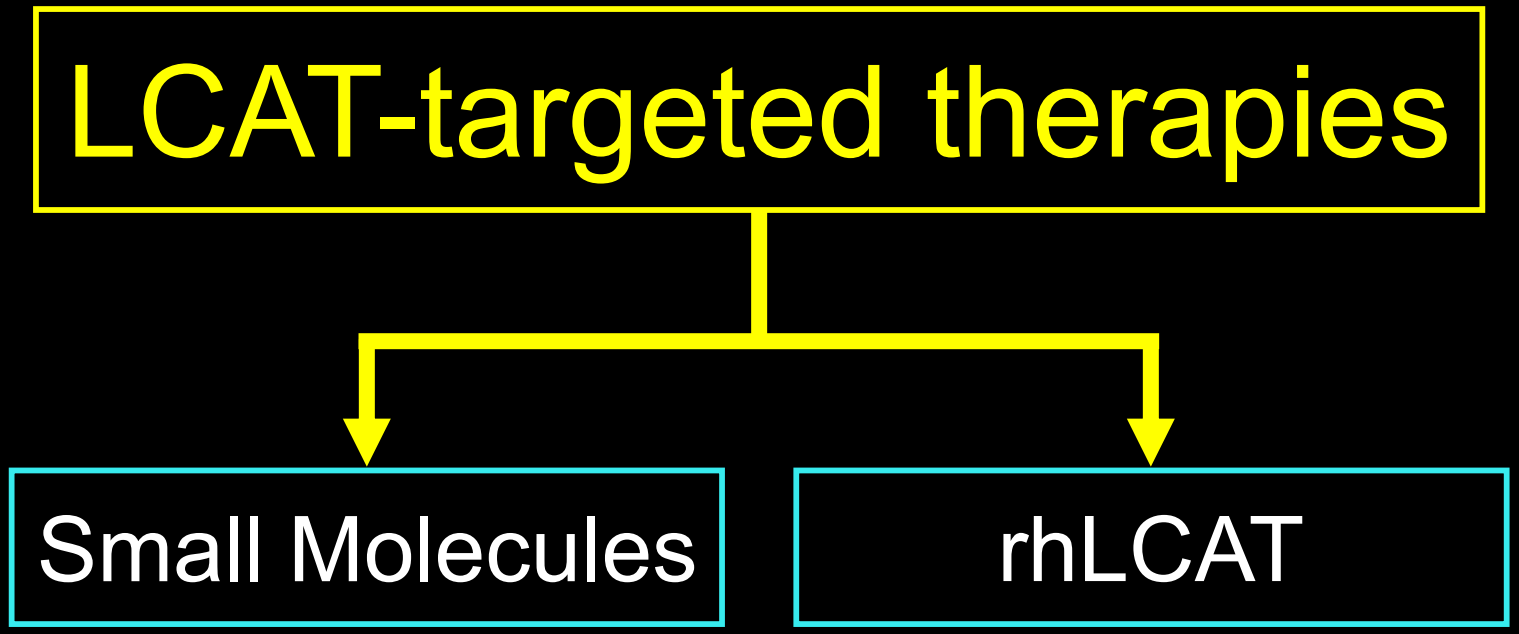
P = 0.003

The events considered were doubling of creatinine levels and/or entry on dialysis

P TREND = 0.010

Baragetti, Simonelli, Norata, Catapano, Calabresi, unpublished

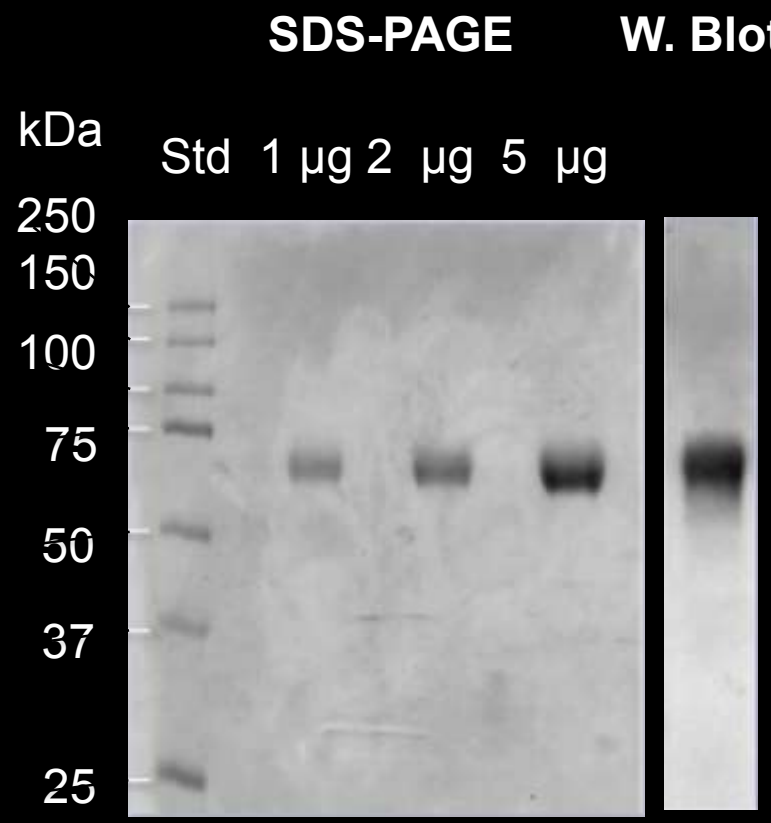
LCAT-targeted therapies



target	LCAT	HDL
mode of action	LCAT modulation	↑ cholesterol esterification
administration	oral	parental

Production of Human Recombinant LCAT

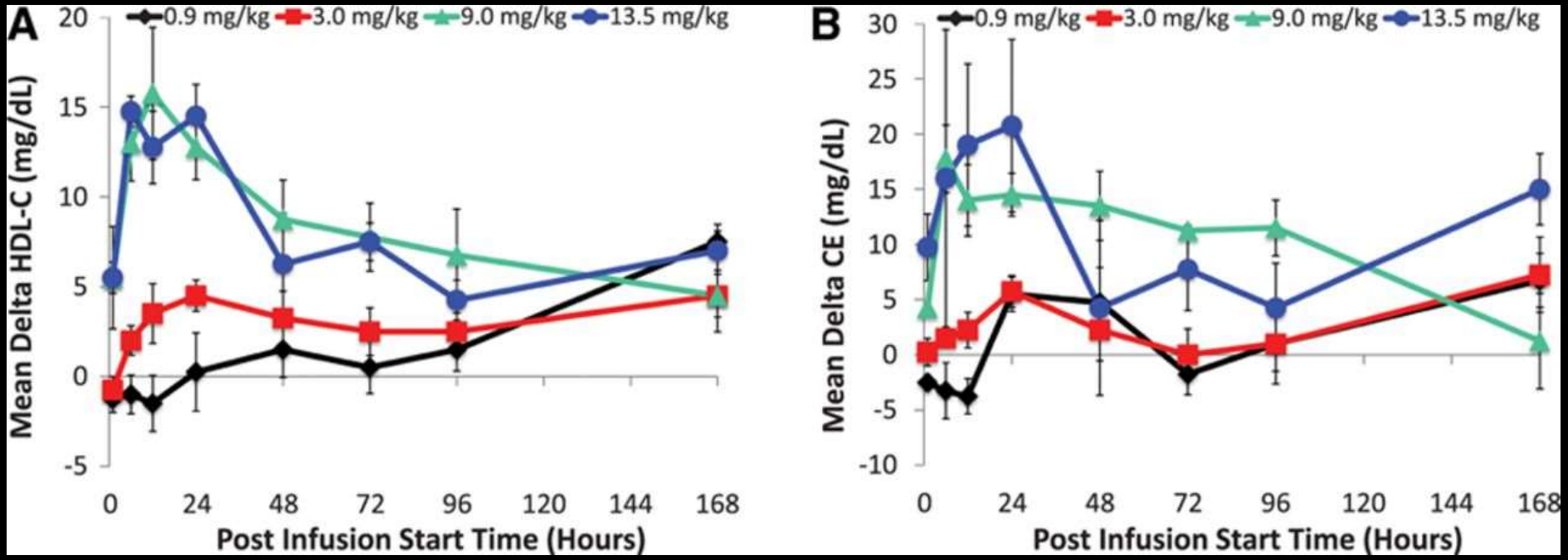
- HEK transfected cells
- 4-step purification following ZnCl ppt.
- > 99.5% purity
- Yield 15 mg/L from conditioned media



MEDI6012 - Phase 2

Rousset X, et al. J Pharmacol Exp Ther. 2010;335:140.

rhLCAT in Low-HDL subjects



Robert D. Shamburek et al. Circ Res. 2016;118:73

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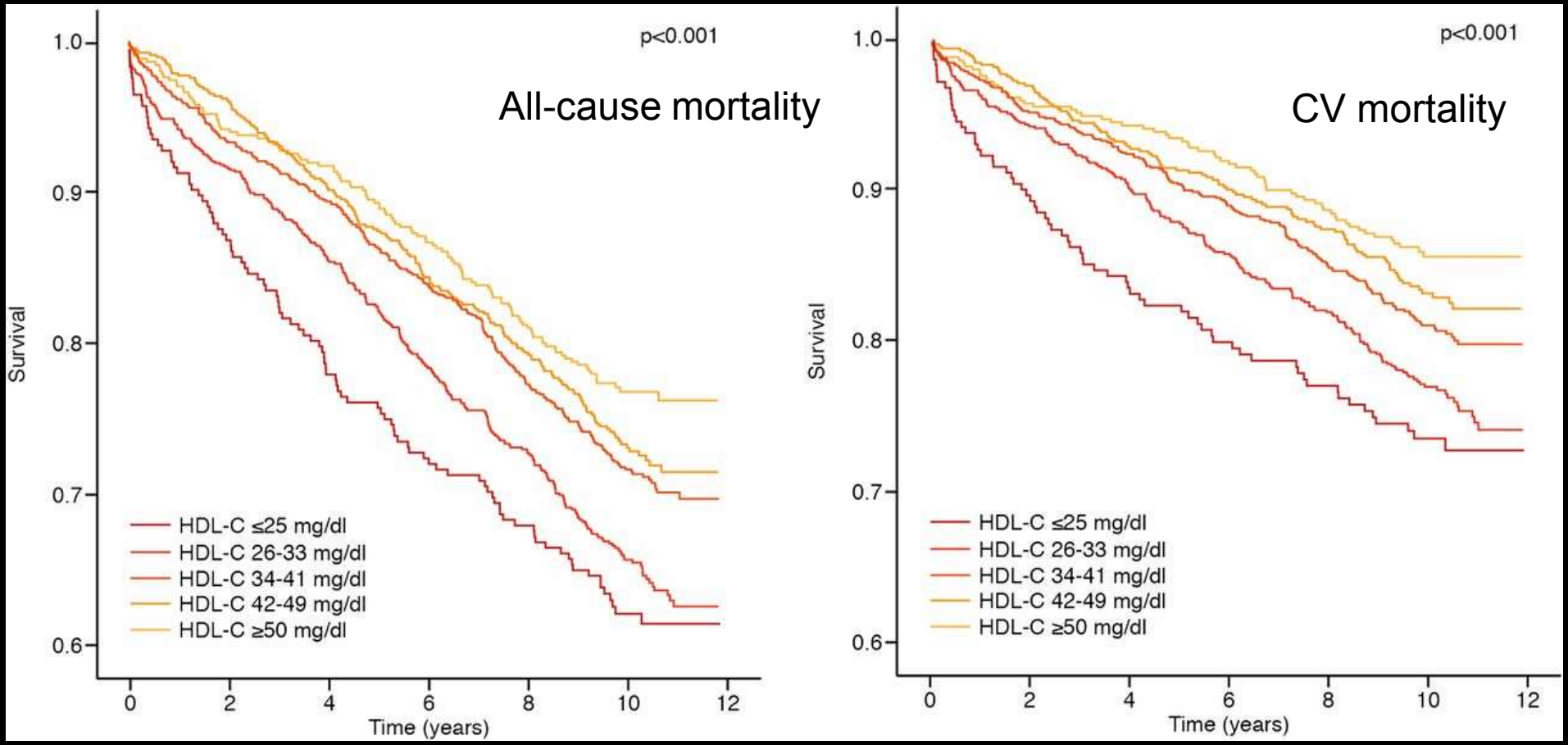
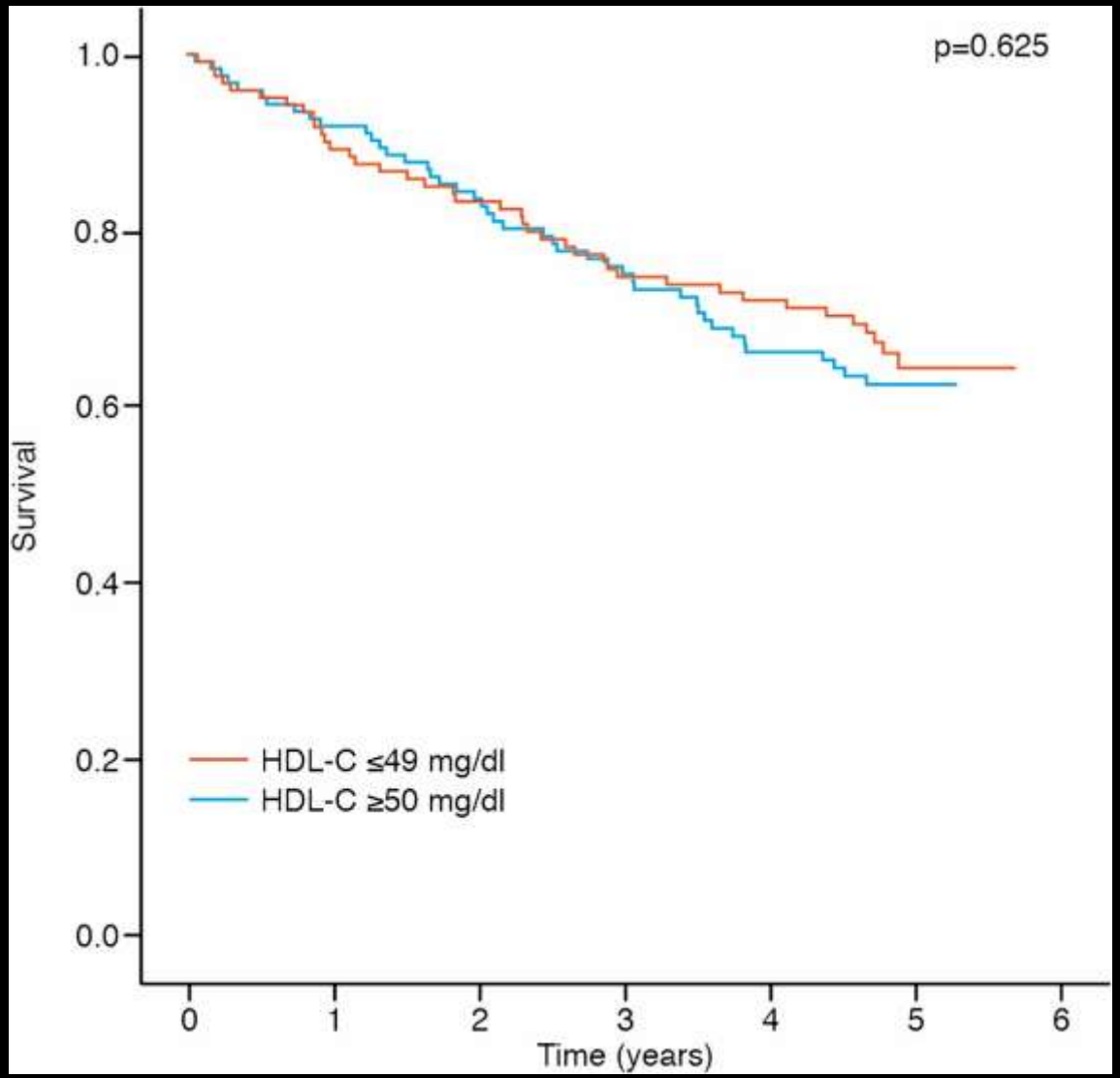
All-cause and cardiovascular mortality according to categories of HDL-C in the LURIC study



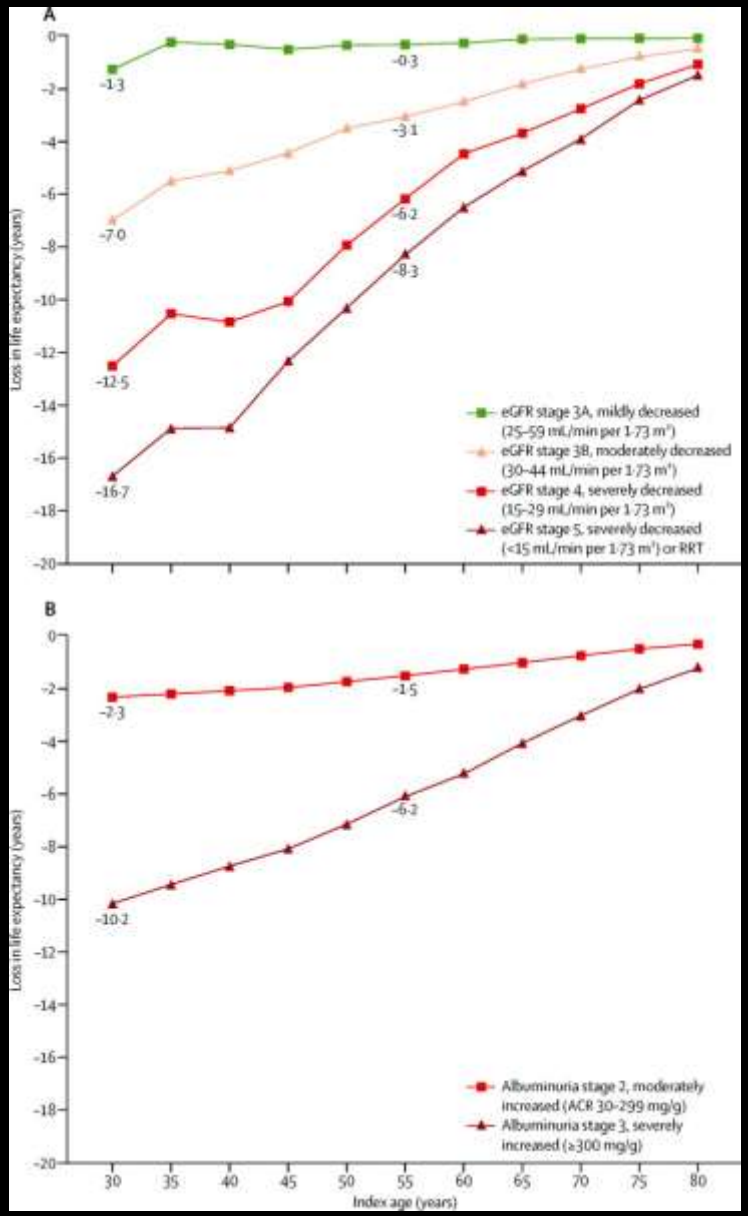
Zewinger S et al. JASN 2014;2:1073

All-cause mortality in CKD patients in the validation cohort stratified into two groups by the median of HDL-C.



Zewinger S et al. JASN 2014;25:1073

CKD and cardiovascular risk



Gansevoorti et al. Lancet 2013;382:339

Loss of life expectancy due to cardiovascular disease, by chronic kidney disease stage