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# Lipoprotection in cardiovascular diseases

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ABSTRACT

Cardioprotection is a well-established term in the scientific world. It describes the protection of various mediators on the cardiovascular system. These protective effects can also be provided by certain lipids. Since lipids are a very specific and clearly definable class of substances, we define the term lipoprotection as lipid-mediated cardioprotection. In this review, we highlight high-density lipoprotein (HDL), sphingosine-1-phosphate (S1P) and omega-3 polyunsaturated fatty acids (n-3 PUFA) as the most important lipoprotective mediators and show their beneficial impact on coronary artery disease (CAD), acute myocardial infarction (AMI) and heart failure (HF).



**Contents**



## 1. High density lipoprotein (HDL)

High density lipoprotein (HDL) is one of many transport vehicles of proteins and lipids in the circulation. It is about 8–13 nm in size and has a density of 1.063–1.210 g/mL (Mach et al., 2019). The term high-density has historical reasons based on the behavior in ultracentrifugation (Jonas et al., 2008). The synthesis of HDL is extremely complex. The precursor protein, pre-β-HDL, is mainly formed in the intestine and liver. It is able to take up cholesterol from macrophages in the vascular wall, resulting in mature HDL. Within the HDL particle, cholesterol is esterified via lecithin cholesteryl acyltransferase (LCAT). The resulting cholesterol esters (CE) can then be transferred to the low-density

*Abbreviations:* AA, arachidonic acid; ALA, α-linolenic acid; AMI, acute myocardial infarction; Apo, apolipoprotein; βAR, β-adrenergic receptor; CAD, coronary artery disease; CE, cholesterol ester; CETP, cholesterol ester transfer protein; CV, cardiovascular; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GPCR, G protein-coupled receptor; HDL, high-density lipoprotein; HF, heart failure; IMT, intima media thickness; I/R, ischemia/reperfusion; LA, linoleic acid; LCAT, lecithin cholesteryl acyltransferase; LDL, low-density lipoprotein; n-3 PUFA, omega-3 polyunsaturated fatty acids; PCI, percutaneous coronary intervention; PL, phospholipid; S1P, sphingosine-1-phosphate; S1PR, sphingosine-1-phosphate receptor; Sphk, sphingosine kinase; SR-BI, scavanger receptor B1; TAG, triacylglycerol.

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lipoprotein (LDL) via the cholesterol ester transfer protein (CETP), making cholesterol available for the construction of cell membranes. On the other hand, HDL can be taken up into the liver via the scavanger receptor B1 (SR-BI), where it can be excreted via the bile. In both cases, this is known as reverse cholesterol transport (Fielding & Fielding, 1995). Mature HDL particles are micro emulsion containing a core of various neutral lipids (triacylglycerol (TAG), CE and cholesterol) which is stabilized by a surface monomolecular film of phospholipids (PL), cholesterol and apolipoproteins (Apo). ApoA-1 is probably the most important of the many Apos, as it is responsible for many of the following lipoprotective functions in the cardiovascular (CV) system. However, HDL particles do not form a completely uniform class of lipoproteins but they vary in their composition, size and density (Kontush et al., 2015). The impact of the different HDL subclasses on CV diseases is an emerging topic currently the subject of controversial debate. For this reason, a detailed analysis of these possible differences is not part of this review.

### 1.1. Coronary artery disease (CAD)

Coronary artery disease (CAD) is defined as a *"pathological process characterized by atherosclerotic plaque accumulation in the epicardial arteries. It is a chronic, most often progressive, and hence serious, even in clinically apparently silent periods"* (Knuuti et al., 2020). In addition to interventional and/or drug therapy, which is used to protect patients, HDL also shows a lipoprotective effect in CAD.

This protective effect has been shown in large studies and applies to all age groups. A recently published meta-analysis revealed negative correlation between HDL level and CAD severity throughout twelve clinical studies with 5544 participants including 3009 patients (Hu et al., 2024). Even larger analyses of national insurance data showed a similar picture. Data from the 2010 National Health Insurance Service and the National Death Registry of Korea (1,711,548 patients) were used to associate between HDL levels and all-cause mortality over 10-years in people ≥40 years of age. The negative impact of low HDL levels remained even after adjusting for several parameters like age, body mass index, LDL-cholesterol and triglycerides. A gender effect could not be observed (Yang et al., 2023).

While most studies included patients with a mean age of 60–65 years, more recent studies also showed a lipoprotective effect of HDL in younger people. Several case-control studies analyzed the association between low plasma HDL and premature CAD in patient ≤55 years of age. Although, population-based large cohort studies are still missing, low plasma HDL was positively associated with premature CAD (Shahid et al., 2016). This effect could also be shown in adolescents. A recently published cross-sectional study of 100 healthy participants, aged 14–18, revealed the positive impact of HDL on carotid intima media thickness (IMT) even at this young age (Martínez-Alvarado et al., 2024). Low HDL levels were associated with increased IMT values. The impact of lipoproteins in childhood on cardiovascular diseases (CVD) was recently demonstrated even more clearly by the *i3C Consortium*. They included 21,126 children (mean age 11.9 years) in a prospective cohort study with an average follow-up of 35 years confirming a higher risk for children who were outside their target values (Wu et al., 2024).

In addition to the clear data on the lipoprotective effect of HDL on CAD and the increased risk associated with low HDL levels, there are currently findings in large cohort studies that very high HDL levels could also be detrimental to cardiovascular health. Large epidemiological studies showed U-shaped relationships between HDL levels and all-cause mortality (Ko et al., 2016; Madsen et al., 2017; Yi et al., 2021). Analyses of the CANHEART (Cardiovascular Health in Ambulatory Care Research Team) dataset with 631,762 individuals revealed increased mortality in men with plasma HDL >70 mg/dl and in women >90 mg/dl. However, there was significant association to all-cause mortality, no statistically significant association could be observed between elevated plasma HDL and CV outcome (Ko et al., 2016). Further studies confirmed this finding. Two prospective population-based studies, the Copenhagen City Heart Study and the Copenhagen General Population Study, also revealed a significant increase in all-cause mortality in patients with very high plasma HDL. Although, there were no associations with CAD, AMI, ischemic stroke or CV-mortality. The authors themselves suspect the influence of genetic mutations, which are responsible for both the very high HDL values and the increased mortality risk (Madsen et al., 2017).

Despite these data, there is consensus on the clear lipoprotective effect of HDL in CAD. Although the effect of very high HDL levels is interesting and has been confirmed in several studies, it remains to be seen whether a mechanistic link can be found here. The positive effects of HDL, on the other hand, can be clearly demonstrated. HDL inhibits LDL oxidation (Negre-Salvayre et al., 2006), is responsible for reverse cholesterol transport (Lewis & Rader, 2005), promotes endothelial repair (Tso et al., 2006) and improves endothelial function via NO (Bisoendial et al., 2003). Additionally, it has anti-thrombotic and anti-inflammatory properties (Cockerill et al., 1995) which both are beneficial in CAD. Taken together, HDL is a lipoprotective agent in CAD.

### 1.2. Acute myocardial infarction (AMI)

The global burden of cardiovascular diseases, and AMI in particular, remains high. Since decades this is the leading cause of death in the world (Vaduganathan et al., 2022). Although, rapid revascularization with percutaneous coronary intervention (PCI) and modern antithrombotic treatment, have been able to further reduce one-year mortality in recent years, it is still 8 % (Thrane et al., 2023). Dyslipidemia, defined as low plasma HDL and elevated LDL and total cholesterol (*Atherosclerosis*, 2019), is one of the main risk factors for AMI. Therefore, a deep understanding of lipoprotective effects of HDL is of great interest.

In the last decades, numerous studies could show that low plasma HDL is associated with higher incidence of AMI (Gordon et al., 1989). Low plasma HDL could also be associated with worse outcome after AMI (El Amrawy et al., 2023). An example for this is a longitudinal study based on 384,093 participants from the UK Biobank that revealed a correlation of low HDL with increased risk of AMI all-cause mortality, hemorrhagic stroke and ischemic stroke (Yuan et al., 2023). This was confirmed by large meta-studies which have identified HDL as an important predictor of cardiovascular risk (Di Angelantonio et al., 2012; Rader & Hovingh, 2014) or cardiovascular death (Lewington et al., 2007). In addition to epidemiological studies and meta-studies, murine studies demonstrated lipoprotective effects of HDL in ischemia/reperfusion injury (Sposito et al., 2019; Theilmeier et al., 2006). This applied both to the application of healthy HDL (Tangirala et al., 1999) and to the application of ApoA-1 (Gu et al., 2007).

On the basis of these data, it seemed reasonable to conduct a clinical trial increasing HDL levels in order to reduce the risk of an AMI. However, the pharmacological approaches to increase HDL in plasma using so-called CETP inhibitors (evacetrapib and anacetrapib) and thus reduce the cardiovascular risk has failed in the human setting in large randomized, controlled studies (Bowman et al., 2017; Lincoff et al., 2017). Additionally, the infusion of pure ApoA-1 did also not result in a lower risk of AMI. This was tested in an international RCT with a total of 18,219 patients (Gibson et al., 2024). The current negative data from the large clinical studies mentioned question the lipoprotective properties of HDL. Further data confirmed that HDL cannot serve as an unrestricted lipoprotective agent. Studies with patients who have low HDL plasma levels due to a genetic mutation have not found an increased risk of AMI (Frikke-Schmidt et al., 2008). Recent analyses with Mendelian randomization showed no predictive power of HDL plasma levels on AMI (Voight et al., 2012) showing that the concept of increasing plasma HDL cannot be uniformly applied to reducing the risk of AMI.

Currently, the question of why there is such heterogeneity in the findings needs to be answered, because the fundamental ability of HDL to mediate lipoprotective effects cannot be doubted. In the search

for possible explanations for the current data situation, different subspecies of HDL may play a possible role. This was discussed at least for the failure of the CETP inhibitors, as a change in the subspecies of HDL was found here (Furtado et al., 2022). However, it is reasonable to assume that it is not so much the quantity as the quality of HDL that is of decisive importance for its lipoprotective effect (Rader & Hovingh, 2014). One possible reason could be the sphingolipid sphingosine-1-phosphate (S1P) which is part of HDL and able to mediate cardioprotection (Polzin et al., 2023a; Polzin et al., 2023b). However, in some disease states, S1P content in HDL is reduced and therefore a reduction of lipoprotective effects of HDL could be possible (Levkau, 2015). In the future, further studies will have to show how HDL has to be composed so that it can mediate the undoubtedly existing lipoprotective effects.

### *1.3. Heart failure (HF)*

Heart failure (HF) can be defined as "*a clinical syndrome with symptoms and or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and or objective evidence of pulmonary or systemic congestion*" (Bozkurt et al., 2021). In addition, this disease can be further categorized according to the remaining ejection fraction, an acute or chronic condition and the severity of the symptoms (McDonagh et al., 2021). Irrespective of any further classification, around 1–2 % of all adults in Europe suffer from this disease (Conrad et al., 2018).

From an epidemiological perspective, HDL has a big impact on the incidence of HF and unfavorable prognosis in patients with HF. In 6860 participants of the Framingham Heart Study (49 % women, mean age 44 years) who had no CAD at baseline, there was an association between raised HDL cholesterol levels and the incidence of HF even after adjustment for AMI and clinical covariables (Velagaleti et al., 2009). Additionally, plasma HDL levels could be negatively associated with mortality in HF patients (Potočnjak et al., 2017). In a prospective cohort study with chronic HF patients, the antioxidant function of HDL was an independent predictor of the combined endpoint of death from cardiovascular events and heart transplantation (Schrutka et al., 2016). However, the lipoprotective effect of HDL appears to depend not only on the quantity, but also on its functionality.

One way to define HDL functionality is the analyses of key lipoprotective functions: cholesterol efflux, anti-oxidative and anti-inflammatory capacity. A recently published study randomly selected 446 patients with HF from BIOSTAT-CHF (A Systems Biology Study to Tailored Treatment in Chronic Heart Failure), analyzed these three HDL functions and associated them with mortality. It could be shown that better HDL cholesterol efflux at baseline was associated with lower mortality during follow-up. Additionally, HDL cholesterol efflux and anti-inflammatory capacity declined during follow-up in patients with heart failure (Emmens et al., 2021). ApoA-1 emerged as the main protein associated with all three HDL functions. Further studies could also show the prognostic power of plasma HDL und ApoA-1 in patients with HF regardless of etiology (Iwaoka et al., 2007).

Mechanistically, HDL mediates beneficial effects on many tissues that account for its lipoprotective effect in HF. HDL protects cardiomyocytes against necrosis via a mechanism involving its main receptor SR-BI (Durham et al., 2018). In addition, HDL showed direct effects in vitro on contractility of cardiomyocytes in rodent (Van Linthout et al., 2008) and it is able to inhibit cardiomyocyte hypertrophy by suppressing angiotensin II type 1 (AT1) receptor upregulation (Lin et al., 2015). Besides its effects on cardiomyocytes, HDL also promotes effects on myocardial endothelial cells (Kimura et al., 2006; Tran-Dinh et al., 2013) and fibroblasts (Spillmann et al., 2016) which are beneficial in HF. Additionally, HDLs overall anti-oxidative and anti-inflammatory impact show favorable effects in HF as both oxidative stress and inflammation are key player in pathogenesis of HF (Okonko & Shah, 2015; Westman et al., 2016). To be more precise, activation of the NLRP3 inflammasome is terminated (Thacker et al., 2016), neutrophil activation is impeded (Murphy et al., 2011), and interleukin-6 production is inhibited by HDL (Gomaraschi et al., 2005). However, all mechanisms found so far on how HDL protects in the context of HF relate to healthy and functional HDL. Several studies in rodent models have shown that HDL may hamper HF development, while dysfunctional (changed composition) HDL may do the opposite (Aboumsallem et al., 2018; Aboumsallem et al., 2019; Amin et al., 2017; Mishra et al., 2020; Muthuramu et al., 2018).

In summary, the clear lipoprotective effect of HDL on the development and progression of HF remains and the mechanisms behind are manifold. Even if the quality or functionality of HDL is a decisive limitation here. This is currently and will continue to be the focus of HDL research in the future to increase the understanding of the lipoprotective effects and to be able to use this therapeutically in HF.

## 2. Sphingosine-1-phosphate (S1P)

S1P is a bioactive sphingolipid with various effects and functions within the cardiovascular system. It is formed from ceramide that is composed of a fatty acid and a sphingosine molecule. This ceramide is then converted into sphingosine via an enzyme called ceramidase (Mendelson et al., 2014). Finally, sphingosine is then phosphorylated by sphingosine kinase (Sphk) generating S1P (Spiegel & Milstien, 2007). Similar to other bioactive lipids, S1P can easily as an intracellular second messenger, and as an extracellular ligand for its five different G protein-coupled receptors (GPCRs) (Cirillo et al., 2021). Because the S1P receptor (S1PR) 4 + 5 are mainly found in the nervous system (Ishii et al., 2004), they do not play a relevant role for the cardiovascular effects of S1P. S1PR1–3, on the other hand, can all mediate cardiovascular effects (Levkau, 2013). As amphipathic molecule, S1P needs to bind to a carrier to be present in biological and aqueous fluids and act as an extracellular ligand subsequently. The majority of S1P (65–80 %) is associated to HDL (Levkau, 2015). For this reason, it is not always easy to clearly distinguish the effects of S1P from those of HDL. Nevertheless, a whole range of positive effects can clearly be attributed to S1P.

### *2.1. Coronary artery disease (CAD)*

Dyslipidemia and therefore a lack of lipoprotection is a risk factor for CAD (Asadi et al., 2015). Patients with CAD are characterized by reduced S1P amount in HDL as compared to healthy subjects (Sattler et al., 2010). Mounting evidence has shown that plasma HDL levels are a negative predictor for CAD. Although the quantity plays a role, the quality of the HDL is much more important (Sattler et al., 2014). One of the established points that determine functional defects of HDL is its reduction in S1P (Sattler et al., 2010). Important findings of studies have shown that some of the atheroprotective actions of HDL are mediated by S1P (Potì et al., 2014). Fittingly, plasma S1P is a strong predictor of occurrence and severity of CAD (Sattler et al., 2014). This was confirmed in a multivariate analysis revealing that S1P was more powerful predictor of obstructive CAD than traditional risk factors likes age, sex, hypertension or the lipid profile (Deutschman et al., 2003). The strong ability to act as a predictor is also evident in patients with carotid stenosis and peripheral artery disease (Soltau et al., 2016). Overall, the predictive power appears to be significantly stronger than for HDL.

The positive and lipoprotective effects of S1P on CAD are distinct and clear. However, the mechanistic explanations are manifold and complex. In routine clinical practice, S1P modulators are used to suppress the immune system in the context of multiple sclerosis (Rae-Grant et al., 2018). These anti-inflammatory effects of S1P also show positive effects on the progression of CAD. S1PR1-signaling showed anti-atherosclerotic effects by the inhibition of macrophage apoptosis and endothelial inflammation. This is mediated by intracellular pathway with phosphatidylinositol 3-kinase (PI3K) and protein kinase B (PI3K/Akt) as central elements (Al-Jarallah et al., 2014). S1P is also able to

inhibit the activation of Toll-like receptor-2 which further underlies its anti-inflammatory and anti-atherogenic role (Dueñas et al., 2008). For the sake of completeness, it must be mentioned that there are also studies that show a pro-inflammatory effect of S1P. There is some evidence that S1P induces NF-κB activation and TNF-α production in adipocytes, macrophages, and monocytes (Keul et al., 2011; Wang et al., 2014; Yogi et al., 2011). However, these do not provide a mechanistic explanation for the clear lipoprotective effect of S1P in CAD. Nevertheless, it is important to illustrate the inflammatory effects of S1P/S1PR axis in CAD more clearly.

Besides its anti-inflammatory effect, S1P showed lipoprotective effects on endothelial cells. That is of great importance as disruption of the integrity of vascular endothelial cells is an important factor in atherosclerosis and therefore in CAD. Several studies have shown that S1P attenuates endothelial cells' apoptosis via S1PR1/3-signaling (Kimura et al., 2003; Nofer et al., 2004). Mechanistically, S1P exert its anti-apoptotic effects through phosphorylation of Akt and Erk via S1PR1 and S1PR3 (Ruiz et al., 2017). Additionally, a recently published study revealed that S1P protects endothelial cells from activation under hemodynamic stress and refrains coronary atherosclerosis (Manzo et al., 2024) and it was shown that S1P-loading improves protective HDL signaling in the endothelium (Sattler et al., 2015). Moreover, S1PR3-signaling was shown to have additional anti-atherosclerotic effects by inhibiting neointima formation (Keul et al., 2011).

### 2.2. Acute myocardial infarction (AMI)

Although large RCTs on the impact of S1P in AMI are lacking and there are few human data on the association of S1P and outcome after AMI, the lipoprotective effects are considered certain. Recently, it was shown that plasma S1P level were associated with and infarct size and cardiovascular death in patients with AMI (Polzin et al., 2023b).

In contrast to the limited human data, there are countless basic scientific studies that have mechanistically investigated the lipoprotective effect of S1P in AMI (Wang et al., 2023). Therefore, a murine model of AMI was used in most of the studies. Many studies have shown the lipoprotective effect of S1P on infarct size and cardiac function post AMI. The positive effect was persistent in both the permanent LAD ligation model (Polzin et al., 2023a) and the ischemia/reperfusion model (Yung et al., 2017). The activation of several intercellular pathways were found to be the mechanistic reason for the improved outcome. Thereby, all of the relevant S1PR (1–3) contribute to lipoprotection. S1PR1 was shown to activate Akt/Erk-signaling which is responsible for cardioprotective effects in ischemia (Keul et al., 2016; Tao et al., 2010). Additionally, S1PR1-signaling negatively regulates inflammation and inhibits myocardial apoptosis, and fibrosis (Cannavo et al., 2013; Ohkura et al., 2017). Besides that, both the survivor activating factor enhancement (SAFE) pathway and the reperfusion injury salvage kinase (RISK) pathway were shown to be activated by S1P (Fang et al., 2017; Frias et al., 2013).

S1PR3-signaling was also shown to mediate lipoprotective effects in case of an AMI. S1P treatment reduced the infarct size via S1PR3-RhoA signaling (Yung et al., 2017). As S1PR1, S1PR3 is also able to activate Akt/Erk signaling pathway (Means et al., 2007). Interestingly, deletion of S1PR3 did not affect infarct size and Akt activation. However, a loss of S1PR2 and S1PR3 increased the infarct area (Deng et al., 2019) suggesting that S1PR2 plays a lipoprotective role as well. Moreover, it was reported that S1PR2 and S1PR3 activation results in Connexin43 (Cx43) phosphorylation which is known to reduce infarct size and ischemia/reperfusion (I/R) injury (Means et al., 2007).

S1P can also mediate an effect on thrombus formation. Although S1P has not yet been shown to mediate direct platelet aggregation, enhanced PAR1-mediated platelet effects have been demonstrated (Liu et al., 2021). Furthermore, mice with low S1P levels show increased platelet adhesion and enhanced thrombus formation (Münzer et al., 2014). Consistent with this, mice with high plasma S1P levels show an antithrombotic phenotype (Urtz et al., 2015). However, the exact mechanism of how S1P affects thrombus formation has not yet been conclusively investigated. Based on the basic scientific data to date, a lipoprotective and antithrombotic effect can be assumed.

In addition to the effects on cardiomyocytes and platelets, S1P-signaling was shown to control vascular permeability and immune cell immersion at the site of I/R injury by the regulation of endothelial dysfunction and immune cell activity (Nitzsche et al., 2021). Besides that, S1P-mediated vasorelaxation is mediated via activation of S1PR3 and in an NO-dependent manner (Theilmeier et al., 2006). Next to numerous studies showing the lipoprotective effect of S1P on the myocardium, there is some evidence indicating that there is a limit of cardioprotection by S1P. Overproduction of S1P led to myocardial degeneration, peripheral vascular resistance, cardiac remodeling and fibrosis in post-AMI condition (Meissner et al., 2012; Takuwa et al., 2010). Nevertheless, the lipoprotective effects of S1P in case of an AMI are secured.

### 2.3. Heart failure (HF)

Heart failure (HF) is a complex clinical state that is characterized by insufficient blood supply of peripheral organs and tissues. HF develops after cardiac hypertrophy and/or myocardial infarction. Additionally, it is related to chronic stimulation of β-adrenergic signaling within the heart. While the data situation in the case of CAD and S1P quite clearly confirmed the lipoprotective effect of S1P, the situation is less clear in the case of HF. This is due on the one hand to the different types of HF (acute vs. chronic, ischemic vs. non-ischemic) and on the other hand to the less pronounced data situation. A look at human data shows that here too there is no simple linear relationship between S1P levels and outcome in HF. There is already inconclusive data on whether plasma S1P in HF is altered at all. A small study with 74 patients with ischemic HF revealed a negative correlation of S1P with the severity of heart failure (Polzin et al., 2017). On the other hand, it was shown that plasma S1P is not altered in patients with chronic HF independently of its underlying cause (Knapp et al., 2012). However, recently a prospective study with 210 chronic systolic heart failure patients observed a U-shaped association between S1P levels and all-cause death. Patients in the bottom quartile and top quartile of plasma S1P were at a higher risk of death (Xue et al., 2020). Moreover, there is no information about the expression and changes of S1PRs in the vasculature of patients with HF (Mann, 2012).

While the complex relationships between S1P and the progression of HF in clinical cohorts have hardly been uncovered, some basic science studies may provide further insights. Usually rodent basic science studies can be divided into studies related to chronic ischemic HF and acute HF, respectively. In chronic HF the expression of S1P1R in the LV as well as plasma S1P significantly increased suggesting that myocardial S1P/S1PR1 signaling is boosted during chronic HF (S et al., 2021). This could be an indication of a kind of lipoprotective rescue mechanism. This could be further confirmed by permanent overexpression of S1PR1 as gene therapy in chronic HF rats. It resulted in significantly improved diastolic function. Additionally, the infiltration of immune cells was reduced and the total plasma membrane β-adrenergic receptor (βAR) density was normalized compared with HF control rats (Cannavo et al., 2013). Therefore, S1P/S1PR1-signaling mediated beneficial effects counteracting the unfavorable overstimulation of β1AR in HF. In acute HF S1P treatment was associated with increased pacemaker ability of the heart and enhanced STAT3-signaling (Deshpande et al., 2018) which is known to have cardioprotective effects (Harhous et al., 2019). On the other hand, there is evidence that S1P activates NF-κB, leads to upregulated expression of cyclooxygenase-2, and increases prostaglandin E2 generation, which could result in apoptosis of cardiac fibroblasts (Yang et al., 2022).

To sum it up, S1P has lipoprotective effects in HF. However they seem to be less pronounced as compared to CAD or AMI and available

data on this topic is sparse. The different types of HF make it difficult to interpret and generalize the data. Therefore, long-term studies should further investigate whether S1P signaling in HF prevents or rather promotes the progression to HF (Jozefczuk et al., 2020).

## 3. Polyunsaturated fatty acids (PUFA)

PUFAs are long-chain polyunsaturated fatty acids. They contain a carboxyl group at the polar end and a non-polar carbon chain. They can be grouped into two classes: n-3 and n-6 PUFAs (Aarsetoey et al., 2012). The precursors of both classes of PUFAs are α-linolenic acid (ALA, 18:3, n-3) and linoleic acid (LA, 18:2, n-6). These two fatty acids are defined as essential because the body cannot produce them itself and they have to be taken in with food (Adkins & Kelley, 2010). ALA, which is present in beans and nuts, is the metabolic precursor of eicosapentaenoic acid (EPA, 20:5 n-3) and docosahexaenoic acid (DHA, 22:6 n-3), the most important n-3 PUFAs when talking about lipoprotection. On the other hand, LA which is primarily contained in soybean and corn oil is the metabolic precursor of arachidonic acid (AA) (Behl & Kotwani, 2017; Landa-Juárez et al., 2016). Despite their synthesis in the liver, the highest amount of EPA and DHA can be ingested via marine fish. As far as their function is concerned, the n-6 PUFAs and oxylipins formed from them have pro-inflammatory properties, unlike the n-3 PUFAs and their derivatives, which are powerful anti-inflammatory mediators. Therefore, the recommended daily intake of PUFAs is in favor of the latter (Akbar et al., 2017; Messamore et al., 2017).

### 3.1. Coronary artery disease (CAD)

The cardioprotection of n-3 PUFAs, especially EPA, has been the subject of controversy for years (Shahidi & Ambigaipalan, 2018). However there is now clear evidence of lipoprotection in CAD by n-3 PUFAs. First of all, CAD patients had significantly lower levels of n-3 PUFA, particularly EPA, in the blood (Wang et al., 2022) which can be taken as an initial indication of a connection. Additionally, treatment with n–3 PUFAs (2 g/d) improved endothelial function and the elastic properties of the arteries via the anti-inflammatory effects (Siasos et al., 2013). The beneficial effects of n-3 PUFAs were confirmed in another study showing improved FMD in patients with hypercholesterolemia (Goodfellow et al., 2000). Several studies confirmed the anti-inflammatory effects as well. EPA was shown to reduce levels of *E*-selectin, intercellular adhesion molecule 1, and vascular cell adhesion molecule 1, which mediate the adhesion of the immune cells. Besides that EPA improved the nitric oxide availability and promoted endothelial nitric oxide synthesis (Bercea et al., 2021; Sakamoto et al., 2019). Additionally, EPA significantly reduced the coronary plaque volume in patients with CAD (Watanabe et al., 2017). Mechanistically, EPA increased the anti-atherosclerotic functions of HDL (Tanaka et al., 2014). The lipoprotective effect of n-3 PUFA, especially EPA, is therefore very multifaceted in CAD. The positive effect on the cardiovascular risk with regard to cardiovascular death and the occurrence of an AMI is even clearer and has been proven by many RCTs.

### 3.2. Acute myocardial infarction (AMI)

The positive effects of a diet rich in fish and thus n-3 PUFA and the associated reduction in AMI risk have been known for almost 50 years. In 1979 in was demonstrated that the increased value of n–3 PUFAs in platelets caused a significantly longer clotting time. This served as an explanation for the low incidence of atherosclerosis-related mortality in Greenland Inuits (Dyerberg & Bang, 1979). Nevertheless, it was a long time before the clear lipoprotective effect of n-3 PUFA was scientifically confirmed. This is because there are a number of studies that have not been able to demonstrate the protective effect of n-3 PUFA. In the VITAL study, a daily dosage of 1 g marine omega-3 fatty acid was not found to significantly reduce cardiovascular events in men over 50 and women over 55 (Manson et al., 2019). Similarly, the data from the ASCEND study including patients with type 2 diabetes without evidence of CVD also show no clear benefit from a daily intake of 1 g n-3 PUFA (Bowman et al., 2018). Moreover, in the ORIGIN trail showed no reduction in cardiovascular deaths during six years in patients taking 1 g n-3 PUFA daily with dysglycemia and additional cardiovascular risk factors (Bosch et al., 2012). There are not only studies that look at cardiovascular risk before AMI, but also studies that look at n-3 PUFAs in secondary prevention. The OMEMI study investigated the effect of daily n–3 PUFA intake (mixture of 930 mg/d of EPA and 660 mg/d of DHA) in subjects with a recent AMI. It showed no benefit for composite primary endpoint at 2-year follow-up (Kalstad et al., 2021). However, secondary analyses of OMENI revealed that increased levels of EPA were associated with lower risk of major cardiovascular events (Myhre et al., 2022). Furthermore, among patients after AMI who received state-of-the-art therapy another low-dose regime of EPA and DHA did not significantly reduce the rate of major cardiovascular events (Kromhout et al., 2010).

The above-mentioned studies could not show any benefit of n-3 PUFA supplementation for a variety of reasons but nevertheless the lipoprotective effect cannot be doubted. The Chicago Western Electric Study was an early comprehensive clinical trial on fish consumption and cardiovascular events. It showed a significant inverse association between the consumption of fish at baseline and 30-year risk of fatal AMI (Daviglus et al., 1997). The beneficial effects of n–3 PUFAs in the prevention of cardiovascular events was already strengthened by RCT several decades ago. The GISSI-Prevenzione trial was one of the very first trails showing that the intake of low dose n–3 PUFAs (1 g/d) led to reduced major adverse cardiovascular events (*Lancet*, 1999). As in the GISSI-Prevenzione study, the JELIS investigators observed a significant lower rate of major adverse cardiovascular events in patients with hypercholesterolemia treated with pravastatin or simvastatin (Yokoyama et al., 2007). In contrast to many previous studies, the JELIS study used pure EPA (1.8 g/d) instead of a combination of EPA and DHA. However, consistent with data from basic and translational research (Poreba et al., 2017; Poreba et al., 2018; Siniarski et al., 2018), no association was identified between n–3 PUFA supplementation (1 g/d) and the cardiovascular risk in patients with type 2 diabetes mellitus. It did not matter whether these patients had existing CVD or not (Bosch et al., 2012; Bowman et al., 2018). As possible reason for this, these trials identified that impaired glucose metabolism limited the beneficial effect of n–3 PUFAs. Two of the most recent studies once again support this. On the one hand, the REDUCE-IT trial was able to reduce the risk of cardiovascular events by a quarter (Bhatt et al., 2019). On the other hand, the STRENGTH trial failed to show positive effects of n-3 PUFAs on cardiovascular events. However, a majority of patients in this trail had type 2 diabetes (Nicholls et al., 2020). This could have significantly limit the n-3 PUFA effect for the reasons mentioned above.

Overall, there is mounting evidence that n-3 PUFAs, especially EPA, mediated lipoprotective effects. Additionally, there are studies showing that n-3 PUFA supplementation post AMI can cause lower odds of sudden cardiac death, independent of traditional risk factors and lipids (Yuan et al., 2021; Zelniker et al., 2021). Looking back on decades of research with n-3 PUFAs, it appears that lipoprotection is not as pronounced in patients with type 2 diabetes. This will require further research in the future to gain an understanding of the mechanism behind this.

### 3.3. Heart failure (HF)

In the case of HF, several studies revealed the lipoprotective effect of n-3 PUFAs (Lavie et al., 2009). The lipoprotection of n-3 PUFA intake, especially in the early stages of HF, has been shown by the results of several clinical studies. The GISSI-HF trial investigated 6975 patients with chronic HF of NYHA class II-IV. Patients treated with 1 g/day of n-3 PUFAs showed a reduction in cardiac death during three years of

follow-up and an improved left ventricular function compared to the placebo group (Marchioli et al., 2002). A few years later, the same investigators analyzed the impact of 1 g n-3 PUFA supplementation per day in symptomatic patients with HF. In treated patients, the mortality rate and the number of hospitalizations due to cardiovascular event were reduced (Tavazzi et al., 2008). Further studies confirmed the lipoprotective effect on n-3 PUFA supplementation in HF. The REDUCE-IT trial investigated patients with established CVD including HF or diabetes with risk factors. Treatment of 2 g icosapent ethyl (EPA ethyl ester) twice daily led to an improvement in cardiovascular outcome compared to placebo (Bhatt et al., 2019). Another RCT was conducted with 205 patients who suffered from chronic compensated heart failure with NYHA classification I–III determined by dilated or ischemic cardiomyopathy. Half of these patients received 1 g of n-3 PUFAs daily for half a year. This supplementation resulted in improved left diastolic function and decreased BNP levels (Chrysohoou et al., 2016).

The important and lipoprotective role of n-3 PUFAs, especially EPA, was further confirmed in the MESA (Multi-Ethnic Study of Atherosclerosis) trial analyzing 6562 participants in total (45 to 84 years of age; 52 % women). Within a mean follow-up of 13 years, the authors revealed that elevated EPA plasma levels were related to a reduced risk for HF (Block et al., 2019). Mechanistically, there are different explanations for these findings. Treatment with n-3 PUFAs in patients with ischemic HF led to optimized inflammatory status and endothelial function. In addition, the diastolic and systolic function of left ventricle was improved (Oikonomou et al., 2019). Additionally, n-3 PUFAs are able to mediate anti-fibrotic effects by activating the free fatty acid receptor 4 (Ffar4). This further leads to activation of the endothelial nitric oxide synthase (eNOS)/cyclic guanosine monophosphate (cGMP)/protein kinase G (PKG) signaling pathway (O'Connell et al., 2017). In addition to the direct effects, n-3 supplementation mediates a whole range of indirect effects via changes in the lipidome (Sellem et al., 2023). Countless other mediators, so-called oxylipins, are produced in the body from the supplied n-3 PUFA. To date, at least some of these have shown their lipoprotective effects in HF as well (Kang et al., 2020). We can expect further analyses in this area in the future. Even if the mechanism is not yet clear because it is so multifactorial, the lipoprotective effect of n-3 PUFAs in HF is undisputed, so that supplementation is recommended in the current guidelines for treatment (Heidenreich et al., 2022).

## 4. Effect of aging on lipoprotection

Aging is a risk factor for all the diseases mentioned above. The impact of aging is multifactorial and reduced lipoprotection might also play a role. However, the influence of decreasing lipoprotection by HDL, S1P and n-3 PUFAs has been little studied to date.

It is known that the HDL composition changes with age and that the functions of HDL are also impaired as a result (Morvaridzadeh et al., 2024). These are, for example, an increase of the acute phase protein serum amyloid A and a reduction in antioxidant properties (Holzer et al., 1831). In addition to the reduced quality of HDL in elderly people, the total quantity of HDL also decrease during aging (Cho et al., 2019; Wilson et al., 1994). This combination makes it clear that the lipoprotective effect of HDL decreases with age. Nevertheless, the mechanisms behind this are not yet fully understood and further research is needed to one day be able to fully utilize the lipoprotective effect of HDL in old age.

Even less data is available on aging and S1P. There is preliminary data from rodents that S1P plasma concentration is reduced with age (Valentine et al., 2023). In addition, basic science studies show that less S1P is associated with more senescence, which may account for a decrease in lipoprotection during aging (Li & Kim, 2021). However, the decrease in S1P shown in rodents has not yet been confirmed in humans. In an analysis of people up to 71 years of age, no decrease in plasma S1P could be found (Daum et al., 2020). Further analyses on significantly older people are certainly necessary to confirm and definitively falsify the findings from rodents.

The situation is somewhat different for n-3 PUFAs. As the plasma concentration is mainly determined by eating behavior, no age-dependent decrease or increase can be analyzed here. Nevertheless, there are studies on the effect of n-3 PUFAs on elderly people. Here it was shown that high n-3 PUFA levels can also mediate lipoprotection in older people in a dose dependent manner (Lai et al., 2018).

In conclusion, too little data is available to make a conclusive judgment on lipoprotection by HDL, S1P and n-3 PUFA in old age. Nevertheless, it appears that decreasing plasma levels of HDL and S1P and a change in the composition of HDL are responsible for a reduced lipoprotective effect in old age. In contrast, n-3 PUFAs have been shown to mediate lipoprotection even in the elderly. Nevertheless, future and larger studies need to provide more data in order to make a more meaningful judgment on the effects of aging on lipoprotection.

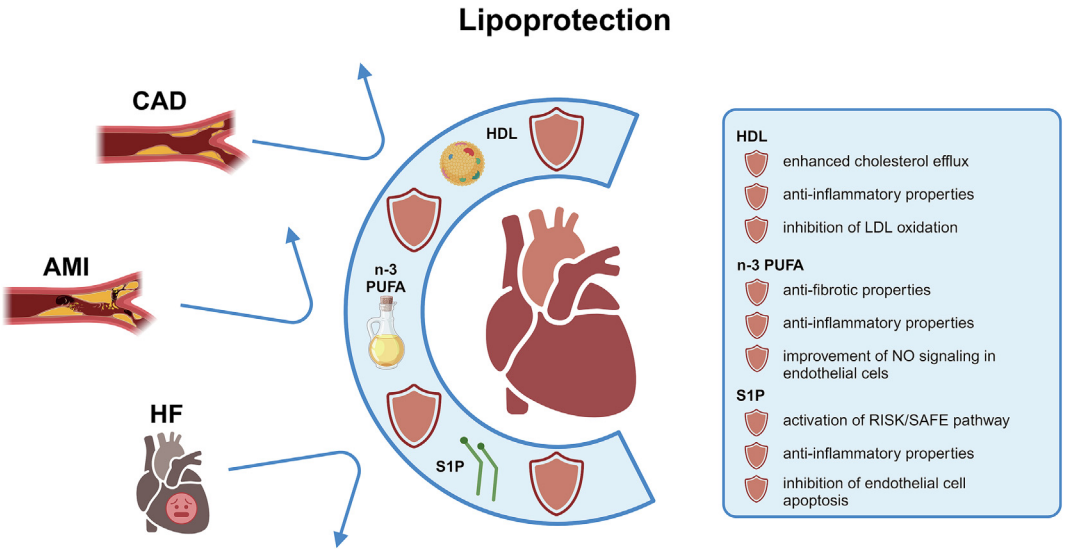


**Fig. 1. Lipoprotection in cardiovascular diseases**. Acute myocardial infarction (AMI), coronary artery disease (CAD), heart failure (HF), low-density lipoprotein (LDL), high-density lipoprotein (HDL), nitric oxide (NO), omega-3 polyunsaturated fatty acids (n-3 PUFA), survivor activating factor enhancement (SAFE) pathway, sphingosine-1-phosphate (S1P), reperfusion injury salvage kinase (RISK) pathway. This figure was created in BioRender.

## 5. Summary and outlook

It can be concluded that lipids and lipoproteins can mediate cardioprotection in various CVD in different ways (Fig. 1). This whole can be summarized under the term lipoprotection and describes cardioprotection by lipids already present endogenously, which can of course also be increased and used therapeutically. However, it has been shown, at least in the case of HDL that a pure increase does not necessarily lead to increased lipoprotection. In future, it will be important to understand exactly which structural changes lead to a loss of lipoprotection. Only in this way, through intensive basic and clinical research, will it be possible to find changes that can be therapeutically addressed in order to optimize the lipoprotective effect of HDL. In addition to clear lipoprotection, S1P also appears to have adverse effects in some diseases. Here it is important to understand more precisely in which groups of people S1P can perhaps also be used therapeutically. In contrast, a sufficiently high dose of n-3 PUFA appears to help almost every patient group. Even if the limitation of patients with diabetes must be made here. The reasons why this is the case must be clearly worked out in the future. Overall, however, it remains that the benefits of lipoprotection have the potential to reduce the burden of CVD in society.

## CRediT authorship contribution statement

**Marcel Benkhoff:** Writing – original draft, Conceptualization. **Amin Polzin:** Writing – review & editing, Conceptualization.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Amin Polzin reports financial support was provided by Deutsche Forschungsgemeinschaft (DFG, German Research Foundation). Marcel Benkhoff reports financial support was provided by Deutsche Forschungsgemeinschaft (DFG, German Research Foundation). If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Data availability

No data was used for the research described in the article.

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