International Urology and Nephrology (2019) 51:1173–1189
https://doi.org/10.1007/s11255-019-02170-w

NEPHROLOGY - REVIEW

A comprehensive review on apolipoproteins as nontraditional cardiovascular risk factors in end-stage renal disease: current evidence and perspectives

Cristiana Vlad[1] · Alexandru Burlacu[2] · Laura Florea[3] · Bogdan Artene[2] · Silvia Badarau[3] · Andreea Covic[1] · Carina Ureche[2] · Dragos Scripcariu[4] · Liliana Foia[5] · Adrian Covic[3,6]

Received: 26 April 2019 / Accepted: 9 May 2019 / Published online: 22 May 2019

Abstract

Purpose Nontraditional cardiovascular risk factors such as lipoprotein(a) (Lp(a)), the genetic polymorphisms of apolipoprotein(a), apolipoprotein E (ApoE), and apolipoprotein B (ApoB) increase the prevalence of atherosclerosis in end-stage renal disease (ESRD) through quantitative and qualitative alterations. Given the high burden of cardiovascular fatal events in ESRD, this review aims to gather studies depicting apolipoproteins' changes in ESRD, to describe current evidence and to explore potential lipid-lowering therapies.

Methods We searched the electronic database of PubMed, SCOPUS, EBSCO, and Cochrane CENTRAL for studies evaluating apolipoproteins in ESRD. Randomized controlled trials, observational studies (including case–control, prospective, or retrospective cohort), and reviews/meta-analysis were included if reference was made to apolipoproteins and cardiovascular consequences in ESRD.

Results 21 studies met the inclusion criteria. We found a significant correlation between Lp(a) plasma concentrations and atherosclerosis. Lp(a) levels were independent risk factors for atherothrombosis and cardiovascular mortality. LMW apo(a) phenotype proved to be the best predictor for coronary events in ESRD. Single nucleotide polymorphisms in ApoE gene affected the expression and function of the protein, increasing the risk of cardiovascular events. ApoB had a significant correlation with the value of carotid intima–media thickness and vascular stiffness.

Conclusions The picture of "lipid milieu" in ESRD has not been clearly described. Novel studies show that specific apolipoproteins suffer modifications in uremic patients, being correlated with cardiovascular events. Probably in the next years, the treatment of dyslipidemia in ESRD will not merely target LDL or total cholesterol, but specific isoforms of apolipoproteins which seem to become the central part of the problem.

Keywords End-stage renal disease · Dialysis · Dyslipidemia · Trials · Apolipoproteins · Lipoprotein (a) · Apo B · Apo E

✉ Alexandru Burlacu
alburlacu@yahoo.com

[1] Department of Internal Medicine-Nephrology, "Grigore T. Popa" University of Medicine, Iasi, Romania

[2] Department of Interventional Cardiology, Cardiovascular Diseases Institute, "Grigore T. Popa" University of Medicine, Iasi, Romania

[3] Nephrology Clinic, Dialysis and Renal Transplant Center, 'C.I. Parhon' University Hospital, and "Grigore T. Popa" University of Medicine, Iasi, Romania

[4] Surgery Department, "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, Romania

[5] Department of Biochemistry, "Grigore T. Popa" University of Medicine, Iasi, Romania

[6] The Academy of Romanian Scientists (AOSR), Bucharest, Romania

Introduction

Atherosclerotic complications of coronary artery disease (CAD), peripheral vascular and cerebrovascular disease are common causes of morbidity and mortality in chronic kidney disease (CKD) [1]. In the past decades, it has become clear that cardiovascular disease (CVD) burden posed by CKD plays a pivotal role in the prognostic of end-stage renal disease (ESRD) patients. In fact, CVD is a principal cause of morbidity and mortality in dialysis patients [2], with 30–40% of all deaths being accounted for by CVD (as reported by the United States Renal Data System), 20% of deaths attributable to CAD and its complications [3]. Furthermore, in CKD patients, the rate of developing major adverse cardiovascular events (MACE) is higher than reaching the ESRD stage requiring renal replacement therapy [4], the latest stages of CKD being associated with the worst outcomes [5].

Several inter-dependent mechanisms contribute to the vascular disease with its forms—'*arteriosclerosis*' and '*atherosclerosis*'. On the one hand, classical cardiovascular risk factors (diabetes mellitus, arterial hypertension, dyslipidemia) are more common in CKD patients than in the general population. On the other hand, novel risk factors such as chronic inflammatory state, disturbances of mineral metabolism, oxidative stress, fluid overload and fluctuation in systemic fluid volume, accumulation of metabolic products, lipoprotein(a) [Lp(a)] levels, the genetic polymorphisms of apolipoprotein(a) [apo(a)], apolipoprotein E (ApoE), and apolipoprotein B (ApoB) increase the prevalence of atherosclerosis [1, 6, 7] (Fig. 1).

In particular, the uremic milieu present in ESRD strongly correlates with extensive vascular calcification, with endothelial dysfunction and chronic inflammation, concurrently appearing to be the primary components of atherosclerotic cardiovascular disease (ASCVD) in patients with CKD [4]. Although ASCVD is more conspicuously associated with the development of MACE among patients with ESRD, it is present across all spectrum of CKD (even from its inception), with a higher prevalence than in the general population [4]. The severity of atherosclerosis in patients with CKD could be affected by qualitative differences in plaque composition in a larger proportion than atheromatous plaque number or volume [7].

Moreover, dyslipidemia in ESRD is represented by normal levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C), increased triglycerides and decreased high-density lipoprotein cholesterol (HDL-C) [8]. Low levels of HDL-C prevail at all stages of CKD and lead to a significant negative risk factor for CVD, and are associated with increased mortality [9]. Hypertriglyceridemia is due to an increased concentration of triglyceride-rich lipoproteins, such as the very low-density lipoprotein (VLDL) [10], the intermediate-density lipoprotein (IDL), or the apolipoprotein profile [11]. Lp(a) levels are significantly higher in nephrotic syndromes due to increased liver production [12], as well as in patients with ESRD (hemodialysis, HD and peritoneal dialysis, PD) [8, 13].

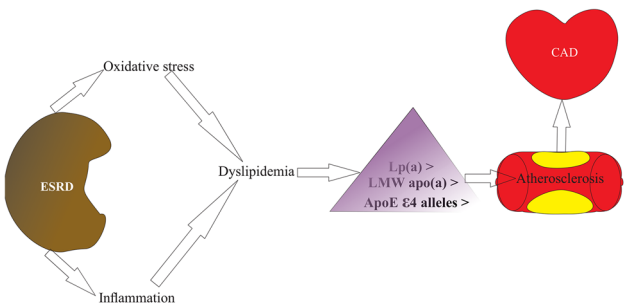

Fig. 1 The role of apolipoproteins and genetic polymorphism in ESRD patients. In ESRD dyslipidemia composed of the triangle of Lp(a), LMW apo(a), and ApoE, epsilon 4 alleles facilitate the development of atherosclerosis contributing to the induction of coronary artery disease

Objectives

This comprehensive review aims to depict current evidence regarding the particularities and the role of apolipoproteins involved in atherosclerosis development (and subsequent cardiovascular events) given the particular setting of dyslipidemia in ESRD. Moreover, we also searched, identified, and mentioned therapeutic solutions and perspectives in managing the specific dyslipidemic milieu of ESRD patients.

Methods

We searched the electronic database of PubMed SCOPUS, EBSCO, and the Register of Controlled Trials (Cochrane CENTRAL) from its earliest date until December 2018 for studies that evaluated the apolipoprotein profile in patients with ESRD and its cardiovascular consequences. The terms used for searching were "*lipoprotein(a)*", "*apolipoprotein E*", "*apolipoprotein B*", "*end-stage renal disease*", "*ESRD*", "*chronic kidney failure*", "*CKD*", "*advanced CKD*", "*dialysis*", "*hemodialysis*", "*peritoneal dialysis*", and "*renal dysfunction*". The reference sections of the relevant articles were manually searched for additional articles. Randomized controlled trials, observational studies, including case–control studies, prospective or retrospective cohort studies, reviews, and meta-analyses were included if reference was made to apolipoproteins and their cardiovascular consequences in ESRD. Case reports were excluded. Studies were selected by two independent reviewers by screening the

title and abstract. In a second phase, the full articles which conformed to the selection criteria were obtained, the essential data (general characteristics of the studies, sample size, the diagnostic criteria for renal impairment, cardiovascular outcome) were extracted independently, and the results analyzed. Discrepancies were resolved by discussion and consensus. 595 studies were found. Duplicates were excluded both manually and through a reference manager software. Of these, only 21 met the inclusion criteria (see Table 1). For the selected studies, we reviewed the full text article and additional relevant publications were added after screening the reference section.

Results and discussion

Lipoprotein (a)

Background

Lipoprotein(a) was first described as a dominantly inherited low-density lipoprotein (LDL)-like particle synthesized in the liver [12–14]. Its structure differs from LDL by a high polymorph glycoprotein apo(a). Apo(a) is covalently bound by the apolipoprotein B (ApoB) moieties of LDL via a disulfide bridge [1, 11, 13]. Plasma concentrations of Lp(a) range from 0.1 to 200 mg/dL [15], strongly and negatively associated with the apo(a) isoform size [14, 15], thus interacting with serum Lp(a) measurement which results in significant under- or overestimation of Lp(a) relative to the reference standard [14]. Most Europeans have Lp(a) concentrations under 10 mg/dL, while only about 25% display concentrations above 30 mg/dL [16].

Lp(a) is an independent risk factor for CAD [17, 18] as well as for multi-sit atherosclerosis [19]. According to the 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias [20], plasma Lp(a) is not recommended for risk screening in the general population, but systematically evaluated in people with high CVD risk or important family history of premature atherothrombotic disease [20].

Proteins sequencing and complementary DNA (cDNA) of apo(a) revealed similarities with plasminogen [13, 15]; in fact, it interferes with its fibrinolytic activity by inhibiting the generation of the thrombolytic enzyme plasmin [11]. Plasminogen contains a signal sequence followed by five structures called kringle (K-I at K-V) and a protease domain, while sequences from KI to KIII are absent in apo(a) [13]. Instead, kringle-IV (K-IV) plasminogen-like is present in a variable number of repeats, whereas kringle-V (K-V) is present in a single repeat [13]. Apo(a) consists of a single kringle V moiety followed by a number of K-IV repeats [12, 18]. Apo(a) shows more than 30 genetically determined size isoforms and is grouped into two phenotypes: low molecular weight (LMW) and high molecular weight (HMW), depending on the number of repeats of K-IV [1, 12, 14, 19]. The cutoff for LMW comprises all isoforms with 14–25 repeats of K-IV, while for HMW it comprises 26 repeats of K-IV or more. These cutoff values are associated with increased susceptibility for atherothrombotic events [11].

In healthy subjects, Lp(a) levels are mainly dependent on the type of isoforms: those with LMW isoforms have high Lp(a) levels, whereas those with HMW isoforms have low Lp(a) levels [11, 12]. Lp(a) levels are not significantly affected by age, gender, diabetes, diet, or statins [1] and are mainly genetically determined by the *LPA* gene [11]. This gene (OMIM 152200) encodes the apo(a) fragment of the Lp(a). K-IV type 2 (KIV-2) size polymorphism is the most important polymorphism of the *LPA* gene. KIV-2 is defined by a variable number of 5.6 kilobases(kb) repeats, resulting in a large number of isoforms other than apo(a). The number of KIV-2 repeats correlates inversely with the Lp(a) levels [21]. The apo(a) phenotype is a stronger predictor for atherosclerosis than the Lp(a) level [13, 18].

ESRD as a particular setting

As the patients with ESRD reach the stage of renal insufficiency, Lp(a) plasma concentrations are similar regardless of apo(a) isoforms. The difference between the two groups of patients, with LMW or HMW apo(a) isoforms, resides in the fact that while HMW apo(a) patients only develop high Lp(a) levels in the final stages of kidney disease, LMW apo(a) patients have life-long high Lp(a) levels, with preinjured vascular system at the start of renal disease, putting them at high risk for developing a "*galloping*" atherosclerosis [13, 18]. Patients with nephrotic syndrome and ESRD have shown an increase in Lp(a) plasma concentrations [13, 14, 18, 19], suggesting a specific role for the kidney in the Lp(a) metabolism. High levels of Lp(a) increase the cardiovascular risk in ESRD patients [13, 18]. In addition, it represents a risk factor for the development and/or progression of renal disease [13].

In advanced CKD, the regulation of Lp(a) concentrations is independent of the regulation of lipoproteins containing ApoB. The catabolism rate of Lp(a) does not correlate with its plasma concentrations, suggesting that these levels are controlled by synthesis rather than by catabolism. Moreover, in homozygous patients with familial hypercholesterolemia, the mechanism consists of the low-density lipoprotein receptor (LDL-R) function impairment and does not result from a delayed catabolism of Lp(a) [13].

Proliferation of arterial smooth muscle cells in ESRD is essential for the pathogenesis of atherosclerosis and Lp(a) stimulates the cell proliferation by inhibiting plasminogen. Plasminogen reduces the activation of transforming growth factor β (TFG-β), which is a cell proliferation inhibitor [13,

Table 1 Characteristics of the included studies for cardiovascular outcomes

Author	Study type	Apolipo-protein used	Outcomes	Population total	CKD patients	CKD stage	Dialysis type	Results
Parsons et al. [1]	Case–control analysis	Lp(a)	Cardiovascular disease	467	239	G4	–	Univariate analysis demonstrated a significant association between Lp(a) levels and CVD ($p=0.02$) Logistic regression analysis identified Lp(a) level as independent risk factor for CVD (OR = 1.010, 95% CI 1.001–1.019, $p=0.03$) In patients with HMW apo(a) isoforms, Lp(a) level remained independent predictor of CVD (OR = 1.016 95% CI 1.006–1.027, $p<0.005$), but in those with LMW apo(a) isoforms, no association was seen between Lp(a) level and CVD Patients with HMW apo(a) isoforms and with low Lp(a) levels displayed far less cardiovascular events than patients with HMW apo(a) isoforms and elevated Lp(a) levels (34 vs. 57%, $p<0.01$)
Emanuele et al. [11]	Cross-sectional study	Lp(a) apo(a)	Atherothrombotic events	300	118	5D	HD	Multivariate analysis showed that LMW apo(a) isoforms are predictors of atherothrombosis ($F=6.036$, $p=0.015$) After removing apo(a) isoforms from the list of predictors, Lp(a) levels achieved statistical significance as an independent and predictive risk factor for atherothrombosis ($F=5.192$, $p=0.027$)
Longenecker et al. [14]	Cross-sectional study	Lp(a) apo(a)	Atherosclerotic cardiovascular disease	871	871	5D	HD + PD	After stratification by age and race, Lp(a) level was associated with ASCVD among young Caucasians (OR = 1.7; $P=0.01$), but not old Caucasians (OR = 1.1; $p=0.52$; P interaction by age = 0.08) Apo(a) isoform size was not associated with ASCVD in HD patients ($p>0.05$)

Table 1 (continued)

Author	Study type	Apolipoprotein used	Outcomes	Population total	CKD patients	CKD stage	Dialysis type	Results
Kollerits et al. [15]	Post hoc analysis of the prospective 4D Study	Lp(a) apo(a)	All-cause mortality Fatal stroke Death from cardiac causes All cardiac events combined All cerebrovascular events combined Combined cardiovascular events	1223	1223	5D	HD	Ln-Lp(a) was associated with fatal stroke in young patients (HR = 1.54, $p = 0.03$), but not in old patients (HR = 1.05, $p = 0.79$) Ln-Lp(a) was not associated with death from cardiac causes (HR = 1.04, 95% CI 0.95–1.14, $p = 0.39$), with all cardiac events combined (HR = 1.01, 95% CI 0.94–1.08, $p = 0.88$), with all cerebrovascular events combined (HR = 0.99, 95% CI 0.88–1.13, $p = 0.93$), and with combined cardiovascular events (HR = 1.04, 95% CI 0.97–1.11, $p = 0.30$) LMW apo(a) isoforms were not associated with death from all causes (HR 1.13, 95% CI 0.94–1.35, $p = 0.21$), with death from cardiac causes (HR = 1.16, 95% CI 0.88–1.52, $p = 0.29$), all cardiac events combined (HR = 1.01, 95% CI 0.81–1.26, $p = 0.91$), combined cardiovascular events (HR = 1.02, 95% CI 0.83–1.27, $p = 0.83$), and with all cerebrovascular events combined (HR = 1.05, 95% CI: 0.72–1.53, $p = 0.79$)
Kronenberg et al. [17]	Cohort	Lp(a) apo(a)	Development of coronary artery disease	440	440	5D	HD	Lp(a) level is predictive of a coronary event, only when the apo(a) phenotype is excluded from the analysis LMW apo(a) phenotype was a predictor for CAD events (RR = 1.87, 95% CI 1.02–3.46, $p = 0.045$) The LMW apo(a) phenotype remained an equally good predictor for a coronary event, only for patients with age < 65 years (RR = 2.55, 95% CI 1.30–5.01, $p = 0.0065$), regardless of whether they had CAD at baseline or not

Table 1 (continued)

Author	Study type	Apolipo-protein used	Outcomes	Population total	CKD patients	CKD stage	Dialysis type	Results
Longenecker et al. [19]	Cohort prospective study	Lp(a) apo(a)	ASCVD events	833	833	5D	HD + PD	Unadjusted Kaplan–Meier curves showed an association between Lp(a) level and ASCVD events among Caucasians, but no association among African-Americans LMW apo(a) isoform was associated with ASCVD events in both Caucasians and African-Americans In multivariate Cox models, Lp(a) level > 52.5 nmol/L was independently associated with a 30–40% increased risk for ASCVD events In multivariate Cox models, Lp(a) level > 206 nmol/L was independently associated with a 60–90% increased risk for ASCVD events, compared with Lp(a) < 206 nmol/L Apo(a) size < 16K-IV repeats (< 10th percentile) was associated with a 40–100% increase risk for ASCVD events, compared with apo(a) size > 16K-IV repeats
Koda et al. [24]	Cross-sectional analysis	Lp(a)	Atherosclerotic cardiovascular death	495	390	5D	HD	The high Lp(a) group [Lp(a) > 30 mg/dL] showed a significantly higher mortality than the low Lp(a) group [Lp(a) < 30 mg/dl] ($p < 0.05$) Elevated Lp(a) levels contributed independently to atherosclerotic cardiovascular mortality (RR = 3.93, $p < 0.01$)
Ohashi H et al. [22]	Observational analysis	Lp(a)	Death from coronary artery disease	268	268	5D	HD	Elevated Lp(a) levels contributed independently to CAD (RR = 0.71, $p < 0.05$)
Zimmermann et al. [27]	Case–control analysis	Lp(a)	Cardiovascular and all-cause mortality and	440	280	5D	HD	In the multivariate Cox model, Lp(a) lost its significance as survival factor for both overall (RR = 1, $p = 0.04$) and cardiovascular mortality (RR = 1, $p = 0.07$)
Longenecker et al. [25]	Cross-sectional and a prospective analysis	Lp(a) Apo(a)	De novo CVD events	629	629	5D	HD	Association between Lp(a) and CVD was stronger and had greater statistical significance for the ELISA (HR = 2, 95% CI 1.1–3.7, $p = 0.03$) at all cutoffs, compared to the IT assay (HR = 1.4, 95% CI 0.7–2.6, $p = 0.33$)

Table 1 (continued)

Author	Study type	Apolipoprotein used	Outcomes	Population total	CKD patients	CKD stage	Dialysis type	Results
Koch et al. [30]	Cross-sectional study	Apo(a)	Prediction for coronary artery disease (CAD)	607	607	5D	HD	In total group, LMW apo(a) phenotype was a significant predictor for the prevalence of CAD (OR = 2.11, 95% CI 1.34–3.31, $p = 0.001$) LMW apo(a) phenotype was associated with CAD in patients between 35–58 years (OR = 3.45, 95% CI 1.47–8.07, $p < 0.005$) LMW apo(a) phenotype was not correlated with CAD in patients over 58 years of age (OR = 1.56, 95% CI 0.93–2.61, $p = 0.09$)
Kronenberg et al. [28]	Observational analysis	Apo(a)	Prediction for carotid atherosclerosis	153	153	5D	HD	After adjustment for confounders, there was a strong association between the LMW apo(a) phenotype and the prevalence of carotid atherosclerosis (OR = 5.02, 95% CI 1.50–16.87, $p < 0.01$) LMW apo(a) phenotype was associated with the degree of carotid atherosclerosis ($p < 0.005$)
Stenvinkel et al. [29]	Cross-sectional study	Apo(a)	Atherosclerotic plaques	131	109	G4	–	By logistic multiple regression analysis, LMW apo(a) phenotype was significantly associated with the presence of unilateral or bilateral carotid plaques (Wald = 3.9, $p < 0.005$) By univariate regression analysis, LMW apo(a) phenotype was not associated with an increased cIMT area ($p > 0.05$)
Lim et al. [52]	Case–control analysis	ApoE	Occurrence of the ischemic cerebrovascular disease	241	157	5D	HD + PD	Univariate analysis showed that the prevalence of ICVD was significantly higher in subjects with ApoE ε4 allele ($p < 0.001$) The stepwise logistic regression analysis indicated that only ApoE genotype (ε4) was significant ($p < 0.05$) and was an independent predictor of the occurrence of the ischemic cerebrovascular disease ($p = 0.0005$)
Imura et al. [42]	Case–control analysis	ApoE	atherosclerotic complications	915	493	5D	HD	There were no significant differences in the prevalence of vascular disease among patient groups with ApoE2/3, ApoE3/3, and ApoE3/4 (22.6 vs. 19.7% vs. 18.8%, p = NS) Multiple logistic regression model showed that ApoE phenotype was not an independent risk factor for vascular disease

Table 1 (continued)

Author	Study type	Apolipoprotein used	Outcomes	Population total	CKD patients	CKD stage	Dialysis type	Results
Guz et al. [38]	Observational analysis	ApoE	Atherosclerotic vascular disease	269	269	5D	HD	Patients with ApoE4/3 phenotype had greater carotid artery IMT than the ApoE3/3 and ApoE3/2 groups, but the differences were not statistically significant (mean IMT, 0.75 ± 0.35 mm for ApoE4/3, 0.63 ± 0.38 mm for ApoE3/3, and 0.59 ± 0.13 mm for ApoE3/2, $p > 0.05$) Patients with ApoE4/3 phenotype had atherosclerosis compared with patients with ApoE3/3 and ApoE3/2 phenotypes, but the differences were not significant ($p > 0.05$)
Winkler et al. [45]	Randomized trial 4D Study	ApoE	Combined cardiovascular events Cardiac death	1177	1177	5D	HD	ε2 allele (ε2+) or the ε3 allele (ε3+) had no effect on any of the cardiovascular outcomes ε4 allele (ε4+) showed a 35% increased risk for CVE in both the unadjusted model and in the model adjusted for age, gender and lipids Patients with at least one ε4 allele (ε4+) had a significant higher risk for the combined cardiovascular endpoints (HR = 1.29, 95% CI 1.03–1.62, $p = 0.026$) compared to ε3/3 homozygotes Genotypes ε2/2, ε2/3, ε3/3 were associated neither with cardiovascular risk nor with the risk of cardiac death
Zheng et al. [51]	Case–control study	ApoE	Cardiovascular complication	354	189	5D	HD	The genotypes in the ε3 group (OR = 0.195, 95% CI 0.04–0.94, $p = 0.042$) and ε4 group (OR = 168,816, 95% CI 3487–8173.253, $p = 0.01$) were correlated with cardiovascular complications
Bevc et al. [63]	Observational study	ApoB	Asymptomatic atherosclerosis (IMT, plaque occurrence and a number of plaques)	91	91	5D	HD	Multiple linear regression analysis of nontraditional risk factors only showed a relationship between ApoB values and cIMT ($p < 0.04$) and the number of plaques ($p < 0.007$) When only nontraditional risk factors were considered, there was a relationship between plaque occurrence and ApoB ($p < 0.011$)

Table 1 (continued)

Author	Study type	Apolipoprotein used	Outcomes	Population total	CKD patients	CKD stage	Dialysis type	Results
Ye et al. [64]	Retrospective observational study	ApoB	Adverse left ventricular (LV) remodeling characterized by extensive left ventricular dilatation	182	182	5D	PD	In unadjusted model, patients with lower ApoB levels experienced significantly higher LVEDV dimensions (β: − 63.01, 95% CI − 98.01 to − 28.01) The multivariate adjusted analyses consistently showed that participants with higher ApoB quartiles showed a decreasing trend in LVEDV dimensions
Cicero et al. [65]	Cohort	ApoB	Arterial stiffness (pulse wave velocity)	417	118 with stage G2 CKD 94 with stage G3 CKD	G2–G3	–	In the univariate analysis, PWV was directly related to ApoB ($p < 0.05$) either in subjects with normal renal function and in those with stage G2 or G3 CKD In the stepwise multiple regression model that included stage G2 CKD, PWV was significantly related to ApoB ($R^2 = 0.301$, 95% CI 0.021 0.154, $p = 0.041$) In the stepwise multiple regression model that included stage G3 CKD, PWV was significantly related to ApoB ($R^2 = 0.255$, 95% CI 0.098 0.233, $p = 0.037$)

22]. Thus, Lp(a) plays an important part in coronary, cerebrovascular and peripheral arterial disease [11, 13]. At the same time, Lp(a) has atherogenic and thrombogenic activities [11], promotes the oxidation of LDL, and facilitates the monocyte adhesion [12]. In HD or PD patients, Lp(a) preferentially binds pro-inflammatory and pro-atherogenic oxidized phospholipids, induces macrophage apoptosis, and is fully involved in the initiation of atherosclerotic lesions and plaques destabilization [23] (Fig. 2).

Trials data

Our search yielded multiple studies with divergent conclusions (see Table 1), a fact that created confusion regarding the role of Lp(a) and apo(a) in the particular setting of ESRD. The explanations of this lack of consistency could reside in: the methodology of different types of studies (cross-sectional/case–control studies), small numbers of patients in the study groups, certain ethnic groups or age groups included, different clinical and laboratory outcomes, lack of homogeneous criteria for inclusion/exclusion, different/no clear definitions of end points, various periods of follow-up, or different statistical approaches [11, 15, 19, 22, 24, 25].

However, as the Die Deutsche Diabetes Dialyze Study (4D) illustrated, clearly defined cardiovascular outcomes, an adequate number of participants, and long follow-up period, were the foundation for demonstrating the relationship that exists between cholesterol and mortality rates in HD patients (where observational studies failed due to numerous confounding factors) [26].

Lp(a) The mean and median of Lp(a) values were significantly higher in HD patients than in non-dialysis control group [24, 27]. Also, Lp(a) median was higher in patients with HMW apo(a) isoforms, 30% of them had low levels of Lp(a) below the median of the control group and 49% were identified with CVD [1]. A study including 268 HD patients also found that increased Lp(a) levels were associated with CVD mortality in HD patients, but not with all-cause mortality (29.3 ± 22.0 mg/dL vs. 19.5 ± 13.8 mg/dL, $p < 0.05$) [22]. Moreover, the Lp(a) assay-related differences were highlighted in a cross-sectional prospective analysis of the Choices for Healthy Outcomes in Caring for ESRD (CHOICE). When comparing enzyme-linked size-insensitive immunosorbent assay (ELISA) and size-sensitive immunoturbidimetric assay (IT) methods for quantifying Lp(a), the authors determined that ELISA assay strongly predicted incident CVD and accurately identified LMW isoforms. This observation provides a clinically available alternative to identify higher-risk patients who have both increased Lp(a) levels and LMW isoforms. Additionally, median Lp(a) concentration by ELISA was much higher for African-American people compared to Caucasian people ($p < 0.0005$) [25].

Trials reporting correlations. Lp(a) plasma concentrations had a positive, significant correlation with atherosclerosis [28], total cholesterol (CT), LDL-C and C-reactive protein (CRP) [24], and amyloid A serum (SAA) [27], but an inverse correlation with serum albumin [27]. Moreover, in pre-dialysis patients, Lp(a) levels were more significantly associated with all-cause mortality rather than with cardiovascular disease(CVD) mortality and have been associated

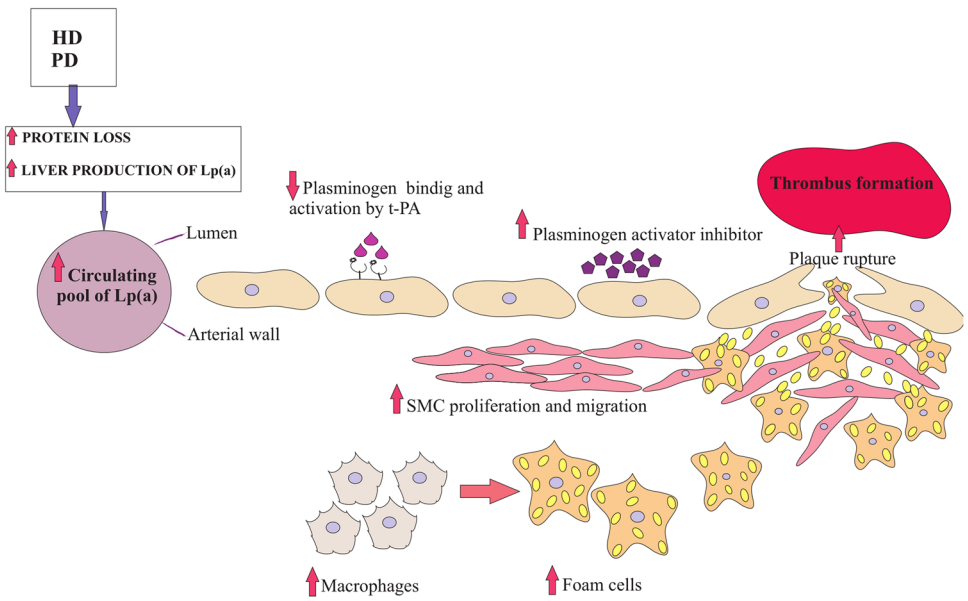

Fig. 2 The pathophysiological mechanism of Lp(a) in the arterial lumen and in the arterial wall. Lp(a) may facilitate thrombosis and may promote atherosclerosis in the arterial wall. *HD* hemodialysis, *PD* peritoneal dialysis, *Lp(a)* lipoprotein(a), *t-PA* tissue plasminogen activator, *SMC* smooth muscle cell

with CVD ($p=0.02$) [1]. Again, Lp(a) level was found to be an independent risk factor for atherothrombosis [1].

In HD patients, Lp(a) levels were predictive and independent risk factors for atherothrombosis [11]. Also, elevated Lp(a) values [Lp(a) over 30 mg/dL] had a significantly higher mortality than the low Lp(a) group under 30 mg/dL ($p<0.05$) [24], its levels being associated with the atherosclerotic cardiovascular disease (ASCVD) events in Caucasian HD patients [19]. Moreover, Lp(a) concentrations over 52.5 nmol/L were independently associated with an increased risk of up to 30–40% for ASCVD events [19]. Nevertheless, Lp(a) was associated with ASCVD only in younger (under 60 years) and Caucasian patients [14]. Likewise, in a post hoc analysis of the prospective 4D study, high Lp(a) values were associated with all-cause mortality in the total group and with fatal stroke in patients under 66 years of age [26]. Elevated Lp(a) levels independently contribute to atherosclerotic cardiovascular mortality as well as to CAD [22, 24].

Trials with no correlations. Zimmermann et al. revealed that after adjusting for confounders, Lp(a) lost its predictive value for both all-cause mortality and cardiovascular mortality [27]. Lp(a) was not associated with the presence or degree of atherosclerosis or any other related events in either HD [15, 28] or CKD pre-dialysis patients [29]. However, the design of the studies (cross-sectional—[28, 29] or post hoc analysis based on a selected cohort of diabetic patients—[15]) and small number of patients included warrant further evaluation of this matter in a prospective randomized controlled study.

Apolipoprotein(a) isoform size *Trials reporting correlations*. Three cross-sectional studies have established that LMW apo(a) phenotypes were more common in HD patients with cardiovascular events compared to those without CVD events (43.9% vs 21.9%, $p<0.001$; 56.9% vs. 33.9%, $p<0.05$; 33.3% vs. 20.6%, $p=0.05$ respectively) [11, 17, 30], while the prevalence of the LMW apo(a) isoforms was 41% among Caucasians and 46% among Afro-American people [25].

The LMW apo(a) phenotype was strongly associated with the prevalence of carotid atherosclerosis in both HD patients and pre-dialysis patients [28, 29]. At the same time, the LMW apo(a) phenotype was associated with CAD in younger patients aged between 35 and 58 years [30] being correlated with a 60–90% higher risk for ASCVD events [19]. Moreover, apo(a) under 16 K-IV repeats was associated with a 40–100% increase of the ASCVD risk versus apo(a) over 16 K-IV repeats [19]. The association of ASCVD with LMW isoforms was stronger than the association with high concentrations of Lp(a) in both races [19]. Also, patients with LMW apo(a) isoform and Lp(a) over 123 nmol/L had an increased risk for ASCVD events compared to HMW apo(a) isoform and Lp(a) level under 123 nmol/L [19]. In addition, HD patients with HMW apo(a) isoforms and with low Lp(a) levels displayed far less cardiovascular events than patients with HMW apo(a) isoforms and elevated Lp(a) levels (34 vs. 57%, $p<0.01$) [1].

Consequently, the apo(a) phenotype proved to be the best predictor for coronary events in HD patients [17, 28], while diabetes mellitus was a risk factor only in the presence of LMW apo(a) phenotype [17]. The LMW apo(a) phenotype remained an equally good predictor for coronary events in younger patients under 65 years of age, regardless of whether they had CAD at baseline or not [17]. In addition, the LMW apo(a) isoform was a predictor for atherothrombosis in HD patients [11], ELISA test for these isoforms revealing stronger CVD events than the immunoturbidimetry test [25].

Trials with no correlations. Contrary to these findings, the apo(a) isoform size was not associated with CVD ($p=0.41$) in pre-dialysis patients [1], nor was it correlated with ASCVD in HD patients [14]. At the same time, Koch et al. pointed out that the LMW apo(a) phenotype was not correlated with CAD in patients over 58 years of age [30]. Although LMW apo(a) isoforms were associated with all-cause mortality, only in younger HD patients (under 66 years of age), they were not associated with other events related to atherosclerosis [15].

Overall, even if the results appear to be contradictory, the measurement of Lp(a) levels and the pinpointing of apo(a) phenotypes may prove clinically useful for cardiovascular risk stratification and could prevent ASCVD in dialysis patients [17, 19].

Therapeutic implications/perspectives

Statins represent the first line of treatment in dyslipidemia, with reduced total cholesterol and LDL-C [10, 31, 32]. In ESRD patients, although statins (atorvastatin and rosuvastatin) significantly reduced LDL-C levels, they did not have statistically significant effects on CVD outcomes [10, 31, 32]. Thus, statins and ezetimibe have no effect on the Lp(a) level [12], while a high Lp(a) level may diminish the effectiveness of statins in reducing the risk of CVD complications [12]. Moreover, statins may worsen the renal function, being relatively contraindicated in ESRD patients [33].

Inactivation of pro-protein convertase subtilisin–kexin type 9 (PCSK9), a hepatic protease that attaches and internalizes LDL receptors into lysosomes, is the latest approved therapeutic target for the treatment of hypercholesterolemia. The anti-PCSK9 antibodies (alirocumab, evolocumab) are effective in the management of hypercholesterolemia, hypertriglyceridemia, and the cardiovascular complications of

CKD [12]. Humanized PCSK9 antibodies decrease plasma Lp(a) levels by up to 30% in a dose-dependent manner, which is a benefit compared to statin therapy [10, 34].

Weekly lipoprotein apheresis is the only therapy available for the effective reduction of Lp(a) levels in patients with Lp(a) over 60 mg/dL. This reduces Lp(a) concentration by approximately 70% with potential regression of atherosclerosis [35].

To date, there are two RCTs that address the decrease of Lp(a) concentrations using antisense oligonucleotides: (1) IONIS-APO(a)-Rx (NCT02160899), a phase 2 trial, where oligonucleotide targeting apo(a) reduced the hepatic synthesis of apo(a) and the plasma Lp(a) up to 77.8%; (2) IONIS-APO(a)-LRx (NCT02414594) a phase 1/2a first-in-man trial, where a ligand-conjugated antisense oligonucleotide reduced Lp(a) levels up to 92% [36]. Both antisense oligonucleotides were safe [36]. There were two serious adverse events (myocardial infarctions) in both the trials, but neither were thought to be treatment related [36]. IONIS-APO(a)-LRx was associated with no injection site reactions, while IONIS-APO(a)-Rx was associated with 12% of injection site reactions [36]. Consequently, the administration of antisense oligonucleotides is a novel, tolerable, and effective therapy to reduce Lp(a) concentrations [36].

Apolipoprotein E

Background

Apolipoprotein E (ApoE) is a 34 kDa protein, consisting of 299 amino acids [37–39]. This is a ligand involved in receptor-mediated catabolism through low-density lipoprotein receptor (LDL-R) and ApoE-receptor, playing an essential role in cholesterol metabolism [38–40]. ApoE is found in chylomicrons, in remnant lipoproteins, and in subfractions of HDL particles [40]. ApoE is the component of all major lipoprotein classes and has multiple functions in various processes related to lipid metabolism and inflammation [37, 40] (Fig. 3).

In the general population, the three ApoE alleles (ε2, ε3, and ε4) [38, 41, 42] produce ApoE2, ApoE3, and ApoE4 isoforms [38, 42]. Changes of ApoE affinity for its receptors influences lipid metabolism [43], while its genetic polymorphism may be associated with variations in serum cholesterol concentration between 14 and 17% [44]. In Caucasians, ε3 is the most common isoform with a frequency of about 0.77, while ε4 and ε2 are less common (0.15 and 0.08) [45]. Cysteine-arginine interchanges at positions 112 and 158 of the amino acid sequences of ApoE explain the differences between ApoE isoforms [38, 41, 46]. These isoforms generate six ApoE phenotypes: three homozygotes (ApoE2/2, ApoE3/3, ApoE4/4) and three heterozygotes (ApoE2/3, ApoE2/4, ApoE3/4) [38, 41, 46].

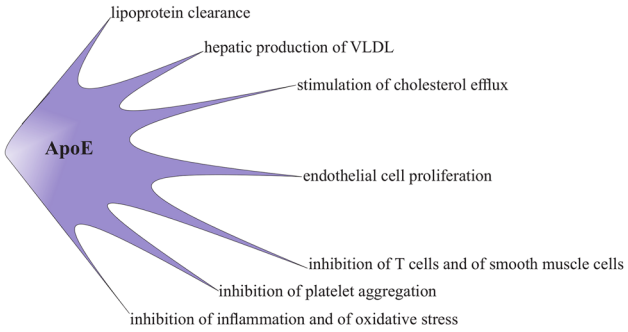

Fig. 3 The role of apolipoprotein E in lipid metabolism and inflammation

Patients with the ApoE2 genotype have the lowest levels of ApoB-containing lipoproteins (the atherogenic lipoproteins), while patients with ApoE4 genotype have the highest levels of ApoB-containing lipoproteins [40, 42]. At the same time, total cholesterol, LDL-C, and ApoB levels are lower in patients with ApoE2 carriers than those with ApoE4 carriers [40, 41].

The presence of the ε4 allele is associated with hyperlipidemia and carotid artery atherosclerosis [42]. In men, the ApoE ε4 allele is a significant genetic risk factor for coronary atherosclerosis during early middle age. Moreover, the ApoE ε4 allele has been associated with an increased risk of Alzheimer's disease [43], since ApoE shares some structural and functional similarities with the amyloid precursor protein [45].

ESRD particular setting

The ApoE genotype is an important factor for the adjustment of lipoprotein levels in both the general population [42] and ESRD patients, contributing to the variability of cholesterol levels among subjects [40]. The *APOE* gene coding the ApoE protein is located on the chromosome 19q and is associated with the susceptibility for diabetic nephropathy type 1 and type 2 [43]. ApoE polymorphisms affect the ApoE concentration in a "*gene–dose manner*" [40]. The apolipoproteins profile in PD patients is characterized by a decrease in HDL-C (the "*anti-atherogenic*" lipoprotein) levels and an increase in ApoB and ApoE levels [40].

At these patients, ApoE3/3 genotype is the most common genotype, while ApoE2/3 genotype is associated with elevated levels of total cholesterol and triglycerides [47]. Unlike PD patients, the apolipoproteins profile in HD patients involves an increase in ApoE levels and a decrease in ApoB levels [48]. Furthermore, in HD patients with ApoE4/3 phenotype, total cholesterol and LDL-C levels were significantly higher than those with ApoE3/3 and ApoE3/2 phenotypes [38, 42, 44]. ApoE polymorphism influences the development of HD [49, 50]. Single nucleotide polymorphisms in

the *APOE* gene affects the expression and function of the ApoE protein, contributing to the increase of the risk of CVD in HD patients, modifying their prognosis [49, 50].

The ApoE ε3/3 genotype, ε3 allele and ε4/3 genotype had an increased frequency in HD group as compared to control group [44, 51]. At the same time, ApoE4/3 phenotype had higher serum CT, LDL-C, and ApoB levels than in patients with ApoE3/3 and ApoE3/2 phenotypes ($p < 0.05$) [38, 42] and significantly lower levels of HDL-C(38).

Trial data

The contradictory results of observational studies produce confusion regarding the role of ApoE in advanced CKD. However, most part of the studies showed similar and consistent correlations regarding cardiovascular end points in ESRD patients.

Trials reporting correlations The ApoE ε4 + genotype, ε4 allele, and ε3 allele were associated with cardiovascular complications in ESRD patients [51]. Also, in a case–control analysis involving 157 dialysis patients followed for 2 years, Lim et al. showed that the prevalence of ischemic cerebrovascular disease was significantly higher in patients who had one or two ApoE ε4 alleles (36.8%) compared to subjects who did not present these alleles (5.6%) [52]. Consequently, the ApoE ε4 genotype was significantly correlated with stroke ($p < 0.001$) [52].

It also appears that the 4D trial (which evaluated 1255 HD patients with type 2 diabetes) highlighted that patients with at least one ε4 allele (ε4+) ran a 30% higher risk of combined cardiovascular end point (myocardial infarction, cardiac death, stroke) and a 36% increased risk of heart failure compared to patients with the ε3/3 allele [45]. Moreover, the addition of ε4 + to the ROC multivariate model for risk prediction in cardiovascular events (including atorvastatin, a history of cardiovascular disease, dialysis, and lipoprotein parameters, hsCRP, and NT-proB-type natriuretic peptide) increased the area under the curve (AUC) from 0.666 (95% CI 0.634–0.698) to 0.671 (95% CI 0.639–0.702, $p = 0.013$) [45].

Trials with no correlations Despite the above-mentioned results, a relatively old trial showed that there was not a significant association between the ApoE 4/3 phenotype and the prevalence of vascular diseases (P = NS) [42]. In addition, the ApoE2/3 and ApoE3/3 phenotypes were not risk factors for vascular diseases [42].

Genotypes ε2/2, ε2/3, and ε3/3 were associated neither with a cardiovascular risk nor with the risk of cardiac death [45]. Additionally, the presence of ε2 (ε2 +) or ε3 (ε3+) allele had no effect on cardiovascular events [45]. Albeit HD patients with ApoE4/3 phenotype had significantly more atherosclerosis and held a higher mean carotid intima–media thickness (cIMT) compared to ApoE3/3 and ApoE3/2 phenotypes, these results did not have statistical significance ($p > 0.05$) [38].

Therapeutic implications/perspectives

ApoE genotype is an important predictor of lipid response to lipid-lowering therapy with statins and fibrates [53]. Individuals with ApoE4 have the lowest response to this therapy, while ApoE2 generates the best response [53]. Although there are new monoclonal antibody therapies for various pathologies with an ApoE4 and ApoE2 carrier profiles (e.g., Alzheimer's disease, Parkinson's disease, familial dysbetalipoproteinemia) [54], they have not been used in ESRD patients. ApoE specific therapy still raises questions about toxicity, prevention and curative treatment of neurodegenerative diseases, and reduction of CVD morbidity (especially CAD) [55, 56].

Apolipoprotein B

Background

Apolipoprotein B (ApoB) is the primary protein component of very low-density lipoproteins (VLDL), intermediate-density lipoprotein (IDL), and LDL [57]. Each particle of these lipoproteins contains an ApoB molecule and consequently the ApoB plasma levels reflect the all the atherogenic particles from the body [57, 58]. ApoB is essential for the linking of LDL particles to LDL-R for cellular absorption and degradation of LDL particles, being a marker of dyslipidemia, as well [59]. In humans there are two types of ApoB: ApoB-48—secreted exclusively by the intestine in chylomicrons; and ApoB-100, secreted exclusively by the liver in VLDL [59].

ApoB-100 has 4536 amino acids, and ApoB-48 is identical to the amino terminal 48% of the ApoB-100 and is made by a unique mRNA (messenger RNA) editing process [59]. ApoB-48 plays a role in assembling and secreting chylomicrons from the small intestine, while ApoB-100 is useful for assembling and secreting VLDL from the liver [59]. The metabolism of ApoB-containing particles depends on gender, APOE genotype, LDLR mutations, estrogen levels and lipoprotein lipase activity, contributing to the interindividual variation of ApoB levels [59]. APOB is a highly polymorphic gene and in subjects without rare mutations, and polymorphisms have a role in determining ApoB and cholesterol level [59].

The 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias recommend measuring ApoB levels as a complementary risk marker, particularly in patients with high levels of triglycerides [20, 60].

ESRD as a particular setting

In certain situations, LDL-C and ApoB degrees increase concurrently (e.g., familial hypercholesterolemia), while in ESRD patients, due to hypertriglyceridemia, malnutrition or metabolic disorders, LDL-C levels are often paradoxically "*normal*", while the ApoB levels are quite high due to overproduction [61, 62]. This situation contributes to the formation of a small, dense LDL-C (type B phenotype) of significant importance in atherosclerosis development [57]. In pre-dialysis and PD patients, ApoB levels are elevated as opposed to HD patients in whom plasma levels are within normal range [48].

Trial data

Trials reporting correlations ApoB had a 100% sensitivity, a 75% specificity, and a cutoff value of 1.26 g/L [57]. Besides, ApoB had a significant positive correlation with the value of carotid intima–media thickness, with the number of plaques in carotid arteries in elderly ESRD patients [63] as well as with cardiovascular morbidity [57]. On the same note, in PD patients, ApoB elevation was significantly correlated with the reduction of the left atrium diameter, the left ventricle(LV) diameter, peak velocities of early filling divided by peak velocities of the atrial filling, and LV volumetric dimension ($p < 0.001$) [64].

ApoB represents an independent predictor of vascular stiffness (measured by pulse wave velocity) only for patients with moderately impaired renal function [65]. Hence, in ESRD patients, it was found a relationship between ApoB and cIMT ($p < 0.04$), the development and number of plaques ($p < 0.007$) [63], and the presence of cardiovascular events [57]. Also, in PD patients, ApoB was an independent determinant of LV dilation [64] and was significantly associated with cardiovascular mortality in HD patients [66].

Trials with no correlations In peritoneal dialysis patients, ApoB was associated neither with all-cause mortality nor with cardiovascular mortality [58]. However, the follow-up time was shorter (2 vs 7 years) compared with other (positive) studies, and the study enrolled only incident PD patients (versus higher HD cohorts). In fact, the authors of the study underlined that "previous studies indicated that apo B was a strong predictor of mortality and cardiovascular risk".

Therapeutic implications/perspectives

Overall, HD patients manifest advanced atherosclerosis associated with nontraditional risk factors (ApoB) [57, 63]. Hence, the reduction of ApoB could reduce eccentric left ventricular remodeling and could be useful for cardiovascular risk stratification in PD patients [64].

In addition to well-known lipid-lowering therapies, new treatments are used to reduce cardiovascular risk in patients with CKD. Cholesterol acyltransferase-2 (ACAT) plays a role in transcriptional and post-translational regulation of liver cholesterol production [67]. ACAT regulates the biosynthesis of cholesterol and fatty acids [12]. ACAT is involved in packaging of cholesterol in ApoB-100 lipoprotein in the liver for its release into circulation [67]. Due to the fact that increased values of ACAT may induce dyslipidemia in CKD, administration of ACAT inhibitors reduces plasma lipid levels [10, 12]. Treatment with low dose of ACAT inhibitor can provide protection for acute cardiovascular events in patients with nephrotic proteinuria without impact on ESRD patients [12].

Mipomersen is an antisense oligonucleotide that binds to mRNA responsible for the synthesis of ApoB-100 and inhibits its production. It is administered subcutaneously once a week and decreases non-HDL-C, LDL-C, TG, ApoB and Lp(a), since ApoB-100 is an essential element for VLDL and LDL. Currently, mipomersen is only approved in the USA for the treatment of homozygous familial hypercholesterolemia [68].

Conclusions

To date, the picture of "*lipid milieu*" in end-stage renal disease has not been clearly described. Novel studies show that specific lipoproteins (Lp(a) with isoforms, apolipoprotein B or E, respectively) suffer modifications in uremic patients (in terms of quantity and quality). Moreover, these apolipoproteins proved to be linked with major cardiovascular adverse events (which are higher than in the general population). Our endeavor developed three directions: (1) to depict the lipoprotein changes in ESRD; (2) to describe current evidence in the field; (3) to explore current and potential therapies to lower CVD in ESRD patients. Probably in the next few years, the treatment of dyslipidemia in ESRD will not merely target LDL or total cholesterol, but specific isoforms of apolipoproteins which seem to become the central part of the problem.

Funding AB: was supported by the Romanian Academy of Medical Sciences and European Regional Development Fund, MySMIS 107124: Funding Contract 2/Axa 1/31.07.2017/107124 SMIS. AC: was supported by a grant of Ministry of Research and Innovation, CNCS—UEFISCDI, project number PN-III-P4-ID-PCE-2016-0908, contract number 167/2017, within PNCDI III.

Compliance with ethical standards

Conflict of interest None declared.

References

1. Parsons DS, Reaveley DA, Pavitt DV, Misra M, Brown EA (2003) Lipoprotein(a) levels in those with high molecular weight apo(a) isoforms may remain low in a significant proportion of patients with end-stage renal disease. Nephrol Dial Transpl 18(9):1848–1853
2. Park KA, Jo HM, Han JS, Kim MJ, do Kwun H, Park MY, Choi SJ, Kim JK, Hwang SD (2013) Features of atherosclerosis in hemodialysis patients. Kidney Res Clin Pract 32(4):177–182. https://doi.org/10.1016/j.krcp.2013.10.002
3. Nusair MB, Rajpurohit N, Alpert MA (2012) Chronic inflammation and coronary atherosclerosis in patients with end-stage renal disease. Cardioren Med 2(2):117–124
4. Mathew RO, Bangalore S, Lavelle MP, Pellikka PA, Sidhu MS, Boden WE, Asif A (2017) Diagnosis and management of atherosclerotic cardiovascular disease in chronic kidney disease: a review. Kidney Int 91(4):797–807. https://doi.org/10.1016/j.kint.2016.09.049
5. Shroff GR, Frederick PD, Herzog CA (2012) Renal failure and acute myocardial infarction: clinical characteristics in patients with advanced chronic kidney disease, on dialysis, and without chronic kidney disease. A collaborative project of the United States Renal Data System/National Institutes of Health and the National Registry of Myocardial Infarction. Am Heart J 163(3):399–406. https://doi.org/10.1016/j.ahj.2011.12.002
6. Olechnowicz-Tietz S, Gluba A, Paradowska A, Banach M, Rysz J (2013) The risk of atherosclerosis in patients with chronic kidney disease. Int Urol Nephrol 45(6):1605–1612. https://doi.org/10.1007/s11255-013-0407-1
7. Drueke TB, Massy ZA (2010) Atherosclerosis in CKD: differences from the general population. Nat Rev Nephrol 6(12):723–735. https://doi.org/10.1038/nrneph.2010.143
8. Mikolasevic I, Zutelija M, Mavrinac V, Orlic L (2017) Dyslipidemia in patients with chronic kidney disease: etiology and management. Int J Nephrol Renovasc Dis 10:35–45. https://doi.org/10.2147/IJNRD.S101808
9. Kon V, Linton MF, Fazio S (2011) Atherosclerosis in chronic kidney disease: the role of macrophages. Nat Rev Nephrol 7(1):45–54. https://doi.org/10.1038/nrneph.2010.157
10. Shrestha P, van de Sluis B, Dullaart RPF, van den Born J (2019) Novel aspects of PCSK9 and lipoprotein receptors in renal disease-related dyslipidemia. Cell Signal 55:53–64. https://doi.org/10.1016/j.cellsig.2018.12.001
11. Emanuele E, Lusignani LS, Peros E, Montagna G, D'Angelo A, Montagna L, Geroldi D (2004) Lipoprotein(a)-associated atherothrombotic risk in hemodialysis patients. Am J Nephrol 24(2):221–229. https://doi.org/10.1159/000077293
12. Vaziri ND (2016) Disorders of lipid metabolism in nephrotic syndrome: mechanisms and consequences. Kidney Int 90(1):41–52. https://doi.org/10.1016/j.kint.2016.02.026
13. Kronenberg F, Utermann G, Dieplinger H (1996) Lipoprotein(a) in renal disease. Am J Kidney Dis 27(1):1–25
14. Longenecker JC, Coresh J, Marcovina SM, Powe NR, Levey AS, Giaculli F, Fink NE, Klag MJ (2003) Lipoprotein(a) and prevalent cardiovascular disease in a dialysis population: the choices for healthy outcomes in caring for ESRD (CHOICE) study. Am J Kidney Dis 42(1):108–116
15. Kollerits B, Drechsler C, Krane V, Lamina C, Marz W, Dieplinger H, Ritz E, Wanner C, Kronenberg F, German D, Dialysis Study I (2016) Lipoprotein(a) concentrations, apolipoprotein(a) isoforms and clinical endpoints in haemodialysis patients with type 2 diabetes mellitus: results from the 4D Study. Nephrol Dial Transpl 31(11):1901–1908. https://doi.org/10.1093/ndt/gfv428
16. Kronenberg F (2014) Causes and consequences of lipoprotein(a) abnormalities in kidney disease. Clin Exp Nephrol 18(2):234–237. https://doi.org/10.1007/s10157-013-0875-8
17. Kronenberg F, Neyer U, Lhotta K, Trenkwalder E, Auinger M, Pribasnig A, Meisl T, Konig P, Dieplinger H (1999) The low molecular weight apo(a) phenotype is an independent predictor for coronary artery disease in hemodialysis patients: a prospective follow-up. J Am Soc Nephrol JASN 10(5):1027–1036
18. Kaysen GA (2007) Hyperlipidemia in chronic kidney disease. Int J Artif Organs 30(11):987–992
19. Longenecker JC, Klag MJ, Marcovina SM, Liu YM, Jaar BG, Powe NR, Fink NE, Levey AS, Coresh J (2005) High lipoprotein(a) levels and small apolipoprotein(a) size prospectively predict cardiovascular events in dialysis patients. J Am Soc Nephrol JASN 16(6):1794–1802. https://doi.org/10.1681/ASN.2004110922
20. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Z, Riccardi G, Taskinen MR, Tokgozoglu L, Verschuren WMM, Vlachopoulos C, Wood DA, Zamorano JL, Cooney MT, Group ESCSD (2016) 2016 ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J 37(39):2999–3058. https://doi.org/10.1093/eurheartj/ehw272
21. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG (2009) Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA 301(22):2331–2339. https://doi.org/10.1001/jama.2009.801
22. Ohashi H, Oda H, Ohno M, Watanabe S, Sakata S (1999) Lipoprotein(a) as a risk factor for coronary artery disease in hemodialysis patients. Kidney Int Suppl 71:S242–S244
23. Willeit P, Kiechl S, Kronenberg F, Witztum JL, Santer P, Mayr M, Xu Q, Mayr A, Willeit J, Tsimikas S (2014) Discrimination and net reclassification of cardiovascular risk with lipoprotein(a): prospective 15-year outcomes in the Bruneck Study. J Am Coll Cardiol 64(9):851–860. https://doi.org/10.1016/j.jacc.2014.03.061
24. Koda Y, Nishi S, Suzuki M, Hirasawa Y (1999) Lipoprotein(a) is a predictor for cardiovascular mortality of hemodialysis patients. Kidney Int Suppl 71:S251–S253
25. Longenecker JC, Coresh J, Klag MJ, Powe NR, Fink NE, Marcovina SM (2008) Lipoprotein(a) level as a predictor of cardiovascular disease and small apolipoprotein(a) isoforms in dialysis patients: assay-related differences are important. Clin Chim Acta 397(1–2):36–41. https://doi.org/10.1016/j.cca.2008.07.012
26. Kollerits B, Krane V, Drechsler C, Lamina C, Marz W, Ritz E, Wanner C, Kronenberg F, German D, Dialysis Study I (2012) Apolipoprotein A-IV concentrations and clinical outcomes in haemodialysis patients with type 2 diabetes mellitus—a post hoc analysis of the 4D Study. J Intern Med 272(6):592–600. https://doi.org/10.1111/j.1365-2796.2012.02585.x
27. Zimmermann J, Herrlinger S, Pruy A, Metzger T, Wanner C (1999) Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. Kidney Int 55(2):648–658. https://doi.org/10.1046/j.1523-1755.1999.00273.x
28. Kronenberg F, Trenkwalder E, Sturm W, Kathrein H, Konig P, Neyer U, Grochenig E, Utermann G, Dieplinger H (1997) LDL-unbound apolipoprotein(a) and carotid atherosclerosis in hemodialysis patients. Clin Genet 52(5):377–386
29. Stenvinkel P, Heimburger O, Paultre F, Diczfalusy U, Wang T, Berglund L, Jogestrand T (1999) Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal

failure. Kidney Int 55(5):1899–1911. https://doi.org/10.1046/j.1523-1755.1999.00422.x
30. Koch M, Kutkuhn B, Trenkwalder E, Bach D, Grabensee B, Dieplinger H, Kronenberg F (1997) Apolipoprotein B, fibrinogen, HDL cholesterol, and apolipoprotein(a) phenotypes predict coronary artery disease in hemodialysis patients. J Am Soc Nephrol JASN 8(12):1889–1898
31. Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, Ritz E, German D, Dialysis Study I (2005) Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 353(3):238–248. https://doi.org/10.1056/nejmoa043545
32. Fellstrom BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Gronhagen-Riska C, De Lima JJ, Lins R, Mayer G, McMahon AW, Parving HH, Remuzzi G, Samuelsson O, Sonkodi S, Sci D, Suleymanlar G, Tsakiris D, Tesar V, Todorov V, Wiecek A, Wuthrich RP, Gottlow M, Johnsson E, Zannad F (2009) Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 360(14):1395–1407. https://doi.org/10.1056/nejmoa0810177
33. Verdoodt A, Honore PM, Jacobs R, De Waele E, Van Gorp V, De Regt J, Spapen HD (2018) Do statins induce or protect from acute kidney injury and chronic kidney disease: an update review in 2018. J Transl Intern Med 6(1):21–25. https://doi.org/10.2478/jtim-2018-0005
34. Kotani K, Banach M (2017) Lipoprotein(a) and inhibitors of proprotein convertase subtilisin/kexin type 9. J Thorac Dis 9(1):E78–E82
35. Castro Cabezas M, Burggraaf B, Klop B (2018) Dyslipidemias in clinical practice. Clin Chim Acta 487:117–125. https://doi.org/10.1016/j.cca.2018.09.010
36. Viney NJ, van Capelleveen JC, Geary RS, Xia S, Tami JA, Yu RZ, Marcovina SM, Hughes SG, Graham MJ, Crooke RM, Crooke ST, Witztum JL, Stroes ES, Tsimikas S (2016) Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials. Lancet 388(10057):2239–2253. https://doi.org/10.1016/S0140-6736(16)31009-1
37. Corsetti JP, Gansevoort RT, Bakker SJL, Dullaart RPF (2016) Apolipoprotein E levels and apolipoprotein E genotypes in incident cardiovascular disease risk in subjects of the prevention of renal and vascular end-stage disease study. J Clin Lipidol 10(4):842–850. https://doi.org/10.1016/j.jacl.2016.03.003
38. Guz G, Nurhan Ozdemir F, Sezer S, Isiklar I, Arat Z, Turan M, Haberal M (2000) Effect of apolipoprotein E polymorphism on serum lipid, lipoproteins, and atherosclerosis in hemodialysis patients. Am J Kidney Dis 36(4):826–836. https://doi.org/10.1053/ajkd.2000.17682
39. Liberopoulos E, Siamopoulos K, Elisaf M (2004) Apolipoprotein E and renal disease. Am J Kidney Dis 43(2):223–233
40. Liu J, Rosner MH (2006) Lipid abnormalities associated with end-stage renal disease. Semin Dial 19(1):32–40. https://doi.org/10.1111/j.1525-139X.2006.00117.x
41. Ilveskoski E, Perola M, Lehtimaki T, Laippala P, Savolainen V, Pajarinen J, Penttila A, Lalu KH, Mannikko A, Liesto KK, Koivula T, Karhunen PJ (1999) Age-dependent association of apolipoprotein E genotype with coronary and aortic atherosclerosis in middle-aged men: an autopsy study. Circulation 100(6):608–613
42. Imura T, Kimura H, Gejyo F (1999) Apolipoprotein E phenotypes in hemodialysis patients. Kidney Int Suppl 71:S245–S247
43. Freedman BI, Bostrom M, Daeihagh P, Bowden DW (2007) Genetic factors in diabetic nephropathy. Clin J Am Soc Nephrol CJASN 2(6):1306–1316. https://doi.org/10.2215/CJN.02560607
44. Wang Y, Wang N, Lu Y, Yu Q, Zhou L, Xu Q (2017) Detection of apolipoprotein E gene polymorphism and blood lipid level in hemodialysis patients. J Clin Med Res 9(8):695–700. https://doi.org/10.14740/jocmr3046e
45. Winkler K, Hoffmann MM, Krane V, Marz W, Drechsler C, Wanner C (2010) Apolipoprotein E genotype predicts cardiovascular endpoints in dialysis patients with type 2 diabetes mellitus. Atherosclerosis 208(1):197–202. https://doi.org/10.1016/j.atherosclerosis.2009.06.036
46. Olmer M, Renucci JE, Planells R, Bouchouareb D, Purgus R (1997) Preliminary evidence for a role of apolipoprotein E alleles in identifying haemodialysis patients at high vascular risk. Nephrol Dial Transpl 12(4):691–693
47. Choi KH, Song HY, Shin SK, Noh H, Kang SW, Kim JH, Lee HY, Han DS (1999) Influence of apolipoprotein E genotype on lipid and lipoprotein levels in continuous ambulatory peritoneal dialysis patients. Adv Perit Dial Conf Perit Dial 15:243–246
48. Kwan BC, Kronenberg F, Beddhu S, Cheung AK (2007) Lipoprotein metabolism and lipid management in chronic kidney disease. J Am Soc Nephrol JASN 18(4):1246–1261. https://doi.org/10.1681/ASN.2006091006
49. Zhang Y, Zhang L, Cao B (2015) The association between serum ApoE genetic polymorphism and serum lipid level in hemodialysis patients. Genet Test Mol Biomark 19(2):93–97. https://doi.org/10.1089/gtmb.2014.0267
50. Wang K, Wang P, Qiao Y, Lu X, Wang X, Liu Z (2015) The effects of serum apolipoprotein E genetic variants and concentration on serum lipid parameters in haemodialysis patients. J Pharm Pharmacol 67(5):696–702. https://doi.org/10.1111/jphp.12356
51. Zheng CZ, Qi XM, Shu YB, Bai YW, Wu YG (2018) Associations between apolipoprotein E gene polymorphisms and cardiovascular complications of uremic patients on maintenance hemodialysis. Blood Purif 46(1):48–55. https://doi.org/10.1159/000486846
52. Lim PS, Liu CS, Hong CJ, Wei YH (1997) Prevalence of apolipoprotein E genotypes in ischaemic cerebrovascular disease in end-stage renal disease patients. Nephrol Dial Transpl 12(9):1916–1920
53. Dergunov AD (2011) Apolipoprotein E genotype as a most significant predictor of lipid response at lipid-lowering therapy: mechanistic and clinical studies. Biomed Pharmacother 65(8):597–603. https://doi.org/10.1016/j.biopha.2011.04.003
54. Conejero-Goldberg C, Gomar JJ, Bobes-Bascaran T, Hyde TM, Kleinman JE, Herman MM, Chen S, Davies P, Goldberg TE (2014) APOE2 enhances neuroprotection against Alzheimer's disease through multiple molecular mechanisms. Mol Psychiatry 19(11):1243–1250. https://doi.org/10.1038/mp.2013.194
55. Singhrao SK, Harding A, Chukkapalli S, Olsen I, Kesavalu L, Crean S (2016) Apolipoprotein E related co-morbidities and Alzheimer's disease. J Alzheimer's Dis JAD 51(4):935–948. https://doi.org/10.3233/JAD150690
56. Safieh M, Korczyn AD, Michaelson DM (2019) ApoE4: an emerging therapeutic target for Alzheimer's disease. BMC Med 17(1):64. https://doi.org/10.1186/s12916-019-1299-4
57. Kirmizis D, Koutoupa E, Tsiandoulas A, Valtopoulou A, Niavis G, Markou P, Barboutis K (2007) Serum lipid profile constituents as markers of cardiovascular morbidity in patients on chronic hemodialysis. Biomark Insights 1:185–192
58. Zhan X, Chen Y, Yan C, Liu S, Deng L, Yang Y, Qiu P, Pan D, Zeng B, Chen Q (2018) Apolipoprotein B/apolipoprotein A1 ratio and mortality among incident peritoneal dialysis patients. Lipids Health Dis 17(1):117. https://doi.org/10.1186/s12944-018-0771-z
59. Ramasamy I (2016) Update on the molecular biology of dyslipidemias. Clin Chim Acta 454:143–185. https://doi.org/10.1016/j.cca.2015.10.033
60. Ferro CJ, Mark PB, Kanbay M, Sarafidis P, Heine GH, Rossignol P, Massy ZA, Mallamaci F, Valdivielso JM, Malyszko J, Verhaar MC, Ekart R, Vanholder R, London G, Ortiz A, Zoccali C (2018) Lipid management in patients with chronic kidney disease. Nat Rev Nephrol 14(12):727–749. https://doi.org/10.1038/s41581-018-0072-9

61. Prinsen BH, de Sain-van der Velden MG, de Koning EJ, Koomans HA, Berger R, Rabelink TJ (2003) Hypertriglyceridemia in patients with chronic renal failure: possible mechanisms. Kidney Int Suppl 84:S121–S124. https://doi.org/10.1046/j.1523-1755.63.s84.34.x
62. Prichard SS (2006) Management of hyperlipidemia in patients on peritoneal dialysis: current approaches. Kidney Int Suppl 103:S115–S117. https://doi.org/10.1038/sj.ki.5001926
63. Bevc S, Hojs R, Ekart R, Hojs-Fabjan T (2006) Atherosclerosis in hemodialysis patients: traditional and nontraditional risk factors. Acta dermatovenerologica Alpina, Pannonica, et Adriatica 15(4):151–157
64. Ye M, Liu Y, Wang H, Tian N, Li W, He W, Lin H, Fan R, Li C, Liu D, Yao F (2018) Serum apolipoprotein B is inversely associated with eccentric left ventricular hypertrophy in peritoneal dialysis patients. Int Urol Nephrol 50(1):155–165. https://doi.org/10.1007/s11255-017-1737-1
65. Cicero AFG, Kuwabara M, Johnson R, Bove M, Fogacci F, Rosticci M, Giovannini M, D'Addato S, Borghi C, Brisighella Heart Study g (2018) LDL-oxidation, serum uric acid, kidney function and pulse-wave velocity: data from the Brisighella Heart Study cohort. Int J Cardiol 261:204–208. https://doi.org/10.1016/j.ijcard.2018.03.077
66. Sato Y, Fujimoto S, Toida T, Nakagawa H, Yamashita Y, Iwakiri T, Fukuda A, Iwatsubo S (2016) Apoprotein B/apoprotein A-1 ratio and mortality among prevalent dialysis patients. Clin J Am Soc Nephrol CJASN 11(5):840–846. https://doi.org/10.2215/CJN.09830915
67. Vaziri ND, Liang K (2002) Up-regulation of acyl-coenzyme A:cholesterol acyltransferase (ACAT) in nephrotic syndrome. Kidney Int 61(5):1769–1775. https://doi.org/10.1046/j.1523-1755.2002.00319.x
68. Zodda D, Giammona R, Schifilliti S (2018) Treatment strategy for dyslipidemia in cardiovascular disease prevention: focus on old and new drugs. Pharmacy 6(1):1. https://doi.org/10.3390/pharmacy6010010