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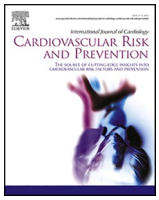

Lipoprotein (a) and lipid-lowering treatment from the perspective of a cardiac surgeon. An impact on the prognosis in patients with aortic valve replacement and after heart transplantation

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ABSTRACT

Lipoprotein(a) is a recognized risk factor for ASCVD. There is still no targeted therapy for Lp(a), however, drugs such as pelacarsen, olpasiran, zerlasiran, lepodisiran and muvalaplin are in clinical trials and have been shown to be effective in significantly reducing Lp(a) levels. Moreover, elevated Lp(a) levels significantly affect the prognosis of patients after aortic valve replacement (AVR) and heart transplantation (HTx). Therefore, the assessment of Lp(a) concentration in these patients will allow for a more accurate stratification of their cardiovascular risk, and the possibility of lowering Lp(a) will allow for the optimization of this risk. In this article, we summarized the most important information regarding the role of Lp(a) and lipid-lowering treatment in patients after AVR and HTx.

1. Lipoprotein (a)

Increased lipoprotein (a) [Lp(a)] levels are important risk factor for atherosclerotic cardiovascular disease (ASCVD) [1–4]. Lp(a) is 5-fold more atherogenic compared to low-density lipoprotein (LDL) and is independently associated with long-term major adverse cardiovascular events (MACE) among individuals with and without baseline ASCVD [4,5].There is still no targeted therapy available, however there are some drugs in the ongoing clinical trials, including antisense oligonucleotides (pelacarsen), siRNA (olpasiran, zerlasiran, lepodisiran); and inhibitors of apo(a) binding to apoB_{100} (muvalaplin), which confirmed to significantly reduce the level of Lp(a) [3,6]. The latest data indicate a possibly important role of Lp(a) in shaping the risk of patients after aortic valve replacement (AVR) and heart transplantation (HTx).

1.1. Aortic stenosis (AS)

AS mainly related to progressive calcification of the leaflets (calcific aortic valve disease, CAVD), is the most common acquired valvular heart disease [7]. The prevalence of diagnosed AS increased by 443 % between 1990 and 2019, and untreated is associated with higher mortality [8,9]. Therefore, the preferred treatment of AS is valve replacement either surgically (surgical aortic valve replacement, SAVR) or percutaneously (transcatheter aortic valve implantation, TAVI) [10]. One of complications of TAVI is paravalvular leak, which occurs in 7–40 % of patients and affects survival [11,12]. Another important complication is the degeneration of the aortic valve bioprosthesis, resulting in the need for reintervention, which may occur in 2–10 % in 10 years to even 40 % in 20 years [13].

1.2. Lp(a) in patients with AS undergoing TAVI

Moderately elevated Lp(a) level [>30 mg/dl/>75 nmol/l] is found in 37 % and 35 % of AS and TAVI populations respectively [14]. Elevated Lp(a) level is an important risk factor for AS. The results of various meta-analyses indicate that elevated Lp(a) levels significantly increase the risk of AS (≥50 mg/dl [≥125 nmol/l]; RR = 1.70; 95 % CI: 1.39–2.07; ≥30 mg/dl [≥75 nmol/l]; RR = 1.38; 95 % CI: 1.19–1.61) [15,16]. In patients with elevated Lp(a) levels, a faster progression of AS is also observed (0.09 m/s/year), especially in those at a younger age (HR = 1.19 *vs.* 1.10), and 39 % higher risk of death [17].

Lp(a) levels >50 mg/dl (>125 nmol/l) are strictly associated with

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the risk of AVR at a younger age [18]. Patients with elevated Lp(a) levels have a 102 % higher risk of requiring AVR (HR = 2.22; 95 % CI: 1.38–3.58) [19]. Patients undergoing TAVI with Lp(a) levels ≥30 mg/dl (≥75 nmol/l) had a 3-fold higher risk of paravalvular leak after the procedure (13 *vs*. 4 %, p = 0.04) and a higher risk of requiring coronary revascularization (65 *vs*. 47 %, p = 0.047) [20]. During the 2-year follow-up increased Lp(a) levels were not found to be a predictor of degeneration of the bioprosthetic aortic valve [21]. Nevertheless, it has been shown that the levels of Lp(a) ≥30 mg/dl (≥75 nmol/l) increases the risk of degeneration of a bioprosthetic aortic valve more than 4-fold (HR_{adj} = 4.4; 95 % CI: 1.9–10.4) in a study with the mean follow-up of 4.4 years [22]. Thus, it seems reasonable to recommended that Lp(a) levels be measured in TAVI patients for the perioperative risk assessment and prosthesis durability although the level of evidence for this statement has not been established.

1.3. Lipid-lowering treatment and AS

The use of statins in patients undergoing TAVI contributes to overall all-cause mortality risk reduction (HR = 0.78; 95 % CI: 0.68–0.89), which is more pronounced with the intensive statin therapy (HR = 0.62; 95 % CI: 0.45–0.85) [23]. It was also shown that the use of statins in patients undergoing SAVR reduced the risk of all-cause mortality (HR = 0.67; 95 % CI: 0.60–0.74). The use of statins does not affect the risk of AS [24]. In a study including 11894 patients after SAVR, it was found that ongoing statin treatment led to a reduced risk of: all-cause mortality (HR_{adj} = 0.70; 95 % CI: 0.64–0.76), cardiovascular mortality (HR_{adj} = 0.86; 95 % CI: 0.77–0.97) and MACE (HR_{adj} = 0.77; 95 % CI: 0.71–0.83). In the context of the impact on the risk of MACE, the beneficial effect of statins was present in various subgroups of patients: gender (female - HR = 0.82; male - HR = 0.74), age (≤75 - HR = 0.81, ≥75 - HR. 0.75), reduced left ventricular ejection fraction (yes - HR = 0.81, no - HR = 0.75), previous myocardial infarction (yes - HR = 0.73, no - HR = 0.76), coexistence of peripheral artery disease (yes - HR = 0.77, no - HR = 0.76), coexistence of hypertension (yes - HR = 0.72, no - HR = 0.85), coexistence of diabetes (yes - HR = 0.73, no - HR = 0.77), coexistence of lipid disorders (yes - HR = 0, 66, no - HR = 0.85), coexistence of chronic kidney disease (yes - HR = 0.86, no - HR = 0.71), and type of prothesis (biological - HR = 0.77 and mechanical - HR = 0.75) [25]. In the FOURIER study found that the use of evolocumab for at least 1 year was associated with a significant reduction in the risk of AS events (HR = 0.48; 95 % CI: 0.25–0.93) [19]. This effect may be due to a 20–30 % reduction in Lp(a) levels with proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors [1,2]. Interestingly, genetically determined lower level of PCSK9 is associated with a decreased risk of AS (OR = 0.64; 95 % CI: 0.44–0.95) [26]. Thus, the use of LLT may significantly improve prognosis of patients after AVR (also regardless of the effect on [Lp(a)]).

1.4. Heart transplantation (HTx)

Heart failure (HF) remains important cause of mortality and hospitalization globally, despite advances in pharmacological treatment [27]. In 2019, the global prevalence of HF was 56.19 million cases [28]. Of patients with HF, 50 % have reduced ejection fraction (HFrEF), while 40 % preserved ejection fraction (HFpEF) [29]. HTx is an established therapy for end-stage HF for both men and women with a 1-year survival of 91 % and a median survival of 12–13 years [30]. Late graft rejection known as cardiac allograft vasculopathy (CAV) (in 1/3 of patients 5 years after HTx) significantly limits survival being responsible for 30 % of deaths 1 year after HTx [31].

Increased Lp(a) levels are associated with a higher risk of HF, especially HFpEF, by 109–153 % [32]. Elevated Lp(a) level is associated with higher risk of CV mortality in HFrEF patients (HR = 1.22; 95 % CI: 1.04–1.64) [33].

1.5. Lipoprotein (a) in patients after HTx

Lp(a) ≥30 mg/dl (≥75 nmol/l) is found in 43 % of patients after HTx, and ≥50 mg/dl (≥125 nmol/l) in even 20 % of them [34,35]. It was shown that increased Lp(a) level in HTx patients may be associated with the risk of CAV (OR = 1.03; 95 % CI: 1.01–1.05) [36]. Another study found that elevated Lp(a) level was an independent risk factor for developing moderate to severe CAV (OR = 8.57; 95 % CI: 2.82–26.04) in the 1st year after HTx. Patients with Lp(a) ≥30 mg/dl (≥75 nmol/l) also showed an earlier onset of CAV compared with those with normal Lp(a) level [34]. In over 10 years of follow-up of HTx patients, it was found that each increase in Lp(a) level by 10 mg/dl (25 nmol/l) independently increased the risk of CAV by as much as 26 % [37]. Thus, it seems reasonable to measure Lp(a) levels in HTx patients to assess the CAV risk.

1.6. Lipid-lowering treatment after HTx

Statins and LLT constitute an important part of care for HTx patients (Table 1) [38–40]. Among patients after HTx, the percentage of those with adherence to therapy is low (54 %) [41]. After 1 year after HTx, the majority use low-intensity statin therapy, while 8 % do not use these drugs at all [42]. It should be emphasized that the use of statins in HTx patients is safe and mostly does not interact with tacrolimus or sirolimus [43]. It should be emphasized that HTx patients who are adherent to statin therapy are characterized by a significantly lower risk of all-cause mortality (HR = 0.32; 95 % CI: 0.13–0.77) and all-cause hospitalization (HR = 0.72; 95 % CI: 0.54–0.96) [44]. Statins also reduce the risk of hemodynamically significant/fatal rejection (OR = 0.37; 95 % CI:0.21–0.65), CAV (OR = 0.33; 95 % CI: 0.16–0.68) and terminal cancer (OR = 0.30; 95 % CI: 0.15–0.63) [45]. Moreover, early initiation of statins after HTx is associated with a reduction in the CAV progression risk as well as decreased CAV-related events and mortality (HR = 0.58; 95 % CI: 0.38–0.91) [45]. Ezetimibe effectively lowers LDL levels in patients after HTx and is safe. Moreover, the use of ezetimibe after HTx was found to be associated with a lower incidence of CAV [46,47]. PCSK9 inhibitors with intensive LDL reduction, reduction of coronary plaque thickness and increased lumen area, slow down the progression of CAV [48]. The results of the EVOLVD study, which assessed the effect of evolocumab on the risk of CAV after HTx, are awaited (NCT03734211) [31]. It is worth mentioning that in the context of CAV prevention, early initiation of sirolimus after HTx is very effective [49]. On the other hand, sirolimus increases the level of PCSK9 [50]. Therefore, in the light of current knowledge, the use of statins, ezetimibe, and PCSK9 inhibitors (depending on the LDL levels and CVD risk) with sirolimus may be optimal in patients after HTx with lipid disorders in CAV prevention.

2. Conclusions

Lp(a) may be used in preoperative assessment of risk factors significantly affecting late survival in structural heart diseases and heart transplant recipients (Fig. 1). While the evidence is still scattered, this paper outs a new light on the importance of this molecule also in cardiac surgical patients.

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Table 1
Recommendations of the PoLA regarding lipoprotein (a) and recommendations of the ESC/EAS and ISHLT regarding lipid-lowering treatment in patients after heart transplantation [2,38,39].

Recommendation	Level of evidence	Class of evidence
Polish Cardiac Society/ Polish Lipid Association 2024 (PCS/ PoLA) – Lp(a)		
Lp(a) concentration is recommended to be determined at least once in the lifetime of every adult	I	C
Lp(a) determination should be considered as early as possible, even in people under 18 years of age, for risk assessment, cascade screening, monitoring, and lifestyle modification	IIa	C
Measurement of Lp(a) should be considered in all patients with premature cardiovascular disease, lack of expected effect of statin treatment, and those with a borderline risk between moderate and high, for better risk stratification	IIa	B
Measurement of Lp(a) may be considered in very high-risk patients with atherosclerotic cardiovascular disease, in patients with familial hypercholesterolaemia, and in pregnant women as an assessment of miscarriage risk, in the case of recurrent pregnancy loss, and intrauterine growth restriction	IIb	B
It is recommended to test the Lp(a) concentration using a method that assesses the number of Lp(a) particles (in nmol/l) and is insensitive to the number of kringle IV-2 repeats (KIV-2)	I	C
If an elevated Lp(a) level is found, it is recommended that each patient be reassessed for cardiovascular risk using the proposed algorithm/recommended risk calculator, followed by an appropriate modification of treatment.	I	C
European Society of Cardiology/ European Atherosclerosis Society 2019 (ESC/EAS)		
Statins should be considered as first-line agents in transplant patients. Initiation should be at low doses with careful up titration and with caution regarding potential drug-drug interactions, particularly for patients on ciclosporin	IIa	B
In patients who are intolerant of statins or those with significant dyslipidaemia despite maximally tolerated statin treatment, alternative or additional therapy with ezetimibe may be considered	IIb	C
International Society for Heart and Lung Transplantation 2023 (ISHLT)		
Biannual measurements of lipid levels should be performed in adult after HTx	I	C
It is reasonable to target LDL levels below 100 mg/dl (2.5 mmol/l) in HTx patients, but there must be close monitoring for potential interactions between lipid lowering therapies and CNI	IIa	C
In adults, the use of statins after HTx is recommended regardless of LDL levels. Due to pharmacologic interactions with CNI and risk for toxicity, statin doses should generally be lower than those recommended for dyslipidaemia	I	A
Routine use of statins is recommended for all pediatric transplant recipients older than 10 years, and younger patients with evidence of hyperlipidemia, CAV or following re-transplantation. Due to pharmacologic interactions with CNI and risk for toxicity, statin doses should generally be lower than those recommended for dyslipidaemia	IIa	C
In HTx recipients, statin therapy has been shown to reduce CAV and improve long-term outcomes regardless of lipid levels and should be considered for all HTx recipients (adult and pediatric)	I	A
PCSK9 inhibitors and ezetimibe can be considered as adjuncts to statin therapy in heart transplant recipients with uncontrolled hyperlipidemia, or as primary therapy in those with statin intolerance (experience in paediatrics is limited to ≥12 years for PCSK9 and ≥10 years for ezetimibe)	IIb	B

Abbreviations: Lp(a) – lipoprotein (a); LDL – low-density lipoprotein; HTx - heart transplantation; CNI - calcineurin inhibitors; CAV - cardiac allograft vasculopathy; PCSK9 - proprotein convertase subtilisin-kexin type 9.

CRediT authorship contribution statement

Stanisław Surma: Writing – original draft, Visualization, Resources, Formal analysis, Data curation, Conceptualization. **Michał O. Zembala:** Writing – review & editing, Supervision. **Bogusław Okopień:** Supervision. **Maciej Banach:** Supervision.

Declaration of competing interest

Stanisław Surma: honoraria from: Novartis/Sandoz, Pro.Med; Michał O. Zembala: honoraria from Boston Scientific; Bogusław Okopień: honoraria from: Sanofi, Bayer, Boehringer Ingelheim; Amgen, Novartis, Viatris, Servier, Astra Zeneca; Maciej Banach: honoraria from: Amgen, Daiichi Sankyo, KRKA, Polpharma, Mylan/Viatris, Novartis, Novo-Nordisk, Pfizer, Sanofi-Aventis, Teva, Zentiva; consultant to Adamed, Amgen, Daiichi Sankyo, Esperion, NewAmsterdam, Novartis, Novo-

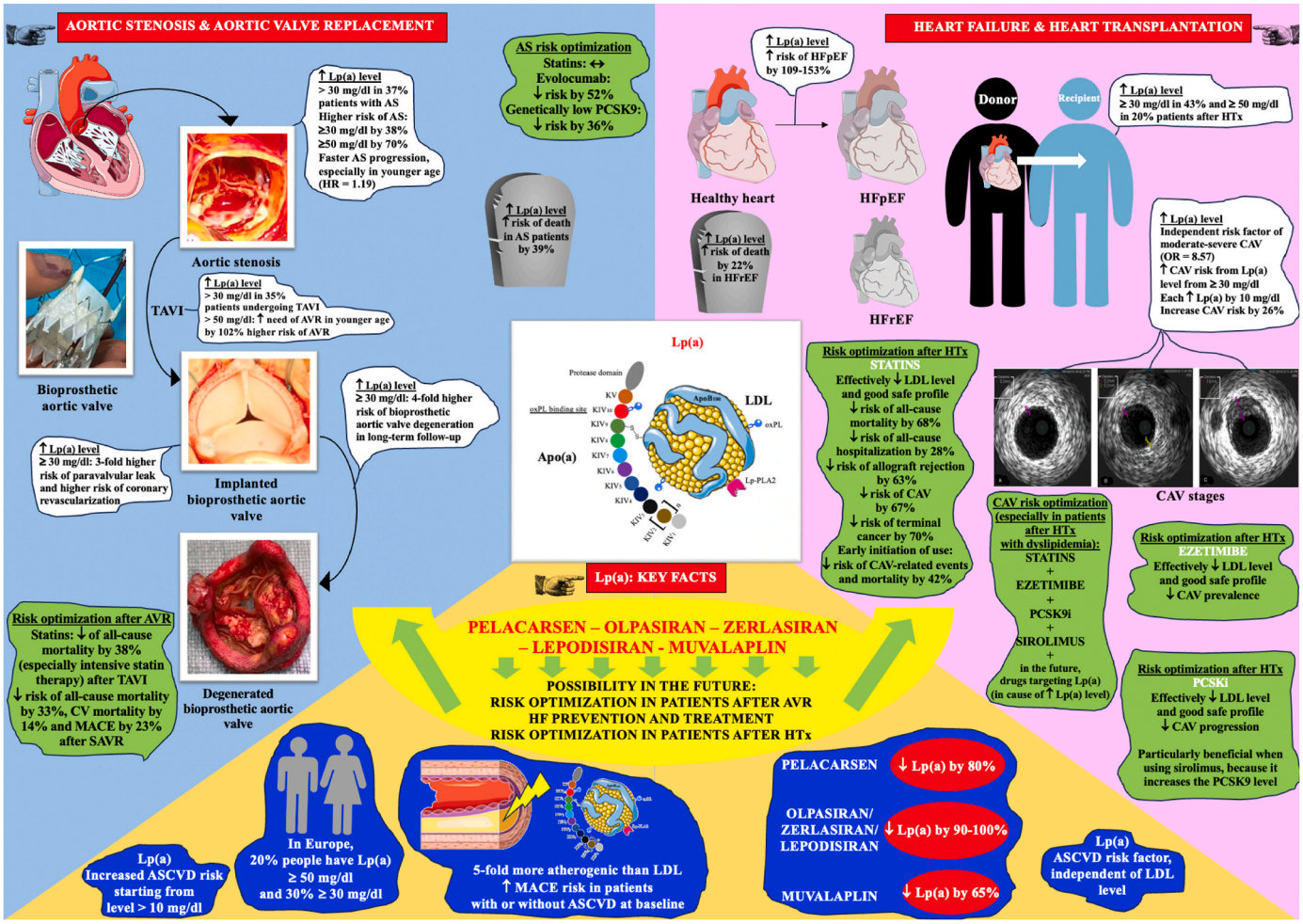

Fig. 1. The role of lipoprotein (a) and lipid-lowering treatment in patients after AVR or HTx. Based on information from Refs. [1–5,14–26,32–37,44–50]. The elements of the figure were created using SERVIER MEDICAL ART (CC BY 4.0). CAV photos used from: Das B.B. et al. Transplantology 2022; 3(3): 241–256 - CC BY license - no permission required. Other photos used are the property of the authors - no permission required. Details about Lp(*a*)-targeted drugs in the text of the article. Abbreviations: Lp(a) – lipoprotein (a); AS – aortic stenosis; HR – hazard ratio; TAVI - transcatheter aortic valve implantation; AVR – aortic valve replacement; MACE – major adverse cardiovascular event; SAVR – surgical aortic valve replacement; ASCVD – atherosclerotic cardiovascular disease; PCSK9 - proprotein convertase subtilisin-kexin type 9; Apo(a) – apolipoprotein (a); LDL – low-density lipoprotein; $ApoB_{100}$ – apolipoprotein B_{100}; oxPL - oxidized phospholipids; Lp-PLA2 - lipoprotein-associated phospholipase A2; HFpEF – heart failure with preserved ejection fraction; HFrEF – heart failure with reduced ejection fraction; HTx - heart transplantation; CAV - cardiac allograft vasculopathy.

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