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Emerging role of sphingolipids and extracellular vesicles in development and therapeutics of cardiovascular diseases

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ABSTRACT

Sphingolipids are eighteen carbon alcohol lipids synthesized from non-sphingolipid precursors in the endoplasmic reticulum (ER). The sphingolipids serve as precursors for a vast range of moieties found in our cells that play a critical role in various cellular processes, including cell division, senescence, migration, differentiation, apoptosis, pyroptosis, autophagy, nutrition intake, metabolism, and protein synthesis. In CVDs, different subclasses of sphingolipids and other derived molecules such as sphingomyelin (SM), ceramides (CERs), and sphingosine-1-phosphate (S1P) are directly related to diabetic cardiomyopathy, dilated cardiomyopathy, myocarditis, ischemic heart disease (IHD), hypertension, and atherogenesis. Several genome-wide association studies showed an association between genetic variations in sphingolipid pathway genes and the risk of CVDs. The sphingolipid pathway plays an important role in the biogenesis and secretion of exosomes. Small extracellular vesicles (sEVs)/ exosomes have recently been found as possible indicators for the onset of CVDs, linking various cellular signaling pathways that contribute to the disease progression. Important features of EVs like biocompatibility, and crossing of biological barriers can improve the pharmacokinetics of drugs and will be exploited to develop next-generation drug delivery systems. In this review, we have comprehensively discussed the role of sphingolipids, and sphingolipid metabolites in the development of CVDs. In addition, concise deliberations were laid to discuss the role of sEVs/exosomes in regulating the pathophysiological processes of CVDs and the exosomes as therapeutic targets.

1. Sphingolipid metabolism

Sphingolipids are eighteen carbon alcohol lipids synthesized from non-sphingolipid precursors in endoplasmic reticulum (ER) (Fig. 1). The sphingolipids serve as precursors for vast range of moieties found in our cells that play a critical role in membrane biology and regulate wide range of functions in cells. Sphingolipids are a diverse group of lipids with a wide range of structural and signaling functions. There are several different types of sphingolipids, including CERs, ceramide-1-phosphate (C1P), sphingosine (Sph), sphinganine, S1P, SM, and countless more glycosphingolipids [1]. Notwithstanding the structural and functional diversity of sphingolipids, their formation and degradation are largely governed by common anabolic and catabolic interconnected metabolic pathways in cells. Sphingolipids govern various cellular processes, including cell division, senescence, migration, differentiation, apoptosis, pyroptosis, autophagy, nutrition intake, metabolism, and protein synthesis [2–4].

Sphingolipids are derived from fatty acid and L-serine to form sphingoid or long-chain bases. The variations in fatty acid, C1 head group, and acylation of C2 amine varying fatty acids chains are baseline to the diversity of sphingolipids. The *de novo* synthesis of sphingolipids occurs on the cytosolic side of ER by the action of enzymes viz., serine palmitoyl transferase, 3-Ketodihydrosphingosine reductase, and (dihydro) ceramide synthases to produce ER membrane-bound

Abbreviations: a-SMase, Acid Sphingomyelinase; n-SMase, Neutral Sphingomyelinase; CER, Ceramide; CVD, Cardiovascular Disease; ECs, Endothelial cells; MI, Myocardial Infarction; LDL, Low-density lipoprotein; HDL, High density lipoproteins; SMCs, Smooth Muscle Cells; SM, Sphingomyelin; SMS, Sphingomyelin Synthase; S1P, Sphingosine-1-phosphate; VC, Vascular Calcification; AMC, Arterial Medial Calcification; VSMCs, Vascular Smooth Muscle Cells; sEVs, Small Extracellular Vesicles; CAD, Coronary artery disease; MVs, Matrix Vesicles; NO, Nitric oxide; AC, Acid Ceramidase; MVBs, Multivesicular bodies; ROS, Reactive Oxygen Species.

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dihydroceramide (DhCER) from serine and palmitoyl CoA [5]. In the first step of synthesis serine palmitoyl transferase condenses L-serine and palmitoyl-CoA to yield 3-ketosphinganine. In the next step, the 3-ketosphinganine is reduced to sphinganine and the later product is acylated to form DhCER by (dihydro) ceramide synthases. In the last step, the DhCER is converted to CER by enzyme DhCER desaturase [6,7]. Through the salvage pathway the released CER is converted to Sph, and the reaction occurs in lysosomes. The Sph is released from the lysosome into the cytosol and is either recycled back to CER or may be phosphorylated to form S1P as shown in Fig. 1. This pathway synthesizes up to 90 % of cellular sphingolipids as reported by Kitatani *et al.* [8]. On the other hand, the catabolism of membrane SM is another source of sphingolipid synthesis. In the plasmamembrane, the sphingomyelinases (SMases) convert SM into CER and phosphocholine. Unlike SMase, which hydrolyzes SM to CER, sphingomyelin synthase (SMS) catalyzes the synthesis of SM from CER. SMS has many isoforms: SMS1 is found largely in the Golgi apparatus, whereas SMS2 is found primarily in plasma membranes [9]. The CER thus generated is central to the network of sphingolipids and yields many products through wide range of metabolic fates. It can be converted into different lipid molecules such as, galactosyl ceramide (Galβ1–1′Cer), ceramide phosphoethanolamine (CPE), glucosylceramide (GlcCer), C1P and SM [10,11]. CERs have also been connected to endothelial cell senescence, cytoskeletal changes, oxidative stress, and growth arrest [12].

In CVDs different subclasses of sphingolipids and other derived molecules such as, increased accumulation of CERs, SM and decreased levels of S1P are directly related to diabetic cardiomyopathy, dilated cardiomyopathy, myocarditis and ischemic heart disease (IHD) [13–15]. Therefore, nowadays the metabolic imbalances in the sphingolipid profile in context to CVDs have emerged as central attention in the current trends of cardiovascular biology, especially in the therapeutic aspect of CVDs.

2. Correlation between circulating sphingolipid level and cardiovascular diseases

Sphingolipids are a significant class of lipids that play an important role in various cellular processes, including cell signaling, apoptosis, and inflammation [16]. Dysregulation of sphingolipid metabolism has been implicated in the pathogenesis of various diseases, including CVDs [17,18]. Several studies have investigated the correlation between circulating sphingolipid levels and the risk of CVDs occurrence. It was observed in a study that high levels of CER, a type of sphingolipid, were associated with an increased risk of CVD events, such as myocardial infarction (MI) and stroke [19]. The study analysed data from over 4000 participants and found that each one-unit increase in CER was associated with a 20 % increase in the risk of CVD events. It was found that high levels of SM were associated with an increased risk of CVD events in a cohort of over 3000 participants [20]. The study found that each one-standard deviation increase in SM was associated with a 23 % increase in the risk of CVD events [21]. These findings suggest that circulating sphingolipid levels may act as useful biomarkers for predicting the risk of CVD occurrence. However, more research is needed to establish the causality of this association and to determine whether targeting sphingolipid metabolism could be a viable therapeutic strategy for prevention or treatment of CVDs.

3. Sphingolipid pathway as a mediator in cardiovascular diseases

Current literature clearly indicates that CVDs are leading cause of global deaths as well as disabilities in humans [22]. The origin of almost

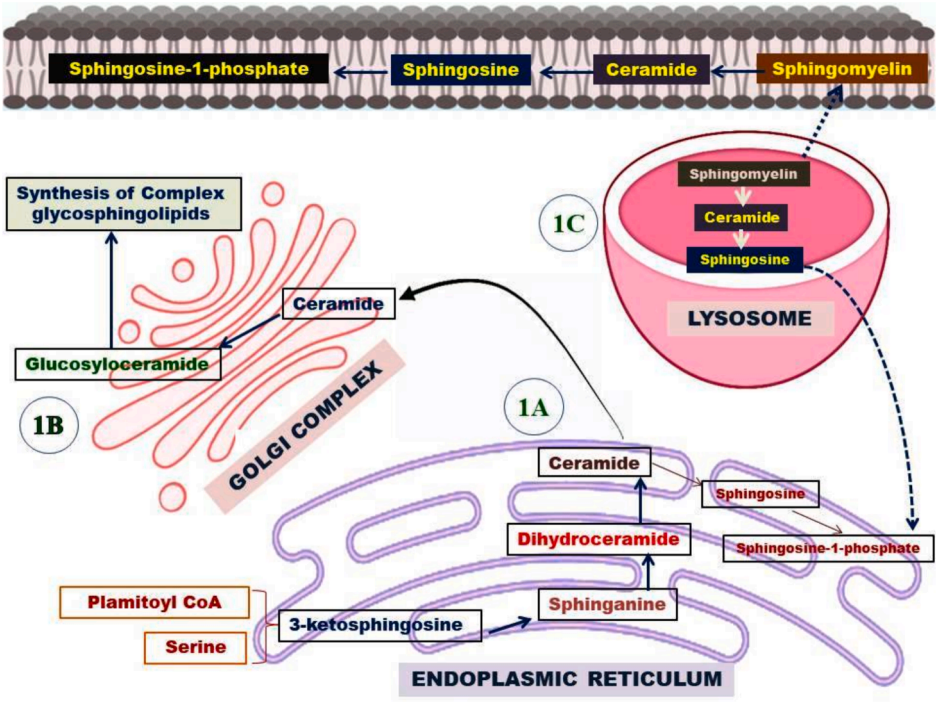

Fig. 1. The sphingolipid metabolism and its interconnecting metabolic fates: 1A) In endoplasmic reticulum the ceramide synthesis by de novo synthesis mainly occurs at the outer membrane. The condensation of serine and palmityl-CoA yields ketosphinganine, the reaction is catalyzed by serine palmitoyltransferase (SPT). Later product is then rapidly converted to sphinganine. In next step the enzyme (dihydro)ceramide synthases (CERS1-6) adds a fatty acid residue to sphinganine molecule, resulting in the formation of dhCER. The last stage of de novo pathway involves the reaction catalyzed by dhCER desaturases (DES1-2), which adds a single 4,5-*trans*-double bond to dhCER to synthesize ceramide. **1.B)** The ceramide is then transported by two major mechanisms to Golgi either by vesicular transport or by the aid of protein ceramide transfer protein (CERT). The ceramide is converted into glucosylceramides by enzyme glucosylceramide synthase (GCS) in *cis*-Golgi. Subsequently glucosylceramides helps in synthesis of large number of complex glycosphingolipids. **1.C)** Shows salvage pathway, which occurs in lysosomes., wherein the ceramide is synthesized from sphingosine and the reaction is catalyzed by enzyme ceramide synthase. The sphigosine is transported to various compartments of the cell for further metabolic outputs.

all the CVDs progression and pathogenesis is atherosclerotic in nature, thus leading to CVDs such as, coronary artery disease (CAD), venous thromboembolism, cerebrovascular disease, MI and cardiac arrhythmias. Due to large high throughput methods, the causes of all these CVDs are well known and are still major focus in diseases biology at global level. Activation of acid or neutral sphingomyelinase (a-SMase or n-SMase) or enhanced *de novo* production led to increased CER synthesis which activates numerous pathways that result in the death of endothelial cells (ECs), such as caspases, Protein Phosphatase 1 (PP1) or Protein Phosphatase2A2 (PP2A2) [23]. CER also increases mitochondrial permeability by creating CER-enriched platforms that can transport proteins [24]. As mentioned earlier, sphingolipids play an important role in the regulation of many cellular processes. Imbalance in two main sphingolipids such as CER and S1P accelerates different processes involved in the pathogenesis of diseases such as MI, stroke and diabetes mellitus type 2 etc as shown in Fig. 2 [25].

3.1. Sphingolipids in Coronary Artery Disease (CAD) and Atherosclerosis (AS)

Last two decades have witnessed that CAD is most common type of CVD responsible for major human deaths on global scale. The CAD cause narrowing of arteries due to build-up of plaque within the arteries of heart, ultimately resulting in heart failures. These plaques result in impairment of blood flow and less oxygen delivery to the myocardium of heart causing myocardial ischemia. Hypercholesterolemia is one of the critical modifiable factors responsible for development of CAD. During atherosclerosis, formation of foam cells due to uptake of oxidized low-density (ox-LDL) by macrophages in subendothelial region which then lead to fatty streaks result in activation of T cells to release cytokines, in turn aggravating the CAD pathology. Reports suggest that oxidized phospholipids induce atherosclerotic plaque formation by activation of platelets, monocyte differentiation and also aid in smooth muscle cell (SMC) de-differentiation and migration [26].

Various stimuli such as nicotine, hyperlipidaemia, ox-LDL,

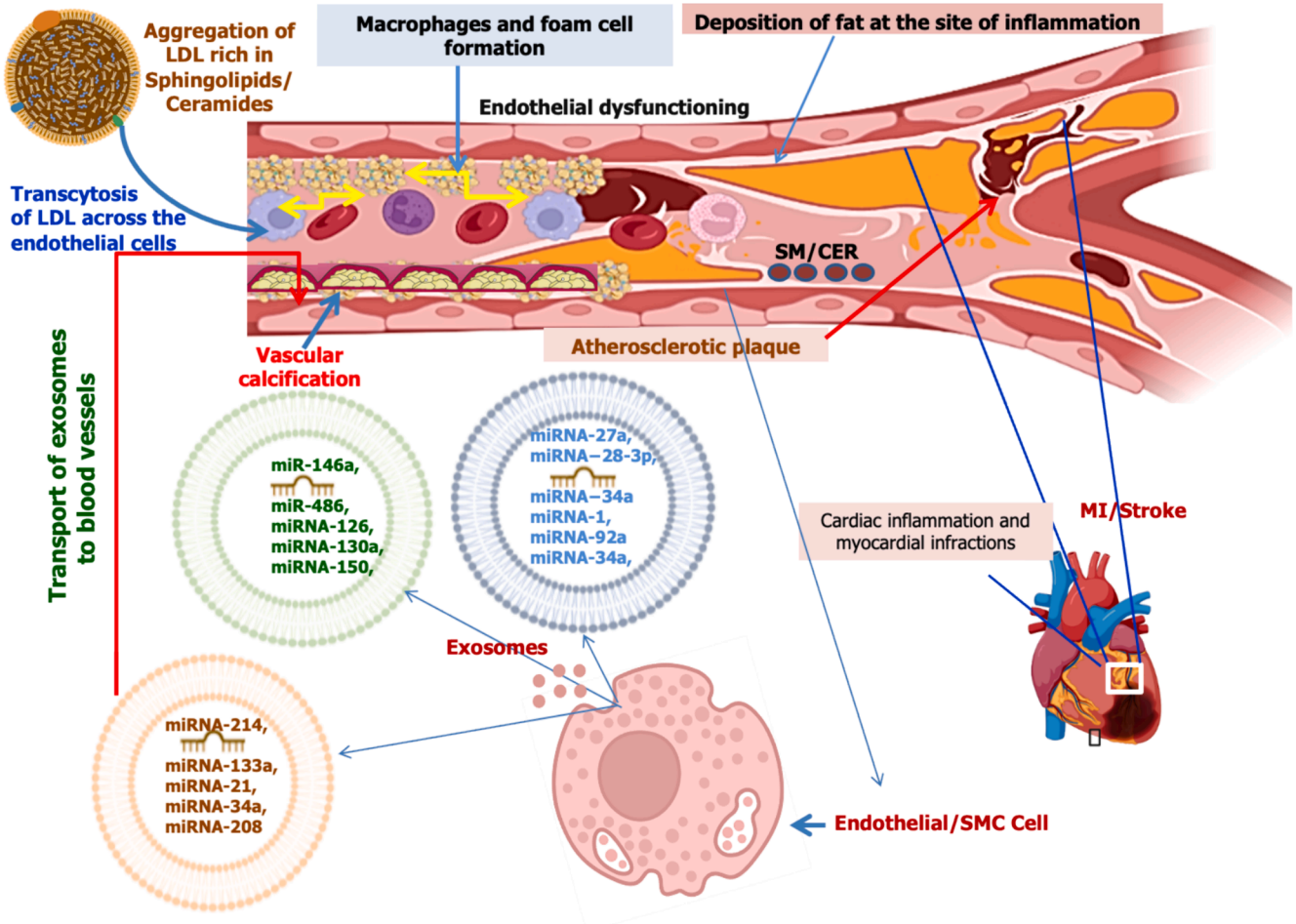

Fig. 2. Displaying the role of sphingolipids such as, sphingomyelin/ceramides as key modulators and triggering molecules aggravating the progression of CAD. The aggregation of LDL rich in sphingolipids/ceramides largely because of sphingomyelinase activity is primary augmentation factor to initiate the CAD. The ceramides in these LDLs aid in transcytosis of LDL across the endothelial cells, which is followed by uptake of LDL into macrophages. This direct uptake is central to the atherosclerosis and lipotoxicity. These macrophages are baseline to the formation of foam cells and subsequent induction of inflammation. Under inflammatory responses due to deposition of fat, there is progressive narrowing of blood vessels, wherein, cells such as, macrophages and lymphocytes are recruited. Moreover, series of inflammatory cytokines triggered by SM/ceramides such as, interleukin-1β, TNFα and interferon-γ further enhance the ceramide synthesis, leading to more chronic effects of ceramides. CER synthesis aided by TNFα in endothelial cells is critical driver to initiate production of superoxide ions and expression as well as activation of pro-inflammatory transcription factor NF-κB. Consequently, the smooth muscle lining vessels are activated to synthesize the elastic fibers and extracellular protein matrices. The process further results in formation of a cap like structure which encloses the fat and inflammatory cells. At the site of arterial stiffness sphingolipids/SM/ceramides are implicated to trigger apoptosis, autophagy and arrests the cell divisions, further worsening the normal conditioning of arteries. Figure also majorly demonstrates the role of exosomes in facilitating the progression of CVDs under pathological conditions such as inflammation. SM; Sphingomyelin, CER; Ceramide, MI; Myocardial Infarction.

cholesterol crystals, palmitate, CER and sphingolipids promote the development of atherosclerosis [27,28]. Higher concentrations of CERs, glycolipids including SM are seen in the atherosclerotic plaque [29]. The suppression of *de novo* CER production slows the progression of atherosclerosis [30]. S1P regulates atherogenesis through interacting to the S1P receptor (S1PR), whereas, S1PR1 and S1PR3 are the anti-atherosclerotic among the five S1PRs [31]. Depending on the receptor's interaction, S1P appears to have a dual impact on the development of atherosclerosis. The interaction between S1P and S1PR1 depicted anti-atherosclerotic effects by suppressing macrophage apoptosis and endothelial inflammation via phosphatidylinositol 3-kinase (PI3K) and protein kinase B (PI3K/Akt) pathway [32]. Likewise, S1PR1 may promote the onset of atherosclerosis by triggering pro-inflammatory endothelial factors like intercellular adhesion molecule (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), as well as by promoting the development of neointima by raising the level of interleukin 6 (IL-6), which stimulates the proliferation and migration of vascular smooth muscle cells (VSMCs). S1P interacting with S1PR2 also have a pro-atherosclerotic impact by promoting the inflammatory response of ECs due to increased production of pro-inflammatory molecules such as TNF-α, interleukin 1 (IL-1) and hence promoting endothelial dysfunction [31]. However, the interaction of S1P with S1PR2 may have anti-atherosclerotic effects by reducing SMC proliferation and migration via the Rac protein and delaying neointima formation. It has been observed that ApoE and S1PR2-deficient (ApoE-/-S1pr2-/-) mice show reduced western diet-induced atherosclerosis associated with decreased fibrous tissue, collagen and lipid content, necrotic core within the atherosclerotic plaque and also decreased number of macrophages within the vessel wall [33].

Additionally, Platelet-activating factor (PAF)-induced CER microdomain formation reduces endothelial Nitric Oxide Synthase (eNOS) activation and results in endothelial barrier dysfunction [34]. CER is regarded as a crucial negative regulator of endothelial nitric oxide (NO) production, it was observed that CER lead to the generation of superoxide anions and reduces the release of NO from human umbilical vein endothelial cells (HUVECs) [35]. CER may therefore enhance atherosclerosis by increasing reactive oxygen species (ROS) generation and promoting endothelial dysfunction by reducing NO [36]. Within atherosclerotic lesions, Ox-LDL stimulates SMase, which converts Low density lipid sphingomyelin (LDL-SM) to CER, thereby leading to conformational shift in apolipoprotein B100 (ApoB100), required for LDL molecules to aggregate. This Phenomena is further accompanied by macrophage-mediated phagocytosis and foam cell formation thereby increasing atherosclerotic lesion progression [37]. According to this study, the sphingolipid synthesis inhibitor myriocin suppresses LDL aggregation and reduces plaque development in mice [38]. CER seems to have a proatherogenic impact mediated by certain types of SMases, such as secretory lysosomal sphingomyelinase (l-SMase), acidic sphingomyelinase (a-SMase), and membrane neutral SMase (n-SMase). l-SMase and a-SMase are endosomal enzymes that can be translocated to the plasma membrane under specific circumstances. All these three types of SMase have been linked to atherosclerosis in different ways [39].

One of the major factors that contribute to the atherosclerotic plaque development and progression is monocyte recruitment and their conversion into macrophages, uptake of modified low-density lipoproteins (LDL) and their storage by these macrophages leads to foam cell formation. Recent studies have demonstrated that sphingolipids such as CER, SMs, and the associated receptors play an important role in the recruitment of monocytes, which is a crucial step in atherosclerotic plaque formation [40].

A study carried out in $ApoE^{-/-}$ and $Smpd3^{fro/fro}$ mice showed that nSMase2 deficiency or inhibition reduced atherosclerotic plaques, and decreased macrophage infiltration and lipid deposition. In ox-LDL stimulated murine ECs, nSMase2 inhibition decreased expression of monocyte chemoattractant protein-1 (MCP-1), ICAM-1 and macrophage recruitment [41]. In mouse models, CER accumulation led to increased MCP-1 levels which is a strong inducer of monocyte migration during atherosclerosis [42]. Lactosylceramide (LacCer) promotes atherosclerosis by increasing macrophage-1 antigen (MAC-1) expression on monocytes or neutrophils, likely aiding their adherence to ECs thereby initiating atherosclerosis [43]. Studies demonstrated that GluCer and LacCer inhibit ApoE synthesis in macrophages and cholesterol-loaded foam cells, respectively, whereas LacCer increases monocyte migration to the endothelium. LacCer recruits Protein kinase C (PKCα/ε) and phospholipase A2 to promote PECAM-1 expression and adherence to ECs in human monocytes [44]. Bietrix et al. also demonstrated that inhibiting GluCer synthase reduced TNF-alpha and MCP-1 mRNA expression in APOE*3 Leiden mice [45]. CER *de novo* production increased high fat diet (HFD)-induced activation of MCP-1 in adipose tissue, indicating that CER may play a role in immune cell recruitment [46]. A study reported that ceramide synthase 1 (CerS1) inhibitor, P053 daily administration to mice fed on high-fat diet led to increased fatty acid oxidation thereby regulate whole body adiposity however, didn't observe any effect against insulin resistance in these mice [47].

The sphingolipid inhibitors like myriocin (a ceramide inhibitor) and d-PDMP (d-*threo*-1-phenyl-2-decanoylamino-3-morpholino-1-propanol, a glycosphingolipid inhibitor) suppressed the expression of MCP-1 and its receptor chemoattractant cytokine receptor 2 (CCR2), which are essential for monocyte recruitment [48]. They also effected the absorption of modified LDL, and reduced pro-inflammatory Ly-$6C^{hi}$ monocytes in apolipoprotein E-deficient mice via suppressing the expression of cluster of differentiation 36 (CD36) and lectin-like ox-LDL receptor-1 (LOX-1). Palmitate, a key precursor of long-chain CER *de novo* production, increased monocyte adherence to arterial bifurcations via increased expression of CD11b, the most common integrin component of monocytes. Also, palmitate treatment to monocytes boosted the expression of CD36, a scavenger receptor which contributes to ox-LDL uptake in macrophages during atherosclerosis [49].

Feuerborn et al. observed that LDL-R-deficient mice with elevated endogenous S1P levels had decreased monocyte recruitment, resulting in decreased atherosclerotic lesion development [50]. S1P decreased monocyte-endothelial interaction under inflammatory circumstances, hence supporting its anti-atherogenic activity. Also, S1P decreased phorbol 12-myristate 13-acetate (PMA)-induced THP-1 adherence to ECs by reducing RhoA activity via p190RhoGAP, a Rho family GTPase-activating protein [51]. A study found that S1PR modulators (FTY720 and BAF312) significantly reduce circulating monocyte levels in mice and rats [52]. A recent study in HUVECs demonstrated that Apolipoprotein M-S1P significantly reduced the expression of pro-inflammatory cytokines, adhesion molecules, and pyroptosis-related proteins by binding to S1PR2 via activation of the PI3K/AKT signalling pathway, thereby inhibiting the inflammatory response and pyroptosis during TNF-α-induced endothelial cell injury. It was observed that S1PR3 deficiency in ApoE-/-mice significantly reduced monocyte recruitment by reducing the release of monocyte chemo attractant protein-1 without affecting the size of atherogenic lesions [53]. On the other hand, binding to S1PR2 enhanced the recruitment of inflammatory macrophages. In S1PR2-/-ApoE-/-double-deficient mice, lower proinflammatory cytokine IL-18 and IL-1β secretion caused impaired interstitial macrophage recruitment and reduced development of atherosclerotic plaques [33]. Literature cites that sphingolipids plays an important role in vascular diseases, more mechanistic approach is needed for their translational purpose. Understanding the specific functions and mechanism of action of sphingolipids and their metabolites and associated enzymes in vascular diseases may lead to the development of novel therapeutics.

Lipoproteins and lipids play a critical role in development and progression of CVDs (Table 1) through synthesis, transport, catabolism, and their concentrations in blood [54,55]. Generally, lipids are categorized into storage lipids (fatty acids, triglycerides, sterols) and structural lipids (phospholipids, glycolipids, ceramides), which are essential for physiological support of organisms [56]. Further, lipoproteins are again sub-

Table 1
Evaluation of pharmacological compounds on the risk factors of CVDs.

Pharmacological compound	Study details	Findings	Reference
Inclisiran	Evaluated the effects of inclisiran on LDL cholesterol levels in patients with atherosclerotic cardiovascular disease.	Inclisiran significantly reduced LDL cholesterol levels with sustained effects, showing potential for reducing CVD risk.	[211]
Bempedoic Acid	Assessed the impact of bempedoic acid on LDL cholesterol and inflammatory markers in hypercholesterolemic patients.	Bempedoic acid reduced LDL cholesterol and inflammatory markers, potentially lowering the risk of cardiovascular events.	[212]
Icosapent Ethyl	Investigated the impact of icosapent ethyl on triglyceride levels and cardiovascular outcomes in high-risk patients.	Icosapent ethyl significantly reduced triglyceride levels and the risk of major cardiovascular events.	[213]
Finerenone	Evaluated the effects of finerenone on kidney and cardiovascular outcomes in patients with chronic kidney disease and type 2 diabetes.	Finerenone improved kidney and cardiovascular outcomes, reducing the risk of heart failure and other cardiovascular events.	[214]
Evinacumab	Assessed the impact of evinacumab on LDL cholesterol levels in patients with homozygous familial hypercholesterolemia.	Evinacumab significantly reduced LDL cholesterol levels in patients with homozygous familial hypercholesterolemia.	[215]
Vericiguat	Investigated the effects of vericiguat on heart failure outcomes in patients with reduced ejection fraction.	Vericiguat reduced the risk of cardiovascular death and heart failure hospitalization in patients with heart failure and reduced ejection fraction.	[216]
Dapagliflozin	Studied the impact of dapagliflozin on heart failure and cardiovascular outcomes in patients with heart failure with reduced ejection fraction.	Dapagliflozin reduced the risk of worsening heart failure and cardiovascular death in patients with heart failure with reduced ejection fraction.	[217]
Omecamtiv Mecarbil	Evaluated the impact of omecamtiv mecarbil on heart failure outcomes in patients with chronic heart failure with reduced ejection fraction.	Omecamtiv mecarbil improved cardiac function and reduced the risk of heart failure-related events in patients with chronic heart failure with reduced ejection fraction.	[218]
Lomitapide	Assessed the effects of lomitapide on LDL cholesterol levels in patients with homozygous familial hypercholesterolemia.	Lomitapide significantly reduced LDL cholesterol levels in patients with homozygous familial hypercholesterolemia.	[219]
Angiotensin Receptor-Neprilysin Inhibitors (ARNIs)	Investigated the impact of ARNIs on heart failure outcomes in patients with reduced ejection fraction.	ARNIs improved cardiovascular outcomes, including reducing the risk of heart failure hospitalization and cardiovascular death.	[220]
Sotagliflozin	Studied the effects of sotagliflozin on heart failure and cardiovascular outcomes in patients with type 2 diabetes and chronic kidney disease.	Sotagliflozin reduced the risk of cardiovascular death and heart failure hospitalization in patients with type 2 diabetes and chronic kidney disease.	[221]
Esperion's Bempedoic Acid	Investigated the efficacy of bempedoic acid in lowering LDL cholesterol and its impact on cardiovascular outcomes.	Bempedoic acid effectively lowered LDL cholesterol and showed a potential reduction in cardiovascular events.	[222]
ALN-PCSsc (Inclisiran)	Examined the effects of inclisiran, a small interfering RNA (siRNA) therapeutic, on LDL cholesterol levels.	Inclisiran provided significant and sustained reductions in LDL cholesterol levels, potentially improving cardiovascular outcomes.	[223]
Evacetrapib	Assessed the impact of evacetrapib on HDL cholesterol and cardiovascular outcomes.	Evacetrapib increased HDL cholesterol but did not reduce major cardiovascular events compared to placebo.	[224]
Inclisiran	Long-term effects of inclisiran on LDL cholesterol levels in patients with cardiovascular disease.	Inclisiran provided sustained LDL cholesterol reduction over 18 months with a favorable safety profile.	[225]
Pemafibrate	Evaluated the effects of pemafibrate on triglyceride levels and cardiovascular outcomes in patients with dyslipidemia.	Pemafibrate significantly reduced triglyceride levels and improved lipid profiles, potentially reducing cardiovascular risk.	[226]

classified into five types viz., LDLs, very low-density lipoprotein (VLDLs), intermediate-density lipoprotein (IDLs), high density lipoproteins (HDLs) and chylomicrons, grossly based densities, and size in blood [56].

HDL is one of five primary lipoproteins that carry lipid molecules throughout the body. HDL molecules are mostly composed of apolipoprotein A (ApoA) and to a lesser extent, apolipoprotein C (ApoC). ApoC-1 major role is to block cholesterol ester transfer protein (CETP) and lipoprotein binding to HDL and VLDL. Studies have reported that higher concentration of HDLs were found to be linked with reduction in the progressiveness of CVDs [56]. Moreover, the mutations that reduce CETP function was found to be linked to increased atherosclerosis development [40]. This pathophysiological mechanism appears to be critical in terms of CER participation in atherogenesis, because ApoC-1-enriched HDL causes apoptosis and cell death in VSMC via n-SMase activation and promotes VSMC growth [57]. a-SMase, which is secreted by ECs and hydrolyzes the surface SM of atherogenic lipoproteins to CER, facilitates the fusion, aggregation and affinity of lipoprotein particles on the endothelium of arteries [58]. *ApoE*$^{-/-}$*/Ldlr*$^{-/-}$*/Smpd1*$^{-/-}$ triple knockout mice revealed that the lack of a-SMase decreased the formation of atherosclerotic lesions and arterial trapping of atherogenic lipoproteins in normally atheroprone *ApoE*$^{-/-}$*/Ldlr*$^{-/-}$ animals which otherwise develop spontaneous atherosclerosis [59]. Ligand interaction to TNF receptors led to activation and translocation l-SMase, like a-SMase, which promotes atherosclerosis [60].

It was found that *SMS1*$^{-/-}$ animals have a reduced atherosclerotic phenotype characterised by fewer atherosclerotic lesions throughout the

aorta as well as lower macrophage content in these lesions [61]. Similar results were obtained with *SMS2*-deficient mice, these mice have lower levels of pro-inflammatory cytokines production, as well as less atherosclerotic lesions, necrotic core development, macrophage content, and collagen content. The pro-atherogenic properties of SM are validated further, adenovirus-mediated insertion of *SMS2* in *ApoE* $^{-/-}$ mice caused an increase in atherosclerotic lesions [61]. *SMS2* has also been demonstrated to modulate NF-κB activation in Human Embryonic Kidney 293 cells (HEK-293), and macrophages in *SMS2*-deficient animals [62]. Consistent with SM's pro-atherogenic nature, overexpression of *SMS1* and *SMS2* boosts proatherogenic lipoprotein potential in mice [63], and simultaneous deficiency of *SMS1* and *SMS2* results in decreased plasma SM and pro-inflammatory cytokine release [64]. Also, it has been found that inhibiting *SMS1* alone results in a reduction in SM content which in turn reduced atherosclerotic phenotype, whereas increased plasma levels of DhCER and CER augmented atherosclerotic phenotype. In addition, sphingolipid metabolites have important roles in the regulation of immune cell trafficking activities, and there are studies which demonstrated that inflammation may change sphingolipid metabolism and S1PRs [65]. Recently, several studies indicated that sphingolipid mediators such as CER, ceramide 1-phosphate, and S1P play an important role in inflammation [1,66]. DhCER levels in atheromatous plaques are positively correlated with proinflammatory cytokines such MCP-1, IL-6, and macrophage inflammatory protein-1 [29]. DhCER can also promote the production of IL-6 in human coronary SMCs [67].

Oxidized lipids and lipoproteins in cell membranes are the major endogenous molecules also considered as damage associated molecular patterns (DAMPs) sharing similarities with certain motifs of microbial pathogen-associated molecular patterns (PAMPs) [68]. Therefore, it is clear that oxidized lipids behave like microbial pathogenic markers to trigger chronic inflammatory response. During pathogenic stimuli, proinflammatory cytokine induced inflammation is also controlled by inflammasomes which act as innate immune receptors/sensors. The inflammasomes are innate immune system receptors/sensors that control caspase-1 activation and release of proinflammatory cytokines IL-18 and IL-1β which trigger inflammation in response to pathogenic stimuli. A recent study found that a-SMase and CER signaling are important in hypocholesterolemia-induced endothelial NLRP3 inflammasome formation and activation, which results in endothelial dysfunction, vascular inflammation and cell phenotypic transition during atherosclerosis [69]. Several sphingolipids also activate NLRP3 in differentiated THP-1 human macrophage-like cells and murine macrophages [70–72]. Also, S1PR2 signaling regulates macrophage retention and inflammatory cytokine release in the plaque macrophage, which promotes atherosclerosis [33]. Studies have shown that a-SMase gene (Asm encoded by Smpd1 gene) and CER-associated membrane raft (MR) clustering contributed in endothelial inflammasome activation and dysfunction in the carotid arteries of Asm$^{+/+}$ mice. Endothelial NLRP3 inflammasome activation and subsequent atherogenic alterations in the artery wall is mediated via a-SMase or CER-mediated MR redox signaling and NADPH oxidase activation during hypercholesterolemia in mice [73]. Furthermore, it has also been observed that Acid Ceramidase (AC encoded by *Asah1* gene), which hydrolyses CER to Sph, regulates exosome-mediated release of NLRP3 inflammasome products in coronary arterial ECs (CECs), which is exacerbated by AC loss, resulting in an exaggerated arterial inflammatory response during hyperglycemia in Asah1$^{fl/fl}$/EC^{cre} mice [74]. During hypercholesterolemia, NLRP3 inflammasome-dependent IL-1 production promotes VSMC phenotypic change to synthetic state via extracellular vesicle machinery, which is regulated by lysosomal AC activity [75]. Together, all these studies provided evidences that sphingolipids regulate vascular pathologies through various mechanistic pathways.

3.2. Sphingolipids in arterial stiffness and vascular calcification

The mineralization of vascular tissue within the walls of arteries is known as vascular calcification (VC). The pathophysiology of VC includes the osteogenic differentiation of VSMCs and matrix mineralization. Contractile VSMCs are the quiescent cells which play a key role in the conductive function of the vasculature by maintaining vessel wall integrity and regulating arterial tone. Due to some pathological conditions, there is a contractile to synthetic phenotypic transition of VSMCs. This phenotypic modulation contributes to a range of vascular pathological conditions such as restenosis, atherosclerosis, thoracic aortic aneurysms, transplant vasculopathy, pulmonary hypertension, arterial stiffness and VC [76–78]. A process of mechanical homeostasis between extracellular matrix (ECM) and VSMCs is a fundamental concept in arterial stiffness [79]. Age-related medial and intimal thickening, arterial rigidity, as well as the development of cardiovascular illnesses are primarily caused by increased VSMC proliferation, migration, senescence, and mineralization. Vascular tone is specifically regulated by VSMC in the tunica media of elastic arteries. VSMC elasticity failure results in altered vascular homeostasis with age and the emergence of serious CVDs [80]. Extensive research over the last few decades has revealed that the mechanism of VC is not simply a result of a high-phosphorous and calcium environment, but also occurs through delicate and well-organized biologic processes, such as an imbalance between osteochondrogenic signaling and anti-calcific events. Arterial stiffness which contributes to VC, is the process in which there is remodeling of ECM, including elastin degradation and excessive collagen deposition and glycosylation. This process of remodeling is critically regulated and leads to the development of CVDs [81,82].

Recent research has paved a way towards the role of bioactive sphingolipids, CER and S1P in the development of embryonic bone [83]. CER and S1P control mineralization of the VSMC matrix via p38 mitogen activated protein kinase (MAPK) activity in bovine aortic SMCs. Also, C2-CER accelerated calcification in human VSMCs in a dose-dependent manner [82]. A study showed that lysosomal enzyme a-SMase is associated with the production of sEVs and the phenotypic transition in arterial SMCs that causes AMC [84]. Another study showed that lysosomal acid ceramidase (AC) regulating CER metabolism may be significantly implicated in phenotypic maintenance and sEV excretion in arterial SMCs, which is related to action of AC on the regulation of lysosomal TRPML1-mediated Ca^{2+} release and fusion between lysosome with multivesicular bodies (MVBs) [85]. Recently, Bhat et al. demonstrated that lysosomal AC- associated CER-mTOR signaling regulate lysosome fusion with MVBs, increased CER levels lead to activation of mTOR that enhanced exosome secretion and arterial stiffening which represents a novel molecular mechanism involved in the development of AMC [86].

3.3. Sphingolipids in hypertension

Hypertension is not only a major risk factor for CVDs but a public health challenge worldwide which contribute to the global health burden and mortality. Imbalanced intrinsic network of bioactive lipids classified as sphingolipids have remarkable impact on endothelial dysfunction and vascular tone which mainly contribute to hypertension [87–89]. S1P is crucial in vertebrate development and defective S1P signaling result in embryonic lethality due to impaired vasculocardiogenesis. In mature organism, S1P regulates various pathological processes including vascular dysfunction such as endothelial dysfunction, atherosclerosis, arterial hypertension and angiogenesis. In heart diseases, S1P is associated with MI, hypertrophic/fibrotic heart disease and heart failure [90].

A study in VSMCs showed that S1P via S1P1R activates p38MAPK and JNK/SAPK, induces inflammatory mediators, and stimulates inflammatory pathways through receptor tyrosine kinase phosphorylation. This phenomenon was enhanced in spontaneously hypertensive rat

strains—the stroke-prone (SHRSP) due to increased phosphorylation of platelet-derived growth factor and epidermal growth factor receptor [91]. Recently, in a study two well-validated SHRSP and the stroke-resistant (SHRSR) models were assessed against the normotensive Wistar Kyoto (WKY) rat strain for sphingolipid metabolic anomalies in the brain and kidneys. According to their findings, brain and renal tissues of both hypertensive strains of rat had altered sphingolipid metabolisms when compared to rats with normal blood pressure. However, only a few abnormalities were specifically found in the SHRSP, such as reduced expression of enzymes involved in the metabolism/catabolism of S1P and in the *de novo* biosynthesis pathways. These findings suggested that defects in particular lipid molecules and/or their associated metabolic pathways may likely contribute to the pathogenesis of hypertensive target organ damage and may be exploited as future therapeutic targets in hypertension [92].

In hypertensive rat model, empagliflozin reduced SM, S1P and a-SMase levels in the liver, kidney, and plasma, and in diabetic model, empagliflozin down regulates both catabolic and *de novo* pathways of sphingolipid metabolism whereas in Angiotensin II dependent hypertension, it solely affects the catabolic pathway [93]. Another study in isolated bovine small coronary arteries and in human ECs observed that CER promotes the generation of ROS causing EC dysfunction and decreased bioactive NO production [94,95]. In addition, it was found that n-SMase contributed to endothelial-dependent vasoconstriction, which was not seen in normotensive Wistar Kyoto rats, and shifting the CER/S1P ratio toward CER dominance by the administration of a sphingosine kinase inhibitor (dimethyl sphingosine) in isolated carotid arteries from spontaneously hypertensive (SHR) rats [96]. Di Pietro et al. demonstrated that circulating sortilin in EC's, a glycoprotein as a biomarker associated with high blood pressure that altered sphingolipid/ ceramide homeostasis and initiated a signaling cascade from S1P leading to increased reactive oxygen species production [97]. Further evidence showed that the total CER (primarily C16:0, C22:0, C24:1, and C24:0) and Sph plasma concentrations were elevated in SHR rats [96]. On this basis, it may be assumed that the plasma concentration of CERs may serve as a possible indicator for the early detection of hypertension. Endothelial deletion of serine palmitoyl transferase long chain subunit 2 (SPTLC2, the first enzyme of the *de novo* pathway) in mice revealed an important role of endothelial CERs produced via *de novo* biosynthesis in vascular and blood pressure homeostasis, as well as a key source of plasma CERs [98]. Siedlinski *et al.* in their study revealed that in wild type (C57BL/6J) mice, AngII-induced hypertension was associated with increased plasma concentrations of S1P, and chronic infusion of S1P caused a moderate increase in systolic blood pressure, endothelial dysfunction, and vascular contractility in the mesenteric arteries [99]. Meissner *et al.* demonstrated that AngII increased blood pressure in wild type mice, whereas the blood pressure response to AngII was significantly lower or even absent in Sphingosine Kinase 1(SPHK1) knockout mice. Furthermore, administration of SPHK2 antagonists, but not SPHK1 antagonists, significantly reduced blood pressure in wild type mice with prior injection with AngII [100]. In a study in S1PR1 mutant mice, following a 10-day deoxycorticosterone acetate (DOCA) salt therapy, Hu *et al.* found that this therapy caused decreased urinary sodium excretion in the renal collecting ducts, impaired pressure natriuresis, and developed more severe hypertension. By aiding sodium excretion, S1PR1 signaling can be a substantial antihypertensive channel. It was hypothesized that renal medullary S1PR1 malfunction may be a novel mechanism for salt-sensitive hypertension [101]. In hypertensive patients, S1P has been linked to increased baseline plasma renin activity and a diminished blood pressure response to hydrochlorothiazide [102].

3.4. Sphingolipids in myocardial infarction (MI) and stroke

Recent research indicates that abnormal sphingolipid signaling and metabolism are key factors which also contributes in MI and stroke. A study showed that Nogo-B, endoplasmic reticulum membrane protein in vascular wall downregulates serine palmitoyltransferase (SPT) enzyme thereby preventing sphingolipid de novo biosynthesis inturn impact vascular functions and blood pressure. Nogo A, splice variant of Nogo in cardiomyocytes has been found to preserve the mitochondrial function, autophagy and metabolic gene expression alleviating progression of HF during stress situation [103]. In male Wistar rats, ligation of the left coronary artery induced-MI showed significant alterations of sphingolipid levels in plasma, erythrocytes and platelets. S1P plasma levels declined dramatically, although plasma CER levels increased significantly at 1 and 6 h post MI, but both sphingolipids restored to control levels within 24 h [104]. A study showed that 1/3rd of the mouse myocardial sphingolipid pool is comprised of SPTLC3 derived d16-sphingoid based sphingolipids [105]. Besides, upon placement of left-ventricular assist devices (LVAD) reduced SPTLC3 was found in HF patients [106]. Earlier findings reported association of SPTLC3 SNPs with MI and other cardiovascular events [107,108].

Literature cites that an elevated amount of CER post-MI/ inflammatory phase acted as a biomarker and was associated with cardiac dysfunction. Several genome-wide association studies showed an association between genetic variations in sphingolipid production genes and risk of MI [107]. The primary metabolite of sphingolipids, CER, has been found to have a strong association with MI. Patients who had acute MI had significantly higher plasma CER levels on day 1 and 2 post infarction [109]. Another study reported that, after admission to the intense heart care unit, the plasma concentration of CER in patients with acute MI was not substantially different from the control group, although the concentration of S1P was considerably reduced by 50 % [110]. A few research groups have recently shown that CER levels are high in rodent and human heart tissues post-acute MI, and preventing *de novo* CER synthesis in rats can improve heart function post-MI [111–113]. A study reported that S1P might be exploited as a therapeutic target in patients with heart failure and MI, extending cardiac cell lifespan and therefore enhancing heart function [114,115]. Hadas *et al.* demonstrated that enhancing AC activity reduced harmful neutrophil numbers and cell death in the left ventricle post-MI, and that inhibiting CER *de novo* production might reduce cardiac reperfusion damage and inflammation [116]. MI led to a decrease in plasma dihydrosphingosine, Sph, S1P, and dihydrosphingosine 1-phosphate (DHS1P) levels and an increase in total CER levels [104]. Long-chain CERs are associated with the causes and clinical consequences of acute ischemic stroke (AIS). A recent study in 2021 has shown that cardiomyocytes require cardiac glycosphingolipids to sustain β-adrenergic signaling and contractile ability, as well as to maintain proper heart function [117]. Therefore, controlling CER metabolism enzymes has been proposed as a possible therapeutic method for stroke therapy [118]. As a result of an acute case of cerebral occlusion, Kubota *et al.* presented the first evidence that CER levels were elevated in ischemic human brains [119]. a-SMase activation and glucosylceramide synthase inhibition caused CER build up in severe cerebral ischemia and ischemia reperfusion (IR) [120]. Rise in S1P levels lead to disruption of the blood–brain barrier and cause cerebral edema, which is once again connected to the oxidative stress of micro ECs after acute ischemia [121]. The high concentration of ganglioside-sphingolipids seen in the central nervous system are thought to be the cause of this rise in sphingolipids. Gangliosides are found in the outer leaflets of plasma membranes and cell surface microdomains, where they play a role in signal transduction, cell–cell recognition, and adhesion [122]. After 30 min and 24 h following a 5-minute period of ischemia, Nakane *et al.* found a substantial increase in CER levels and a significant decline in SM levels in the gerbil's hippocampus [120]. Besides, sphingolipids are components of the cardiomyocyte cell membrane and acts as a second messenger, promoting the apoptosis of these cardiomyocytes [123–125]. Studies carried out using an animal model of myocardial ischemia/reperfusion indicated a considerable rise in CER levels and a decrease in both a-SMase and n-SMase activity [126]. Isolated mouse hearts subjected to ischemia preconditioning under *in vitro* conditions showed dramatically increased sphingosine kinase activity

along with elevated levels of S1P, and decrease in the infarction area [127]. All these findings suggest that sphingolipids contribute to the etiology of MI and stroke.

As discussed, sphingolipid metabolism plays an important role in CVDs, and various sphingolipid-based drugs targeting sphingolipid metabolism or associated signaling pathways. Recently, sphingolipids have been exploited as a potential therapeutic target for CVDs [89]. Drugs against these sphingolipid moieties mainly target inflammation caused due to imbalance in sphingolipid metabolism which in turn contribute to CVDs. Since there is no single drug for CVDs, these sphingolipid-based drugs also have several limitations besides their preclinical evidences which need to be addressed before considering them for therapeutic purposes.

4. Exosomes and exosomal miRNA as intercellular communicators: Impact on CVDs

In addition to the conventionally recognized mediators, such as chemokines, cytokines, and hormones that influence cells as well as organ communication, a new class of modulators called as extracellular vesicles (EVs) have evolved. The sEVs/exosomes are endosomal-derived, nanosized lipid vesicles that play a crucial role in intercellular communication by transporting many macromolecules from their parent cells (Tables 2 and 3). These small vesicles are released in response to a variety of stimuli, including as alterations in the physical surroundings of cells (pH, temperature, irradiation), or cell stress and activation induced by chemical agents [128–131]. Exosomes transport a variety of molecules called cargo, including signal lipids, functional proteins, salts, mRNAs, miRNAs, sphingolipids and non-coding RNAs. These cargo molecules can mediate intercellular communication by enabling recipient cells to undergo a variety of biological reactions [132–135]. Exosomes have recently gained acceptance as possible indicators for the onset of CVDs. Exosomes have been linked to cellular signaling pathways that contribute to the development of atherosclerosis, including immunological responses, inflammation, cell migration and proliferation, cell death, and vascular remodelling as the disease progresses [136].

Densmore *et al.* demonstrated that EVs-derived from pre-stimulated ECs inhibited NO generation in ECs and impaired endothelial function [137]. Heat shock protein 27 (HSP27) has been found to decrease the binding and uptake of ox-LDL via downregulation of scavenger receptor A and increased secretion of anti-inflammatory cytokine IL-10 via NF-κB activation. Also, study showed that HSP27 packed into EVs result in activation of TLR-4/NF-κB pathway which leads to release of anti-inflammatory cytokine IL-10 in ECs, thereby reducing vascular and plaque inflammation, lower cholesterol levels, and inhibit atherogenesis in animal models [138]. A study in ST-segment-elevation myocardial infarction (STEMI) patients depicted significantly increased EV-ceramides dhCER, and sphingomyelins as compared to matched controls. And these sphingolipids were found correlated to hs-troponin, leucocyte count, and ejection fraction indicating sphingolipids may act as novel biomarkers in cardiac ischemia [139]. In patients undergoing carotid endarterectomy (CEA), it was demonstrated that plasma EVs containing bioactive lipids such as ceramides and phospholipids like phosphatidylcholine serve as potential biomarkers to predict high-risk CEA patients in CAD [140].

Furthermore, Phytohaemagglutinin P (PHA-P) stimulated T-cell derived EVs increased cholesterol accumulation in monocytes and macrophages, resulting in the formation of foam cells, and boosting lipid accumulation in macrophages [141]. Exosomes secreted by foam cells decreased endogenous activity of ECs and their progenitors, modulating endothelium-dependent vasodilation and preventing intravascular blood cell adhesion and thrombosis [142]. It has been seen that sphingolipid pathway plays an important role in the production of sEVs/exosomes, n-SMase activity can influence basal exosome synthesis [78]. In hepatocytes, the chemokine receptor CXCR2 inhibits n-SMase activity, and cells lacking CXCR2 expression secrete much more exosomes than wild-type hepatocytes [143]. Exosomes and other EVs are high in CER, as well as other more complicated glycosphingolipids such gangliosides [132]. It has been observed that CER is required for exosome biogenesis and secretion, the sphingomyelin synthase 2 inhibitor D609 has been used to promote exosome generation and secretion by inhibiting the conversion of CER to SM (which often exceeds CER by 100 folds) [144].

The literature cites that VC is associated with the increase in sEVs/exosomal secretion, and the sphingolipid pathway plays an important role in the production of these sEVs/exosome [144]. Kapustin et al. in their study revealed that pro-inflammatory cytokines, growth factors and mineral imbalance stimulate exosome secretion by VSMCs due to activation of sphingomyelin phosphodiesterase 3 (SMPD3), they also found that inhibition of SMPD3 blocks exosome secretion and inturn VSMC calcification [145]. Trajokovic *et al.* demonstrated that the ESCRT-independent biogenesis of intraluminal vesicles (ILVs) that are released as exosomes takes place inside MVBs with the help of SM hydrolysis and CER production. In oligodendrocyte cell line (oli-Neu), it was found that total CER was enriched more than 3-fold in a subset of exosomes containing proteolipid protein (PLP). Treatment with GW4869, an inhibitor of n-SMase 1 and n-SMase 2, as well as two

Table 2
Preclinical studies depicting role of sphingolipids and EVs in various CVDs.

Sphingolipids	Ceramide in atherosclerosis	Ceramide accumulation associated with the progression of atherosclerosis and plaque instability in animal models.	[227]
Sphingolipids	Sphingosine-1-phosphate (S1P) in myocardial ischemia/reperfusion injury	S1P reduced infarct size and improved cardiac function in animal models of myocardial ischemia/reperfusion injury.	[228]
Sphingolipids	S1PR modulators in heart failure	S1PR agonists improved cardiac function and reduced fibrosis in heart failure models.	[229]
Sphingolipids	Inhibition of sphingosine kinase in hypertension	Inhibitors of sphingosine kinase reduced blood pressure and vascular remodeling in hypertensive animal models.	[230]
Sphingolipids	Targeting ceramide metabolism in cardiomyopathy	Modulating ceramide metabolism reduced cardiac hypertrophy and improved heart function in mouse models of cardiomyopathy.	[231]
Extracellular Vesicles	Exosomes in cardiac repair	Exosomes derived from stem cells promoted cardiac repair and improved cardiac function in animal models of myocardial infarction.	[189]
Extracellular Vesicles	Microvesicles in vascular remodeling	Microvesicles released from endothelial cells contributed to vascular remodeling and angiogenesis in preclinical models.	[232]
Extracellular Vesicles	Role of exosomes in endothelial function	Exosomes from endothelial progenitor cells enhanced endothelial function and reduced atherosclerosis in animal models.	[233]
Extracellular Vesicles	Exosomes from cardiac progenitor cells	Exosomes from cardiac progenitor cells improved cardiac function and reduced fibrosis in heart failure models.	[234]

Table 3
Clinical studies depicting role of sphingolipids and EVs in various CVDs.

Sphingolipids	Plasma S1P levels in coronary artery disease (CAD) patients	Lower S1P levels were associated with increased severity of CAD.	[31]
Sphingolipids	Ceramide levels as biomarkers for CVD risk	Elevated plasma ceramide levels were predictive of adverse cardiovascular events.	[235]
Sphingolipids	S1PR modulators in acute myocardial infarction	Early-phase trials showed potential benefits in reducing myocardial damage post-infarction.	[114]
Sphingolipids	Ceramide-targeted therapies in dyslipidemia and atherosclerosis	Ongoing trials are investigating the effects of ceramide synthesis inhibitors on lipid profiles and plaque stability.	[236]
Extracellular Vesicles	Circulating microvesicles as biomarkers in acute coronary syndrome	Elevated levels of circulating microvesicles were associated with increased risk of major adverse cardiovascular events in patients with acute coronary syndrome.	[237]
Extracellular Vesicles	Exosome-based therapy in heart failure	Preliminary clinical trials suggest that exosome-based therapies may improve cardiac function in heart failure patients.	[189]
Extracellular Vesicles	Microvesicles in atherosclerosis and thrombosis	High levels of procoagulant microvesicles were linked to the progression of atherosclerosis and increased risk of thrombotic events.	[238]
Extracellular Vesicles	Cardioprotective effects of mesenchymal stem cell-derived exosomes	Early-phase clinical trials showed that mesenchymal stem cell-derived exosomes reduced infarct size and improved cardiac function in myocardial infarction patients.	[209]

structurally unrelated n-SMase blockers, spiroepoxide and glutathione to Oli-neu cells, it was observed that CER is the most significant sphingolipid which is involved in the generation of intraluminal vesicles (ILVs) that are secreted as one class of exosomes [146]. Also, studies have shown that mammalian target of rapamycin complex 1 (mTORC1) signaling on lysosomes controls cargo selection, membrane biogenesis, and exosome secretion which in turn is regulated by lysosomal sphingolipids such as CER. In this context, Bhat *et al.* explored the lysosomal-CER- mTOR signaling pathway in Coronary Arterial Smooth Muscle Cells (CASMCs) and mice models. The study observed that lysosomal CER-mTOR signaling play a significant role for the regulation of lysosome–MVB interaction and exosome secretion which leads to the arterial stiffening during arterial medial calcification [86]. Also, It has been reported that TRPML1 channel (Ca^{2+} signaling channel) is regulated by AC which is associated with lysosome-MVBs interaction and secretion of sEVs / exosomes that contributes to the phenotypic transitions of SMCs inturn to vascular calcification both *in vivo* and *in vitro* [85]. Another study revealed that overexpression of a-SMase, (murine gene code: *Smpd1*) in SMCs contributes to increased calcium deposition, phenotypic change and sEV secretion which eventually leads to AMC [84]. Together these findings indicate that lysosomal sphingolipid pathway plays a critical role in the sEV/exosome biogenesis and release in SMCs that lead to the phenotypic transition of SMCs which may contribute to the CVDs.

More in-depth research in recent years indicated that exosomes and type 1 diabetes milletus (T1DM) have relationship with each other [147]. On the one hand, exosomes transport immunological materials (proteins or nuclei) that can activate immune cells like T cells and B cells and induce ß-cell apoptosis, which can lead to the development of T1DM [148,149]. However, it was discovered that human T1DM, glutamic acid decarboxylase (GAD65), islet antigen-2 (IA-2), and proinsulin intracellular β-cell autoantigens are also released through exosomes by rat and human pancreatic islets, which are then taken up by and activate dendritic cells [150]. Recent research has demonstrated that adipocytes can produce and release exosomes, which operate as a means of cell-to-cell communication and increase insulin resistance. As an illustration, adipocyte-derived exosomes carrying sonic hedgehog (SHH), a protein known to modulate immunity, induce proinflammatory or macrophage (M1) polarization of bone marrow-derived macrophages by regulating the Ptch/PI3K signaling pathway and contribute to insulin resistance [151]. Besides adipocytes, exosomes from other cells or organs, such as capillary ECs, human placental cells, and bone marrow mesenchymal cells, also contribute to insulin resistance [138,152–154]. Recent studies demonstrated that exosomes can be exploited as a potential therapeutic target in type 2 diabetes treatment option.

As mentioned earlier exosomes are comprised of a lipid bilayer membrane, soluble proteins, lipids and RNA (Non-coding RNAs such as mRNA, miRNA, LncRNA, and circRNA) [132,134,135]. miRNAs are small single stranded non coding RNA molecules found in plants, animals and some viruses which play a vital role in RNA silencing and post transcriptional regulation of gene expression [155,156] Rooij *et al.* in their study revealed that miRNAs and other mediators secreted through exosomes participate in CVDs via paracrine and endocrine communication [157]. A study found that miR-92a transfer from EC-derived EVs to macrophages boosted LDL absorption and macrophage motility, whereas inhibiting miR-92a expression reversed these effects, indicating that vesicular miR-92a plays a regulatory function in vascular disease [158]. Recent findings show that EV-packaged microRNA-145, microRNA-150, and microRNA-126 have a causal effect on the endothelial dysfunction and atherosclerosis *in vivo* [159]. Interestingly, X-box binding protein 1 (XBP1) splicing in vascular SMCs may influence endothelial cell motility via EVs-mediated microRNA-150 transfer and microRNA-150-driven vascular endothelial growth factor-dependent PI3K/Akt pathway activation, therefore maintaining vasculature homeostasis [160] It has been observed that thrombin-stimulated platelet-derived exosomes containing miRNA 223, miRNA 339 and miRNA 21 inhibit platelet-derived growth factor receptor-β expression in VSMCs [161]. Recently, Mone et al 2024, demonstrated that post coronavirus disease 2019 (COVID-19) exposure, an endothelial cell specific circulating EV microRNA-34a is able to act as progonostic marker for predicting the risk of developing diabetes. The study showed 2-fold increased association between COVID-19 and diabetes which was independent of dyslipidemia, smoking age, sex, body mass index (BMI), hypertension, status, and D-dimer [162]. A study reported that treatment of serum from COVID-19 patients to human ECs induced release of exosomal miR-145 and miR-885 significantly correlated with D-dimer levels, a degradation product of crosslinked (by factor XIII) fibrin. Furthermore, these ECs showed increased apoptosis and impaired angiogenetic properties which are essential in modulating thromboembolic events in COVID-19 [163]. Studies have shown that exosomes mediates intercellular communication during the process of VC [164]. It has been observed that the sEV/exosomal miRNA play a vital role in the phenotypic modulation of VSMCs which contribute to VC [165]. Matrix vesicles (MVs) are involved in formation of phosphatidylserine (PS)-annexin membrane complexes involved in mineralization thereby promoting VC, [166] and also by mediating the transport of miRNAs such as miRNA-153 and miRNA-223 [167] During the process of VC, some miRNAs in MVs facilitate deposition of calcium orthophosphate, which can change calcium phosphate structure from an amorphous form to crystalline structures, such as hydroxyapatite. However, some miRNAs have the opposite effect which inhibits the mineral deposition [168]. Exosomes that carry miRNA have the capability of operating more effectively in distant tissues. A study in murine model indicated that cardiomyocyte derived exosomal miR-92a transferred to fibroblasts is

crucial for cardiac myofibroblast activation in MI. Furthermore, the author validated that miR-92a as a transcriptional regulator of SMAD7, a known inhibitor of α-smooth muscle actin (α-SMA) and established marker of myofibroblast activation [169]. During diabetes exosomal miRNA which are pathogenic contributors may target important proteins which act as essential modulators for insulin sensitivity. Employing serum-derived exosome-enriched EVs, Katayama and colleagues examined the miRNA expression profile in type 2 diabetic patients and healthy controls, they found that exosome-derived extracellular miR-20b-5p is highly abundant in type 2 diabetic patients [170]. Furthermore, *in vitro* research revealed that exosomal miR-20b-5p targeted AKT-interacting protein (AKTIP), which interacts directly with AKT and modulates AKT activity by increasing the phosphorylation of AKT regulatory sites and reducing glycogen accumulation in primary human skeletal muscle, resulting in insulin resistance. In a study, selected exosomal miRNA (miR-192, miR-122, miR-27a-3p, and miR-27b-3p)

Table 4
Role of exosomal miRNAs in CVDs.

Type of CVD	Type of EV miRNA	Cellular origin	Functional dynamics	Reference/s
Atherosclerosis (AS)	miR-143/145	Human umbilical vein endothelial cells	Reduce the formation of aortic sclerosis injury	[239,240]
	miR-let7	Mesenchymal stem cells (MSCs)	Promoting the polarization of M2 macrophage	[241]
	miR-342-5p	Mesenchymal stem cells (MSCs)	Anti-atherosclerosis	[242]
	miR-155	ECs	Inhibiting inflammatory reaction	[243]
	miR-92a	ECs	The formation of atherosclerotic Plaque	[158,244]
	miR-155	Vascular smooth muscle cells (VSMCs)	Promoting endothelial cell injury	[245]
	miR-21-3p	Macrophages (MACs)	Promoting VSMCs proliferation and migration	[246]
	miR-106a-3p	Macrophages (MACs)	Promoting VSMCs proliferation and inhibiting VSMCs apoptosis	[247]
	miR-146a	Dendritic Cells (DCs)	Regulating inflammation response	[248]
	miR-223	Platelets	Inhibiting inflammatory reaction	[249]
Acute Myocardial Infarction (AMI)	miR-125b	Mesenchymal stem cells (MSCs)	Reducing the area of myocardial infarction	[250]
	miR-208, miR-499	Myocardial cells	Enters the bone marrow to down-regulate the expression CXCR4 and increase the number of circulating monocytes.	[251]
	miR-122-5p	–	Can be used to predict the degree of coronary artery stenosis	[252]
	miR-21a-5p	Mesenchymal stem cells (MSCs)	Myocardial protection	[200,253]
	miR-301	Mesenchymal stem cells (MSCs)	Inhibiting autophagy of myocardial cells	[254]
	miR-25-3p	Mesenchymal stem cells (MSCs)	Reducing the area of myocardial infarction	[255]
	miR-144	Mesenchymal stem cells (MSCs)	Improving the apoptosis of cardiomyocytes under hypoxia	[256]
Myocardial ischemia reperfusion injury (MIRI)	miR-423-3p	Cardiac fibroblasts cells	Reducing myocardial cells apoptosis	[257]
	miR-486-5p	Mesenchymal stem cells (MSCs)	Repairing myocardial injury	[258]
	miR-125b	Bone marrow mesenchymal stem cells (BMSCs)	Reduces MIRI by targeting SIRT7.	[250]
	miR-182	MSCs	Inhibiting inflammatory reaction	[259]
	miR-126	Cardiac fibroblasts (CFs)	Improves cardiac function by reducing MIRI by targeting and regulating ERRFI	[260]
Pulmonary Arterial Hypertension (PAH)	miR-181a-5p	ECs	Reversing vascular remodeling	[261]
	miR-324-5p	ECs	Reversing vascular remodeling	[261]
	miR-143/145	Vascular smooth muscle cells (VSMCs)	It was significantly increased in pulmonary vascular tissue in an animal model of pulmonary hypertension.	[262]
	miR-429-3p	TGB1 modified Telocytes	Helps to alleviate hypoxia-induced pulmonary arterial hypertension by tight regulation of Rac1 expression	[263]
Abdominal Aortic aneurysm (AAA)	miR-106a	–	Promoting VSMCs apoptosis	[264]
	miR-24	–	Regulating inflammation response	[265]
	miRNA-155	Macrophages (MCs)	Regulates the characteristics of fibroblasts while the heart is damaged	[266]
Vascular Calcification (VC)	let-7e-5p	–	Regulating vascular calcification	[267]
	miR-135, miR-762, miR-714,miR-712	Vascular smooth muscle cells (VSMCs)	Participate in VC by interfering with calcium efflux protein.	[268]
	miR-324-3p	–	Regulating vascular calcification	[267]
	miR-3960miR-2861	Vascular smooth muscle cells (VSMCs)	Responsible differentiation of osteoblasts and promoting the formation of VC.	[269]
Rheumatic Valvular Disease (RVD)	miR-155-5p	=	Regulating inflammation and fibrosis	[270]
Heart FailureHF	miR-21 miR-425miR-744	–	Inhibit the synthesis of collagen and cellulose induced by angiotensin, and also inhibit myocardial remodeling, by targeting TGF-b.	[271]
	miR-25-3p	Bone marrow mesenchymal stem cells (BMSCs)	It protects against myocardial ischemia/reperfusion injury by limiting M1-like macrophage polarization to control HF	[272]

which were earlier observed to be increased in obese mice were injected in lean mice. The findings depicted that exosomes from obese mice induced glucose intolerance and insulin resistance in lean mice [171]. Numerous exosomal miRNAs have been discovered to be upregulated in the plasma or urine of diabetic patients, which can act as circulating biomarkers linked to type 2 diabetes. Examples include exosomal miR-21-5p, miR-375-3p, miR-133b, miR-342, and miR-30, which are all upregulated in the serum of diabetic subjects [172–174] and miR-451-5p, let-7c-5p, miR-362-3p, miR-877-3p, miR-150-5p, and miR-15a-5p are upregulated in the urine of diabetic subjects [175–177]. Exosomal miRNA have been demonstrated to control numerous aspects of diabetic progression, including the metabolic and insulin signals in target tissues. Exosomes undoubtedly seem to play essential and important roles not only in pathogenesis but also in the diagnosis and treatment of diabetes.

As far as CVDs is considered, further research is required to determine how exosomal miRNAs are involved in the pathogenesis and onset of the CVDs in order to diagnose diseases more effectively and quickly. This demands more investigation into additional potential resources that may be useful for early disease detection, prevention, and therapy.

5. Therapeutic potential of extracellular vesicles in cardiovascular complications

EVs have several features that can be exploited to develop next generation drug delivery system. Firstly, they are biocompatible, cross biological barriers which can improve pharmacokinetics of drugs and reduce toxic side effects associated with other delivery systems. These EVs are potent immunomdulators [178], facilitate tissue regeneration [179] and regulate uptake at cellular, tissue and organ level via their specific components present on surfaceome [180,181]. EV biology and their therapeutics lead to revolution in drug delivery system with many companies focusing on their application aspect in various disease [182,183]. The extracellular vesicles are considered as major communicating architects that establish intimate intercellular communication playing an important role in signaling and exchange of biomolecules in cellular microenvironments and as well as long range communications [184–186].

Table 4 summarized the role of various exosomal miRNAs in CVDs. EVs derived from cardiac cells contain miRNAs like miR-26a, miR-146a and miR-181b which improve the cardio-protective effects [187–189]. Similarly, EVs derived from cardiomyocytes containing miR-214, miR-424, miR-378, let-7f, and miR-23a-3p have approved cardio-protective functions [190]. EVs also bear therapeutic lncRNA HCP5 which possess therapeutic properties [191]. The EVs derived from mesenchymal stromal cells (MSCs) have been shown to display cardioprotective effects and reports suggest that MSC- EVs have been employed to treat MI [192–197]. This function of MSC- EVs was attributed to the presence different classes of non-coding RNAs that largely inhibit remodeling of MI [198–200]. The Y RNA fragment EV-YF1 comprising major portion of exosomal RNAs are reported to mimic the cardioprotective effects through their ability to alter expression of IL-10 [201,202].

Consequently, EVs from progenitor cells contains bioactive compounds that possess key therapeutic potential in CVDs and hence may overcome the limitations posed by stem cell therapies [189,203,204]. Similarly, the EVs from cardiosphere-derived cells (CDCs) were reported to alleviate cardiac fibrosis, attenuate the cardiomyocyte apoptosis post MI and enhance tube formation of ECs [205,206]. Under *in vitro* conditions exosomes from CDCs of neonatal rats induced cardiac rejuvenation in old rats. This administration, aided to alleviate the myocardial fibrosis, cardiac hypertrophy and result in improvement of cardiac systolic and diastolic functions [207]. Cardiac progenitor cells (CPCs) derived exosomes containing miR-21 are reported to diminish the oxidative stress-induced programmed cell death of cardiomyocytes [208]. It must be noted that, EVs from embryonic stem cells promote cardiomyocyte survival and neovascularization in infarcted hearts. In addition, these EVs help to enhance the endogenous repair due to exosomal miR-294 [209]. Hence it is evident from above discussion that EVs play an important critical role in regulation of pathophysiological processes and therapeutics of CVDs [185]. Still there are challenges which needs to be addressed and explored with respect to the EV contents and their role in exchange of biomolecules. Specificity, targeted transport, efficacy and their cargo delivery along with off-target accumulation presents a major challenge for EV-based therapeutics [210]. In addition, we are still in infancy to optimize the efficiency and cargo delivery of EVs for clinical applications.

6. Conclusion and future Perspectives

The sphingolipids serve as precursors for vast range of moieties found in the cells that play a critical role in membrane biology and regulate wide range of functions in cells including cell division, senescence, migration, differentiation, apoptosis, pyroptosis, autophagy, nutrition intake, metabolism, and protein synthesis. Different subclasses of sphingolipids and their metabolites such as SM, CERs and S1P are directly related to diabetic cardiomyopathy, dilated cardiomyopathy, myocarditis and IHD. Recent research has paved a way towards the role of bioactive sphingolipids, CER and S1P in the development of embryonic bone. In this context, CER and S1P was shown to control mineralization of the VSMC matrix and accelerated calcification in VSMCs. Sphingolipid metabolisms was found to be associated with hypertension, endothelial dysfunction, vascular contractility and cardiac dysfunction. Genome-wide association studies showed an association between genetic variations in sphingolipid (and specifically glycosphingolipid) production genes and CVDs.

Literature cites, that sphingolipids increased the exosome secretion during CVDs such as atherosclerosis, VC and obesity. Extracellular vesicles/Exosomes are considered major intercellular communicating source playing crucial role in cellular signaling and exchange of cargos in cellular microenvironments and long-range communications. Extracellular vesicles and exosomal miRNA's derived from various cells possess therapeutic properties. Exosomal miRNA's derived from cardiac cells, mesenchymal stromal cells, embryonic stem cells showed cardioprotective effects. Consolidated experimental evidence suggest that pharmacological interference with sphingolipids, sphingolipid metabolites may offer novel therapeutic approaches for treatment and prevention of CVDs and associated complications. Furthermore, exosomes or exosomal miRNA's may be exploited for therapeutic aspects in regulation of pathophysiological processes of CVDs. Therefore, current knowledge of sphingolipids and its physiological roles may serve as appropriate platform to develop new therapeutics or adjuvant therapy for more effective treatment strategy against the CVDs.

7. Sphingolipids and Extracellular vesicles as prognostic markers of cardiovascular risk profile of individuals

1. Integrate biomarker Evaluation into routine clinical practice

   a. Establish a Standard Protocol:

- Develop a protocol for regularly assessing sphingolipid levels and extracellular vesicle (EV) markers.
- Define the specific sphingolipids (e.g., ceramide, sphingosine-1-phosphate) and EV markers (e.g., specific surface proteins, RNA content) to be measured.
- Ensure the protocol aligns with current clinical guidelines and evidence.

   b. Training and Education:

- Train clinical staff on the importance of sphingolipids and EVs in cardiovascular disease (CVD).

- Provide detailed training on sample collection, handling, and processing techniques to ensure accuracy and reliability of results.

2. Implement advanced diagnostic tools

a. Utilize High-Throughput Analytical Techniques:

- Employ techniques like mass spectrometry and liquid chromatography for precise quantification of sphingolipids.
- Use flow cytometry, nanoparticle tracking analysis, or next-generation sequencing for detailed EV profiling.

b. Partner with Specialized Laboratories:

- Collaborate with labs that specialize in lipidomics and EV analysis to ensure accurate and comprehensive evaluations.
- Ensure these labs provide detailed reports that integrate well with clinical data systems.

3. Routine patient assessment and monitoring

a. Initial and Follow-Up Testing:

- Conduct baseline assessments of sphingolipid and EV levels in new patients at risk of CVD.
- Schedule regular follow-up tests (e.g., every 6–12 months) to monitor changes over time and adjust treatment plans accordingly.

b. Correlate with Traditional CVD Risk Factors:

- Compare sphingolipid and EV levels with traditional risk factors like LDL cholesterol, blood pressure, and inflammatory markers.
- Use this integrated approach to identify patients at high risk and those who may benefit from early intervention.

4. Personalized treatment plans

a. Risk Stratification:

- Use sphingolipid and EV profiles to stratify patients into different risk categories.
- Tailor treatment plans based on individual risk profiles, incorporating lifestyle changes, pharmacotherapy, or other interventions as needed.

b. Monitor Treatment Efficacy:

- Regularly evaluate sphingolipid and EV levels to assess the efficacy of prescribed treatments.
- Adjust therapeutic strategies based on patient response to optimize outcomes.

5. Patient Education and engagement

a. Educate Patients:

- Inform patients about the role of sphingolipids and EVs in CVD and the importance of regular monitoring.
- Explain how these biomarkers can provide early indications of cardiovascular risk and the potential benefits of early intervention.

b. Encourage Lifestyle Modifications:

- Emphasize the impact of diet, exercise, and other lifestyle factors on sphingolipid metabolism and EV release.
- Provide resources and support for patients to make sustainable lifestyle changes.

6. Research and continuous improvement

a. Participate in Clinical Trials:

- Engage in or refer patients to clinical trials investigating the role of sphingolipids and EVs in CVD.
- Stay updated on the latest research to continually refine and improve clinical practices.

b. Collaborate with Researchers:

- Work closely with researchers to contribute to the growing body of knowledge on sphingolipids, EVs, and their role in CVD.
- Implement new findings and best practices into routine clinical care.

CRediT authorship contribution statement

Owais Mohmad Bhat: Supervision, Data curation, Conceptualization. **Rakeeb Ahmad Mir:** Writing – review & editing, Writing – original draft, Data curation. **Iqra Bashir Nehvi:** Writing – original draft. **Nissar Ahmad Wani:** Data curation, Conceptualization. **Abid Hamid Dar:** Conceptualization. **M Afzal Zargar:** Conceptualization.

Declaration of competing interest

The authors 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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