HDL Cholesterol Efflux is not Predictive of Cardiovascular Risk in Dialysis Patients

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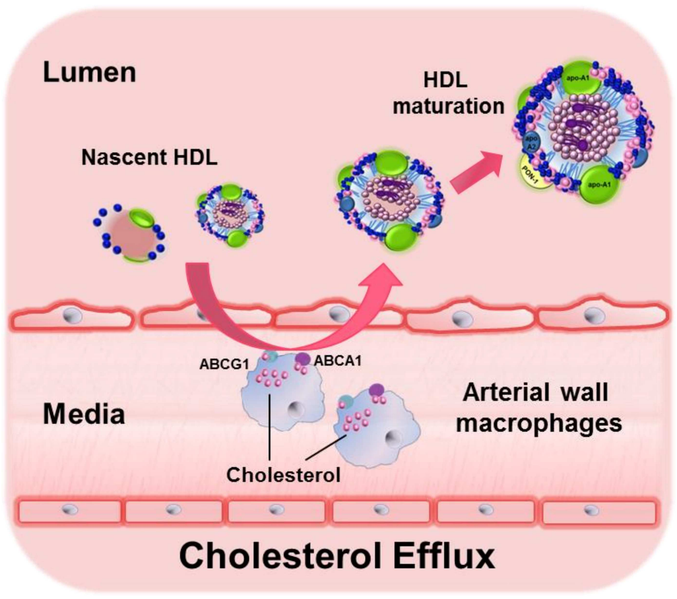
Aims

Cholesterol efflux capacity is a key cardioprotective HDL function and was shown to correlate inversely with cardiovascular outcomes in high-risk populations. Patients with end-stage renal disease (ESRD) harbor an exceptionally high cardiovascular risk, which cannot fully be explained by traditional risk factors. Here, we determined for the first time if cholesterol efflux capacity is predictive for cardiovascular risk and overall mortality in type 2 diabetic patients on hemodialysis.



Overview of macrophage cholesterol efflux.

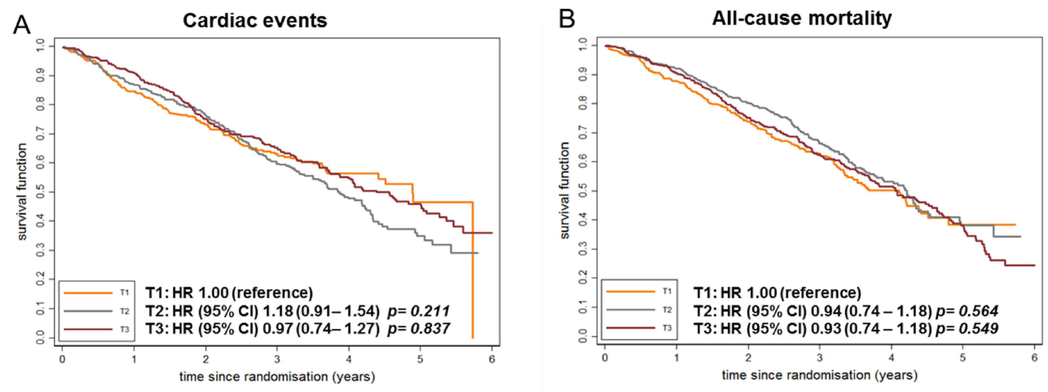
HDL migrates into the arterial wall and takes up excess cholesterol from macrophages via ABCA1 or ABCG1. Free cholesterol is then esterified and mature HDL particles are formed with increasing density as the cholesteryl esters are accumulating in the core of the HDL particles.

Methods

In this *post hoc* analysis of the German Diabetes Dialysis study (4D study) HDL cholesterol efflux was measured in 1,147 hemodialysis patients with type 2 diabetes mellitus, who were randomly assigned to treatment with 20 mg atorvastatin daily or placebo. We quantified the efflux capacity by incubation of macrophages with apolipoprotein B depleted serum from the study participants and assessed the relation of cholesterol efflux with cardiovascular outcome.

Results

Prognostic effect of HDL-mediated cholesterol efflux capacity on cardiovascular outcome of dialysis patients



Kaplan-Meier Curves of (A) all cardiac events combined or (B) all-cause mortality according to cholesterol efflux capacity. Models adjusted for traditional risk factors (age, sex, CAD, arrhythmia, TIA, congestive HF, PVD, smoking, SBP/DBP, BMI, albumin, phosphate, Hb, HbA1c, duration of HD), LDL-C, HDL-C and apoA-I.

During a mean follow-up of 4.1 years, a total of N=410 experienced cardiac events (cardiac death and non-fatal myocardial infarction) and N=561 died (all-cause mortality). Cholesterol efflux capacity of HDL was divided into tertiles based on ratios of normalized cholesterol efflux capacity: first tertile, median [IQR] 0.73 [0.67–0.77]; second tertile, 0.89 [0.86-0.94]; and third tertile, 1.08 [1.02-1.20].

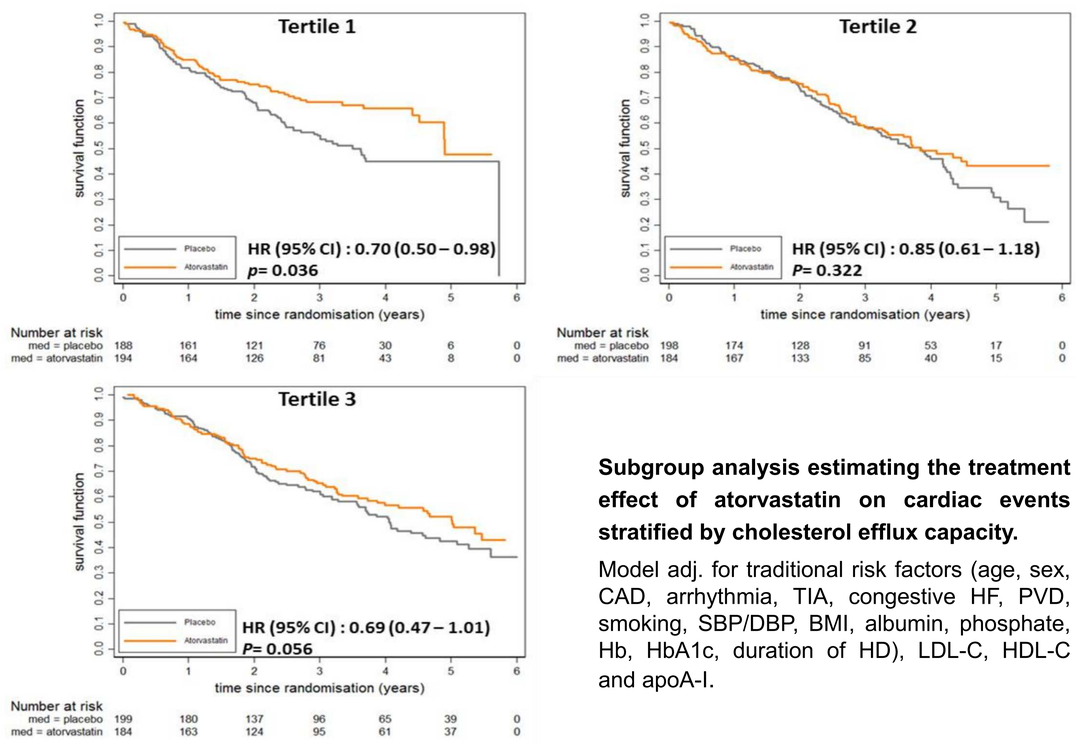
Patient characteristics

Baseline characteristics of study participants

Parameter	Tertile 1 (n=383)	Tertile 2 (n=382)	Tertile 3 (n=382)	*P value*
Cholesterol efflux capacity	0.71 (0.10)	0.89 (0.05)	1.16 (0.40)	
Age, years	66.7 (8.2)	66.2 (8.4)	66.0 (8.2)	*0.486*
BMI, kg/m^2	27.5 (4.7)	27.7 (5.0)	27.42 (4.8)	*0.723*
Duration of diabetes, years	17.8 (8.2)	18.4 (8.9)	18.1 (8.5)	*0.623*
Duration of dialysis, months	7.6 (6.5)	8.1 (6.8)	8.9 (7.1)	***0.033***
Sex (men), %	233 (61.0)	207 (54.2)	188 (49.1)	***0.004***
History, n (%)				
Arrhythmia	81 (21.2)	69 (18.1)	62 (16.2)	*0.196*
Congestive heart failure	166 (43.5)	130 (34.0)	115 (30.0)	***<0.001***
Stroke/TIA	68 (17.8)	66 (17.3)	68 (17.8)	*0.978*
Peripheral vascular disease	174 (45.6)	166 (43.5)	174 (45.4)	*0.808*
MI/CABD/PTCA/CAD	128 (33.5)	106 (27.8)	109 (28.5)	*0.166*
Hypertension	336 (88.0)	341 (89.3)	341 (89.0)	*0.830*
Systolic blood pressure, mmHg	144.4 (23.2)	146.5 (20.9)	146.4 (21.8)	*0.324*
Diastolic blood pressure, mmHg	74.6 (10.7)	76.3 (10.5)	76.6 (11.4)	***0.024***
Total cholesterol, mg/dL	209.8 (42.0)	221.5 (41.8)	226.9 (40.8)	***<0.001***
LDL cholesterol, mg/dL	119.1 (27.9)	126.9 (28.9)	131.9 (30.2)	***<0.001***
HDL cholesterol, mg/dL	31.2 (9.9)	35.6 (12.5)	42.3 (15.6)	***<0.001***
Apolipoprotein A-I, mg/dL	115.8 (19.9)	125.5 (20.0)	137.6 (25.5)	***<0.001***
C-reactive protein, mg/L	12.7 (20.4)	10.2 (16.0)	9.3 (12.1)	***0.014***
Albumin, g/dL	3.75 (0.26)	3.80 (0.33)	3.90 (0.29)	***<0.001***
Hemoglobin, g/dL	10.87 (1.44)	10.91 (1.33)	10.90 (1.29)	*0.901*
HbA1c, %	6.69 (1.25)	6.69 (1.28)	6.76 (1.18)	*0.693*
Phosphate, mg/dL	5.8 (1.7)	6.1 (1.6)	6.2 (1.6)	***0.006***

Data shown are means (SDs) or medians [interquartile ranges]. Cholesterol efflux capacity is shown as normalized ratio. BMI, body mass index; CABG, coronary artery bypass grafting surgery; CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; TIA, transitory ischemic attack.

Statin effect modification



Subgroup analysis estimating the treatment effect of atorvastatin on cardiac events stratified by cholesterol efflux capacity.

Model adj. for traditional risk factors (age, sex, CAD, arrhythmia, TIA, congestive HF, PVD, smoking, SBP/DBP, BMI, albumin, phosphate, Hb, HbA1c, duration of HD), LDL-C, HDL-C and apoA-I.

Conclusion

HDL cholesterol efflux capacity is not a prognostic cardiovascular risk marker in diabetic patients on hemodialysis. Assessment of cholesterol efflux might be used as novel stratification tool to identify subgroups of patients, who might benefit from statin treatment.

53 ERA 479--SP

Dialysis. Cardiovascular complications.

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DOI: 10.3252/pso.eu.53era.2016

ePosters supported by F. Hoffmann- La Roche Ltd.

53rd CONGRESS ERA-EDTA VIENNA AUSTRIA MAY 21-24, 2016 Held jointly with Österreichische Gesellschaft für Nephrologie

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