

# Sphingolipid Metabolism and Signalling Pathways in Heart Failure: From Molecular Mechanism to Therapeutic Potential

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**Abstract:** Sphingolipids are essential components of cell membranes and lipoproteins. They are synthesized de novo in the endoplasmic reticulum and subsequently undergo various enzymatic modifications in different organelles, giving rise to a diverse range of biologically active compounds. These molecules play a critical role in regulating cell growth, senescence, migration, apoptosis, and signaling. In recent years, the sphingolipid metabolic pathway has been recognized as a key factor in heart failure (HF) pathophysiology. Abnormal levels of sphingolipid metabolites, such as ceramide (Cer) and sphingomyelin (SM), contribute to oxidative stress and inflammatory responses, ultimately promoting cardiomyocyte apoptosis. Conversely, sphingosine-1-phosphate (S1P) and ceramide-1-phosphate (C1P) regulate vascular function and influence cardiac remodeling. Additionally, enzymes such as diacylglycerol acyltransferase 1 (DGAT1) and sphingosine-1-phosphate lyase 1 (SGPL1) modulate cardiac lipid metabolism. Given their role in HF progression, monitoring sphingolipid alterations offers potential as valuable biomarkers for assessing disease severity, prognosis, and diagnosis. Given the complexity of sphingolipid metabolism and its involvement in diverse regulatory biological processes, a comprehensive understanding of its roles at both the cellular and organismal levels in physiopathology remains incomplete. Therefore, this review aims to explore the physiological functions, regulatory mechanisms, and therapeutic potential of sphingolipid metabolism. It will summarize the specific molecular mechanisms driving key pathological processes in HF, including ventricular remodeling, myocardial fibrosis, vascular dysfunction, and metabolic disorders. Finally, the review will highlight targeted sphingolipid metabolites as potential therapeutic strategies, offering new insights into HF diagnosis and treatment, with the goal of advancing adjunctive clinical therapies.

**Keywords:** sphingolipids, ceramide, cardiovascular disease, heart failure, mechanisms

## Introduction

Heart failure (HF) is a multifaceted clinical syndrome characterized by insufficient cardiac output and/or elevated intracardiac pressure, resulting from impaired ventricular pumping, reduced filling capacity, or structural and functional abnormalities of the heart.<sup>1</sup> HF is stratified into three categories based on left ventricular ejection fraction (LVEF): HF with preserved ejection fraction (HFpEF; LVEF  $\geq 50\%$ ), HF with mildly reduced ejection fraction (HFmrEF; LVEF 41–49%), and HF with reduced ejection fraction (HFrEF; LVEF  $\leq 40\%$ ).<sup>1,2</sup> The clinical presentation typically involves dyspnoea, ankle swelling, and fatigue, and is often associated with elevated jugular venous pressure, pulmonary wet rales, and peripheral oedema.<sup>3</sup> Recent data indicate that the prevalence of HF has exceeded 60 million cases worldwide.<sup>4</sup> Despite advancements in medical technology, the five-year survival rate of HF remains below 50%,<sup>5,6</sup> and projections suggest that the prevalence of HF will increase by 46% by 2030.<sup>7,8</sup> The low quality of life, high readmission rates, and poor prognosis associated with HF impose significant challenges and substantial economic burdens on global healthcare

systems.<sup>9</sup> Therefore, gaining an in-depth understanding of the pathological mechanisms underlying HF and exploring effective therapeutic approaches is of paramount importance.

Although numerous studies have investigated the pathological mechanisms of HF, significant gaps in understanding persist.<sup>10–12</sup> This is especially true for cardiac lipid homeostasis, which recent research has shown to play a crucial role in HF pathogenesis.<sup>13–18</sup> However, comprehensive knowledge regarding the roles of specific lipids, such as sphingolipids, in HF remains limited. Sphingolipids, as essential components of cell membranes and lipoproteins,<sup>19</sup> significantly influence various cellular physiological properties and biological processes, including cell growth, senescence, migration, and apoptosis, as well as inflammation, immune responses, and oxidative stress.<sup>20–23</sup> Studies have shown that sphingolipids are not only crucial for cardiac development but also play a key role in the pathophysiology of cardiovascular diseases.<sup>24,25</sup> On one hand, the accumulation of sphingolipids can trigger inflammatory responses and lipid deposition in cardiomyocytes,<sup>26</sup> leading to cardiac and vascular dysfunction.<sup>27</sup> Consequently, sphingolipids, such as ceramide (Cer), sphingomyelin (SM) and glycosphingolipid (GSL), are commonly used as lipid biomarkers for cardiovascular diseases.<sup>28</sup> On the other hand, the activity of enzymes involved in sphingolipid metabolism can reduce sphingolipid levels, decrease cardiomyocyte death,<sup>29</sup> slow myocardial fibrosis progression, mitigate inflammatory responses,<sup>30</sup> and promote cardiac function recovery. This regulatory mechanism presents a promising therapeutic target for cardiovascular disease treatment.<sup>31</sup>

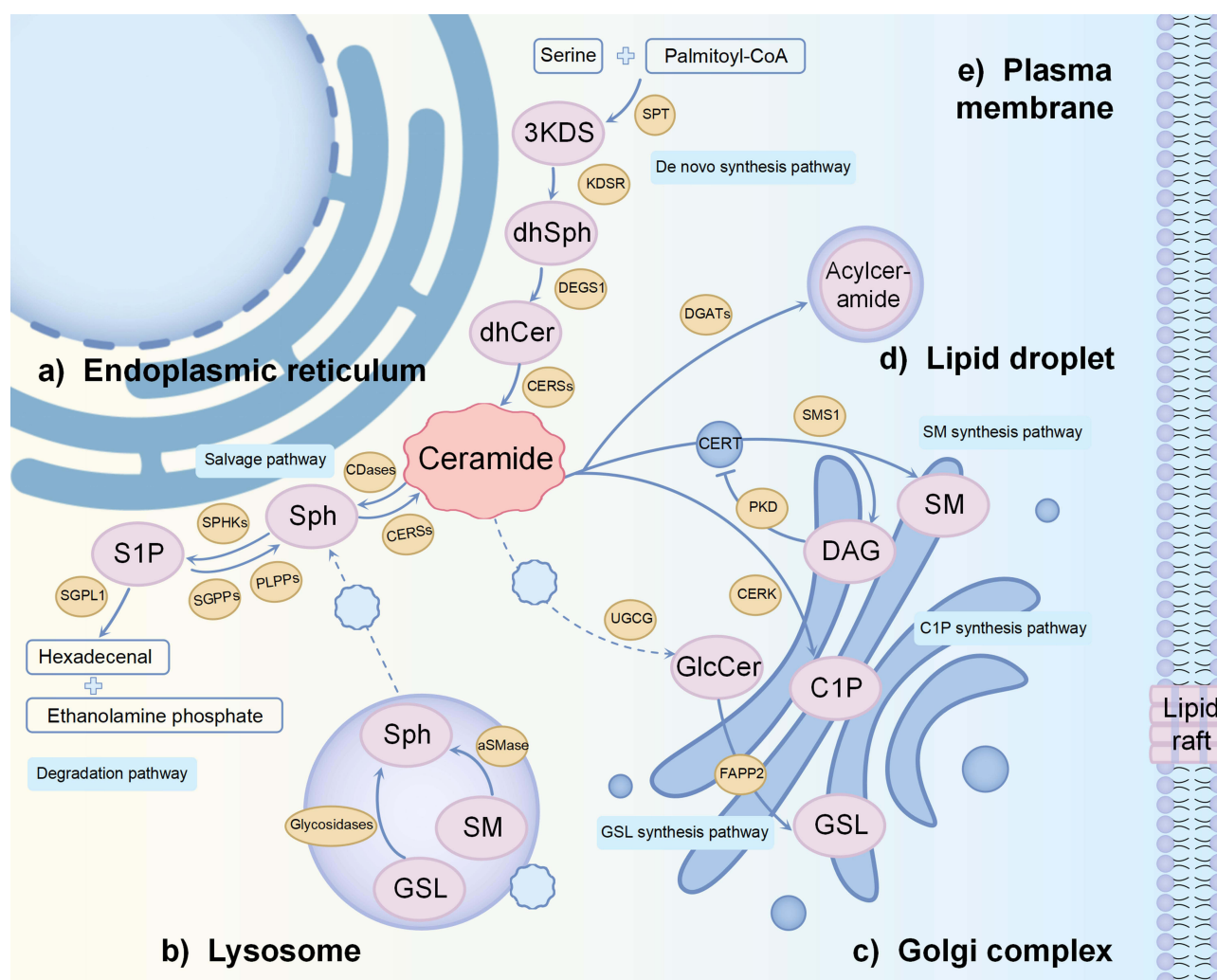
Due to the complexity of sphingolipid metabolism and the multidirectional regulation of biological processes, a comprehensive understanding of the role of sphingolipids at both the cellular and organismal levels, as well as their involvement in pathophysiology, remains incomplete. In this paper, we review the critical roles of sphingolipid metabolic pathways in HF, highlighting their physiological functions, mechanisms of action, and potential therapeutic targets. Our goal is to offer valuable insights and strategic guidance for future research on HF.

## Sphingolipid Metabolism

Since their discovery and naming in the late 19th century, sphingolipids have garnered widespread attention.<sup>32–34</sup> In previous studies, the biological structure and the metabolic processes of sphingolipids have been clearly elucidated (for a summary of the metabolic pathways, see [Figure 1](#)). Sphingolipids are a class of amphipathic lipids whose sphingoid backbone is N-acylated with various fatty acid chains ([Figure 2](#)).<sup>35</sup> The main lipids involved in sphingolipid metabolic processes are Cer, SM, GSL, sphingo-sine-1-phosphate (S1P), and ceramide-1-phosphate (C1P), which all share the same sphingolipid base.<sup>21</sup> Sphingolipids, as essential components of biological membranes, play crucial roles in cellular structure and function.<sup>22</sup> Their physiological activities are largely dependent on their association with membranes, vesicles, and membrane contact sites (MCS). These specialized sites facilitate the transfer and exchange of lipids between organelles, ensuring proper sphingolipid metabolism and signaling.<sup>36</sup> The regulatory mechanisms governing sphingolipid involvement in biological processes are closely linked to this membrane-dependent property, highlighting their significance in maintaining cellular homeostasis and function.<sup>37,38</sup> It has been suggested that Cer, Sph, and dihydroceramide (dhCer) are primarily associated with the induction of cell cycle arrest and/or cell death,<sup>19</sup> whereas S1P, C1P, and glucosylceramide (GlcCer) are linked to enhanced cell survival, promoting cell proliferation, adhesion, and migration.<sup>39</sup>

## De novo Synthesis of Sphingolipids

The de novo synthesis of sphingolipids begins in the ER, where enzymes located on the cytoplasmic side of the ER catalyse the synthesis of sphingolipid bases from the substrates L-serine and palmitoyl cofactor A ([Figure 1a](#)).<sup>40</sup> Subsequently, serine palmitoyl transferase (SPT) catalyses the synthesis of 3-keto-dihydrosphingosine (3KDS), which is then reduced by 3-keto-dihydrosphingosine reductase (KDSR) to form dihydrosphingosine (dhSph).<sup>41,42</sup> Catalysed by ceramide synthetases (CERSs), dhSph is converted into dhCer with various acyl chain lengths. dhCer is subsequently converted into Cer following the addition of a double bond catalysed by sphingolipid  $\Delta^4$ -desaturase DES1 (DEGS1) ([Figures 1a](#) and [2a](#)).<sup>43</sup> Cer serves as a key substrate for the synthesis of other sphingolipids and represents a central intermediate in the sphingolipid metabolic pathway.



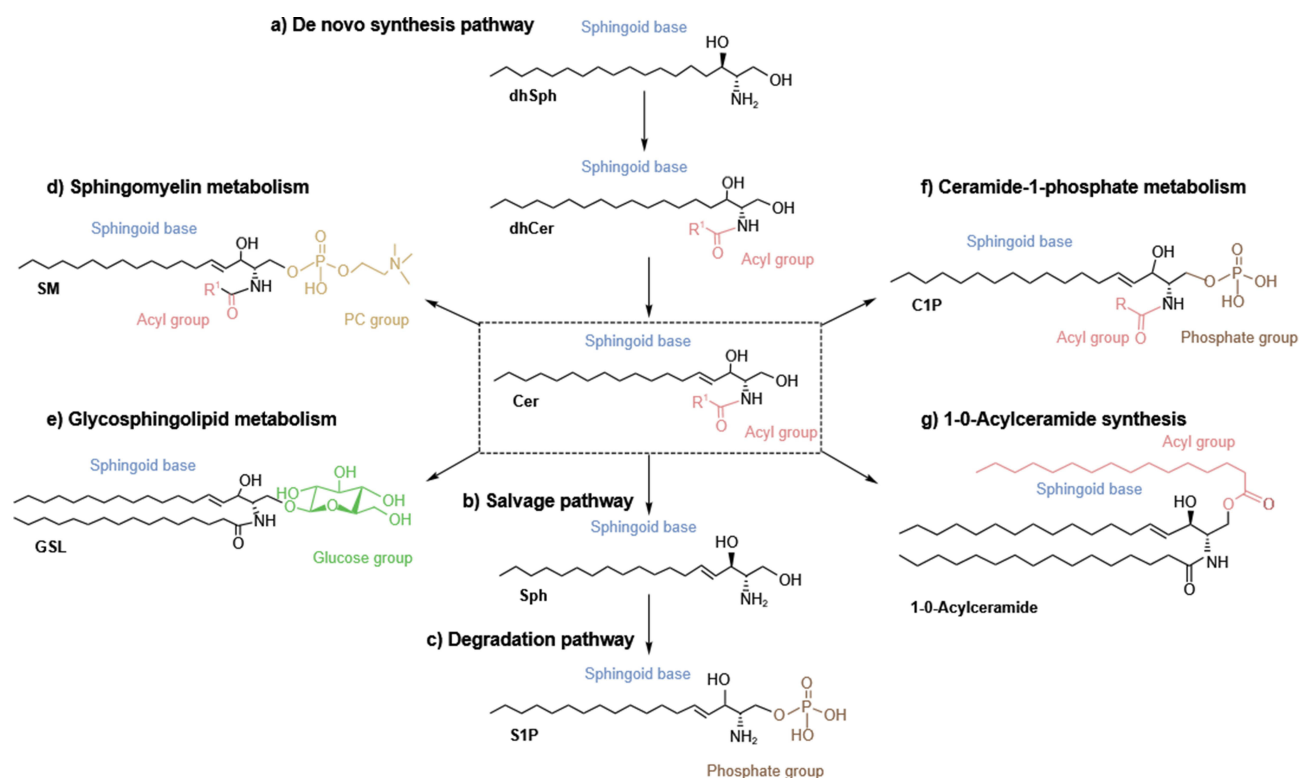
**Figure 1** Overview of sphingolipid biosynthesis and metabolic pathways. The major processes of sphingolipid metabolism include the de novo synthesis pathway, salvage pathway, degradation pathway, SM synthesis pathway, GSL synthesis pathway as well as C1P synthesis pathway. (a) De novo synthesis is initiated by the SPT complex, which completes a series of enzymatic reactions in the ER to produce Cer, which serves as a central hub for other sphingolipid pathways. (b) Cer is shut-tled via vesicular transport to the cytosolic side of the Golgi, where it is converted to GlcCer in the presence of UGCG and transported by FAPP2 into the TGN for further generation of a variety of GSLs. (c) Simultaneously, Cer generates S1P in the presence of CDases and SPHKs. S1P is further degraded into hexadecenal and ethanolamine phosphate through the catalytic action of SGPL1, completing the degradation pathway. Additionally, S1P can be reversed to sphingosine (Sph) by the combined action of SGPPs and PLPPs, allowing its participation in the salvage pathway. Cer is transported to the trans-Golgi complex by CERT. Here, a portion of Cer is catalytically activated by SMS1 to generate SM and DAG; another portion is phosphorylated to C1P by CERK. (d) Alternatively, Cer is converted to acylceramide catalyzed by DGATs, for storage in lipid droplets. (e) Lipids accumulate in the plasma membrane, forming lipid rafts.

**Abbreviations:** 3KDS, 3-Keto-dihydrospingosine; SPT, serine palmitoyltransferase; KDSR, 3-Ketodihydrospingosine reductase; dhSph, dihydrospingosine; CERSs, ceramide synthases; dhCer, dihydroceramide; DEGS1, dihydroceramide sphingolipid  $\Delta$ 4-desaturase DES1; CDases, ceramidase; Sph, sphingosine; SPHKs, sphingosine kinases; S1P, sphingosine-1-phosphate; SGPPs, S1P phosphatases; PLPPs, phospholipid phosphatases; SGPL1, S1P lyase 1; CERT, ceramide transfer protein; SMS1, sphingomyelin synthase 1; SM, Sphingomyelin; aSMase, acid sphingomyelinase; DAG, diacylglycerol; PKD, protein kinase D; UGCG, UDP-glucose ceramide glucosyltransferase; GlcCer, Glucosylceramide; FAPP2, transporter protein phosphoinositol 4-phosphate adapter protein 2; GSL, Glycosphingolipid; CERK, ceramide kinase; C1P, ceramide-1-phosphate; DGATs, diacylglycerol O-acyltransferases.

## Main Pathways of Sphingolipid Metabolism

### Salvage and Degradation Pathway

Acidic ceramidases (CDases) catalyse the hydrolysis of Cer into sphingosine (Sph), which can subsequently be resynthesised into Cer by CERSs,<sup>44</sup> constituting the salvage pathway in sphingolipid metabolism (Figures 1a and 2b). Sph is phosphorylated by sphingosine kinases (SPHKs) to generate S1P.<sup>45</sup> S1P can be converted back into Sph through the combined actions of S1P phosphatases (SGPPs) and lipid phosphate phosphatases (PLPPs), thereby reentering the salvage pathway (Figures 1a and 2c). Alternatively, S1P is degraded into hexadecenal and ethanolamine phosphate by sphingosine-1-phosphate lyase 1 (SGPL1),<sup>46</sup> marking the endpoint of sphingolipid metabolism.



**Figure 2** Overview of the chemical formulae of sphingolipid metabolites. Sphingolipids are a class of amphipathic lipids whose sphingoid backbone is N-acylated with various fatty acid chains. (a) After the generation of dhSph, a sphingoid base is formed, followed by the synthesis of dhCer through the addition of an acyl group. The introduction of a  $\Delta 4$  double bond subsequently converts dhCer into Cer. (b) Cer can be hydrolyzed to release Sph. (c) Subsequently, Sph forms S1P upon phosphorylation. (d) The addition of a PC head group to the 1-hydroxyl group of ceramide converts it into SM. (e) Additionally, Cer can be synthesized into GSL through the sequential addition of a glucose group to the 1-hydroxyl group of ceramide. (f) Furthermore, Cer can be phosphorylated to form C1P upon the introduction of a phosphate group. (g) Alternatively, O-acylation of Cer is catalyzed to generate 1-O-acylceramide.

**Abbreviations:** dhSph, dihydrosphingosine; dhCer, dihydroceramide; Cer, ceramide; Sph, sphingosine; PC, phosphorylcholine; S1P, sphingosine-1-phosphate; SM, Sphingomyelin; GSL, Glycosphingolipid; C1P, ceramide-1-phosphate.

## SM and GSL Synthesis Pathway

Cer is transported to the trans-Golgi network (TGN) by the ceramide transfer protein (CERT).<sup>47</sup> Within the TGN, sphingomyelin synthase 1 (SMS1) catalyses the conversion of Cer into SM and diacylglycerol (DAG) (Figures 1c and 2d). The DAG produced in this reaction can further activate protein kinase D (PKD). Activated PKD inhibits CERT, establishing a negative feedback regulatory system to precisely regulate SM flux.<sup>48</sup> Meanwhile, Cer is transported via vesicles to the cytoplasmic side of the Golgi apparatus, where UDP-glucose ceramide glycosyltransferase (UGCG) catalyses its conversion into GlcCer. Subsequently, phosphatidylinositol 4-phosphate adaptor protein 2 (FAPP2) transports GlcCer within the TGN, where it is further processed to synthesize various GSL (Figures 1c and 2e).<sup>49,50</sup> A portion of GSL and SM is translocated to lysosomes through endocytosis and/or cytosolic pathways, where they are converted back into Cer by the catalytic actions of acid sphingomyelinase (aSMase) and glycosidases, respectively (Figure 1b). The remaining portion is transported to the plasma membrane, where it aggregates with other lipids to form lipid microdomains (Figure 1e).<sup>51</sup>

## C1P and Acylceramide Synthesis Pathway

Two additional conversion pathways for Cer occur in the TGN. In one pathway, Cer is directly phosphorylated by ceramide kinase (CERK) to generate C1P, a bioactive molecule that functions as a second messenger extensively involved in the regulation of diverse biological processes (Figures 1c and 2f).<sup>52</sup> In the other pathway, a portion of Cer is converted into acyl ceramides through a shunt pathway catalysed by diacylglycerol O-acyltransferases (DGATs) and stored in lipid droplets. This step plays a critical role in maintaining Cer flux within the cell (Figures 1d and 2g).<sup>53,54</sup>

## Regulation of Cell Function by Sphingolipid Metabolism

Sphingolipid metabolism is a highly complex biological process, with its regulatory effects on cellular functions largely determined by the key enzymes involved and their metabolic products. As the central molecule in sphingolipid metabolism, Cer plays a crucial role in maintaining cell membrane stability, regulating organelle functions, and mediating cell signaling processes.<sup>35</sup> A primary regulatory mechanism of Cer is its role as a pro-apoptotic driver. Cer can activate the c-Jun N-terminal kinase (JNK) signaling pathway or directly interact with pro-apoptotic proteins of the Bcl-2 family, leading to organelle permeabilization and the regulation of apoptosis.<sup>55</sup> The accumulation of Cer can interfere with mitochondrial fission and promote the generation of reactive oxygen species, inducing oxidative stress that directly impairs mitochondrial function.<sup>56,57</sup> Furthermore, Cer plays a critical role in the formation and secretion of exosomes, thereby regulating intercellular signal transduction.<sup>58</sup> SPT, a complex composed of enzymes from the SPT family, serves as a key rate-limiting enzyme in the sphingolipid metabolic pathway. Additionally, it functions as a negative regulator of Cer, preventing its abnormal accumulation and maintaining intracellular sphingolipid homeostasis.<sup>41</sup>

Sph inhibits protein kinase C (PKC), disrupting calcium homeostasis,<sup>59</sup> thereby exhibiting lysosomal toxicity. To counteract this, Sph can be transported out of lysosomes by sphingosine kinase 1 (SPHK1) and converted into S1P on the cytosolic surface. S1P promotes cell migration, proliferation, and mitosis,<sup>60</sup> while also exerting anti-apoptotic effects by activating extracellular signal-regulated kinase (ERK) and inhibiting JNK signaling.<sup>61</sup> Acting as a “sphingolipid variable resistor”,<sup>62</sup> S1P helps regulate the balance between pro-apoptotic and proliferation-related molecules, in coordination with Cer, to maintain cellular homeostasis. Moreover, S1P participates in the regulation of various physiological processes, including the nervous system, immune system, vascular physiology, and more.<sup>26,63,64</sup> SM is enriched in the outer leaflet of the plasma membrane, where it coexists with other lipids. This lipid composition contributes to an increase in membrane thickness and plays a key role in maintaining the structural integrity of the cell membrane.<sup>65</sup> This aggregated lipid microstructure is referred to as lipid rafts, which regulate the shuttling of molecules across the cell surface, signal transduction pathways, and the entry of pathogens and toxins. Lipid rafts have also been strongly implicated in brain cell aging and neurodegenerative diseases.<sup>51</sup> Additionally, SM associates with cholesterol in the plasma membrane to form SM/cholesterol complexes, which play a key role in regulating cellular cholesterol homeostasis.<sup>66</sup> GSL, also found within lipid microstructure, plays a key role in regulating membrane homeostasis. Its complex glycosyl structure allows interaction with extracellular vesicles (EVs), thereby influencing intercellular signaling and potentially inducing apoptosis.<sup>67</sup> GSL can also increase mitochondrial calcium ( $\text{Ca}^{2+}$ ) influx, leading to changes in membrane potential and promoting mitochondrial fission. These changes can disrupt normal mitochondrial function and trigger alterations in the organism's energy metabolism.<sup>68</sup> Additionally, C1P, produced through Cer phosphorylation by CERK, stimulates fibroblast DNA synthesis and proliferation, thereby promoting cell growth.<sup>69</sup> C1P effectively modulates inflammatory responses by inhibiting the release of pro-inflammatory cytokines, such as TNF- $\alpha$ , IL-6, and IL-1 $\beta$ , and by blocking the NF- $\kappa$ B signaling pathway.<sup>70</sup>

## Sphingolipid Metabolism in CVD

The pathogenesis and treatment of CVD remain a significant challenge and a major focus of research in the cardiovascular field. Several studies have reported abnormal concentrations of sphingolipid metabolites in plasma samples from patients with atherosclerosis (AS), hypertension, and HF. These findings suggest that sphingolipid metabolism plays a critical role in the pathogenesis and progression of CVD.<sup>23–25,71</sup> An increasing number of studies have demonstrated that sphingolipid metabolism plays a pivotal role in pathophysiological processes, including inflammatory responses, oxidative stress, and lipid deposition.<sup>26,27</sup> These metabolites mediate physiological and pathological processes in the cardiovascular system by contributing to pathological alterations such as vascular dysfunction, myocardial abnormalities, and disturbances in cardiac energy metabolism.<sup>31</sup> Studies have further shown that abnormally elevated levels of Cer, SM, and GSL exacerbate AS and HF.<sup>72</sup> Moreover, abnormal changes in S1P levels have been shown to exert dual effects on atherosclerosis, either promoting or inhibiting its development. However, overall, abnormal S1P levels are associated with the exacerbation of pathophysiological processes such as fibrosis and cardiac remodeling.<sup>25</sup> Therefore, sphingolipids, as a class of potential biomarkers, have been extensively studied and utilized in the prediction and diagnosis of CVD.<sup>28,72</sup> Additionally, the modulation of key enzymes involved in sphingolipid metabolism, through dietary or

**Table 1** Roles of Sphingolipid Metabolites in Cardiovascular Diseases

Sphingolipid Metabolite	Role in Cardiovascular Conditions	Associated Cardiovascular Diseases
Cer	Induces oxidative stress and promotes apoptosis; leads to lipid accumulation and endothelial dysfunction <sup>74,75</sup>	AS, HF, MI, hypertension, acute coronary syndrome
SIP	Regulates vascular integrity, angiogenesis, and immune cell trafficking; has both protective and pro-inflammatory roles depending on receptor subtype <sup>76,77</sup>	AS, acute coronary syndrome, hypertension
SPHKs	Promotes endothelial cell migration and participates in vascular remodelling <sup>78,79</sup>	AS, MI, angiogenesis-related disease
CIP	Anti-apoptotic, promotes cell proliferation and inflammation <sup>80</sup>	MI, AS
SGPLI	Regulates vascular function, and impacts inflammatory responses <sup>81,82</sup>	AS, HF
SPT	Catalyzes the formation of ceramide from sphingosine and fatty acyl-CoA; regulates lipid metabolism and stress responses <sup>83</sup>	AS, MI
DES1	Involved in the desaturation of ceramide to form sphingolipids with specific structures, contributing to membrane properties and signaling <sup>84</sup>	AS, metabolic syndrome
SM	Involved in inflammatory signaling, foam cell formation, and oxidative stress <sup>85</sup>	AS, HF
Sph	Inhibits protein kinase C, promotes apoptosis, and affects calcium homeostasis <sup>86</sup>	HF, hypertension
aSMase	Hydrolyzes sphingomyelin to ceramide, promoting inflammatory and apoptotic pathways <sup>87,88</sup>	AS, hypertension
GSL	Modulate immune responses, endothelial function, and platelet activation <sup>89</sup>	HF, AS
GlcCer	Involved in inflammatory signaling, foam cell formation, and oxidative stress <sup>90</sup>	AS, MI, HF
DGAT1	Involved in the conversion of diacylglycerol to triglycerides; regulates lipid storage and energy balance <sup>91</sup>	AS, HF

**Abbreviations:** Cer, Ceramide; SIP, Sphingosine-1-phosphate; SM, Sphingomyelin; SPHKs Sphingosine kinases; CIP, Ceramide-1-phosphate; SGPLI, Sphingosine-1-phosphate lyase I; SPT, Serine palmitoyl transferase; DES1, dihydroceramide desaturase 1; Sph, Sphingosine; aSMase, acid sphingomyelinase; GSL, Glycosphingolipid; GlcCer, Glucosylceramide; DGAT1, diacylglycerol O-acyltransferase I; AS, Atherosclerosis; HF, Heart failure; MI, Myocardial infarction.

pharmacological interventions, as well as the supplementation or inhibition of related metabolites, has emerged as a promising therapeutic strategy for CVD.<sup>73</sup> (Table 1 that outlines the roles of various sphingolipid metabolites in different cardiovascular conditions).

Effects of Sphingolipid Metabolism on Cardiovascular Function

Role of Sphingolipid Metabolism in Vascular Function

Vascular endothelial cells are a single layer of flattened squamous epithelial cells lining the inner surface of blood vessels. They form a barrier between blood vessels and tissues, regulate the exchange of substances between blood and tissue fluids, and control vascular tone.<sup>92</sup> Abnormal regulation of sphingolipid metabolites or their key enzymes can act as mediators that influence the functional state of endothelial cells.<sup>93</sup> This dysregulation can alter vascular permeability, promote vasoconstriction, and trigger inflammatory responses. Collectively, these processes contribute to vascular dysfunction, forming the pathophysiological basis of CVDs.<sup>94</sup>

Regulation of Endothelial Cell Function

Sphingolipid metabolism exerts a bidirectional regulatory effect on endothelial cell function. Its detrimental effects on endothelial cells are primarily manifested through the induction of oxidative stress and apoptosis. In contrast, its protective effects include anti-apoptotic properties, inhibition of inflammatory responses, and the promotion of cell proliferation and growth. Specifically, the accumulation of Cer in endothelial cells enhances the activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, promoting the production of reactive oxygen species (ROS). This

process impacts the activity of endothelial nitric oxide synthase (eNOS), reduces nitric oxide (NO) bioavailability, and induces oxidative stress, ultimately leading to vascular dysfunction.<sup>74</sup> Additionally, Cer induces apoptosis in endothelial cells through various pathways, including the stimulation of cAMP-dependent protein kinase (CAPK) and the SAPK/JNK cascade reaction. Cer can also directly regulate the physical properties of cell membranes, further driving apoptosis and contributing to destructive effects on vascular function.<sup>75</sup> S1P binds to different sites on sphingosine-1-phosphate receptors (S1PRs), exerting distinct effects.<sup>76</sup>

### Promote Vascular Remodelling

Binding of S1P to S1PR2 activates the phosphatase and tensin homolog (PTEN) pathway, which inhibits AKT phosphorylation, disrupts adhesion junctions, and increases paracellular permeability.<sup>77</sup> Conversely, S1PR1 enhances the production and exocytosis of S1P, promoting vascular smooth muscle cell migration to facilitate vascular repair.<sup>95</sup> SPHK1 is one of the key enzymes regulating sphingolipid metabolism. As a downstream effector of the LIM domain 2 (Lmo2) transcription factor, it promotes endothelial cell migration and participates in vascular remodeling.<sup>78</sup> SGPL1 prevents damage to the endothelial cell barrier caused by pro-inflammatory factors, ensuring the stability of endothelial cell function under inflammatory conditions and exerting a protective effect on blood vessels.<sup>96</sup>

### Role of Sphingolipid Metabolism in Cardiac Function

Abnormalities in cardiac structure and function are central to the pathological progression of CVDs. Current studies have shown that sphingolipid metabolites play a crucial role in regulating key biological processes such as myocardial contraction, cardiomyocyte apoptosis, and myocardial fibrosis.<sup>97</sup>

### Regulation of Myocardial Contraction

The modulation of these metabolites may hold potential for reversing pathological changes in cardiac structure and improving cardiac function.<sup>98</sup> Research indicates that Cer and S1P directly regulate contractile function in cardiomyocytes. S1P activates specific G-proteins, reducing Ca<sup>2+</sup> influx and inhibiting isoproterenol-induced cAMP accumulation, thereby producing a negative inotropic effect.<sup>26,99</sup> Cer increases the phosphorylation of the myofilament proteins cardiac troponin I (cTnI) and cardiac myosin-binding protein-C (cMyBP-C), thereby inhibiting myocardial contractility.<sup>100</sup> CDase facilitates Cer degradation, reducing Cer levels in the heart and alleviating cardiac remodeling, thereby improving cardiac function.<sup>101</sup>

### Improvement in Myocardial Fibrosis

S1P plays a pivotal role in tissue fibrosis.<sup>97</sup> S1P regulates fibroblast migration, myofibroblast differentiation, and TGF- $\beta$  signaling via its receptor S1PR3, mediating the fibrotic response of tissues.<sup>102</sup> SPHK1 plays a critical role in regulating myocardial fibrosis under both physiological and pathological conditions. Under physiological conditions, it facilitates myocardial cell proliferation and growth. Under pathological conditions, particularly in myocardial hypoxia, SPHK1 exerts anti-inflammatory effects and effectively suppresses the progression of cardiac fibrosis. Additionally, inhibiting the overexpression of SPHK1 can attenuate myocardial fibrosis mediated by the S1P-S1PR2 signaling pathway.<sup>76,79</sup> Inflammation is a critical factor in fibrosis and remodeling following cardiac injury. C1P contributes to cardiac fibrosis by modulating the inflammatory response, primarily through the activation of prostaglandin synthesis and release. CERK, an upstream regulator of C1P, also participates in this process.<sup>80</sup>

### Involvement in Cardiomyocyte Apoptosis

In addition, cardiomyocyte apoptosis is a critical contributing factor to cardiac insufficiency. The abnormal accumulation of sphingolipid metabolites may initiate apoptosis in cardiomyocytes. Cer has been shown to induce apoptosis in cardiomyocytes, with mitochondria as a key target. Cer promotes apoptosis by activating the caspase-3 signaling pathway, promoting mitochondrial fission, and increasing the permeability of the outer mitochondrial membrane.<sup>81,98</sup> Furthermore, overexpression of serine palmitoyltransferase 1 (SPTLC1) and/or serine palmitoyltransferase 1 (SPTLC2) results in Cer accumulation, which disrupts mitochondrial respiration and further promotes apoptosis in cardiomyocytes.<sup>82</sup>

## Regulation of Cardiac Energy Metabolism by Sphingolipid Metabolism

Under normal conditions, the heart primarily derives its energy from the  $\beta$ -oxidation of fatty acids in the mitochondria, using free fatty acids and glucose as substrates. These substrates undergo oxidation reactions catalyzed by acetyl coenzyme A, producing ATP to meet the heart's energy demands.<sup>103</sup> When energy metabolism is aberrant, a failure to utilize these substrates results in lipid deposition in the vasculature, further contributing to the progression of CVD.<sup>13</sup> Sphingolipid metabolism products can both mediate and reverse this process.<sup>31</sup> The accumulation of Cer has been shown to induce mitochondrial fission factor, leading to mitochondrial calcium overload and apoptosis, thereby interfering with lipid metabolism. Similarly, GSL can regulate mitochondrial calcium retention capacity and energy production.<sup>104</sup> SPT, as an initiator of sphingolipid metabolism, regulates the de novo synthesis of sphingolipids. Silencing SPT gene expression reduces the accumulation of Cer, GSLs, and other sphingolipids.<sup>83,105</sup> Targeted ablation of DES1, a key enzyme in Cer synthesis, ameliorates disorders of lipid metabolism.<sup>84</sup> Specific depletion of SPTLC2 in non-adipose cells exhibits similar effects, modulating steatosis and enhancing energy expenditure.<sup>106</sup> It has been shown that inhibition of sphingolipid expression in cardiomyocytes improves mitochondrial respiration and regulates insulin signaling, glucose uptake, and related metabolic pathways.<sup>107</sup> In addition, sphingolipids activate the expression of protein phosphatase 2A (PP2A), which inhibits Akt/protein kinase B (Akt/PKB) signaling. This inhibition alters glucose uptake and oxidation while limiting fatty acid availability, thereby impacting cardiac energy metabolism.<sup>108</sup>

During ischemia, the limited availability of oxygen forces the heart to rely on anaerobic glycolysis as a compensatory mechanism. This shift results in reduced ATP production and lactate accumulation, leading to intracellular acidosis and mitochondrial dysfunction.<sup>109</sup> Once blood flow is restored, mitochondrial oxidative phosphorylation resumes, accompanied by the reactivation of fatty acid oxidation and a sudden surge in reactive ROS. These events further impair mitochondrial function, and ischemia-reperfusion (I/R) injury induces maladaptive myocardial remodeling, ultimately leading to hypertrophy and heart failure.<sup>110</sup> Studies have shown that GSL and SM are significantly reduced at ischemic sites, whereas Cer levels are markedly increased.<sup>111</sup> Cer exacerbates this metabolic imbalance by promoting oxidative stress, further worsening ischemic injury. Myriocin inhibits the expression of SPT, reducing Cer synthesis. This, in turn, enhances mitochondrial  $\beta$ -oxidation, accelerating ATP production, and plays a crucial role in regulating cardiac remodeling and energy generation.<sup>112</sup> Additionally, CDase promotes the hydrolysis of Cer in cardiomyocytes, enhancing mitochondrial respiration and supporting metabolic adaptation under ischemic conditions.<sup>113</sup> Activation of S1P signaling helps modulate mitochondrial homeostasis in I/R injury, restoring lipid metabolic balance in vivo.<sup>114</sup>

## The Role of Sphingolipid Metabolism in CVD

An increasing number of studies have focused on monitoring sphingolipid levels as key indicators of CVD progression and exploring their potential as therapeutic targets for intervention.<sup>25,26,28,73</sup> Research has demonstrated that sphingolipids play a critical role in the pathogenesis of AS.<sup>28</sup> The pathological process of AS is characterized by the release of pro-inflammatory cytokines, such as TNF- $\alpha$  and IL-1 $\beta$ , which stimulate SM hydrolysis to produce Cer, which acts as a signaling intermediate. Cer, in turn, induces IL-6 gene expression, aggravates inflammation, promotes endothelial cell apoptosis, and facilitates the formation of atherosclerotic plaques.<sup>75,85</sup> Meanwhile, oxidized low-density lipoprotein (oxLDL) stimulates the enzymatic activities of CERSs, SPHKs, and acid aSMase, thereby promoting the production of S1P. S1P binds to S1PR2 to regulate macrophage infiltration and inflammatory cytokine secretion, promoting atherosclerotic progression. Conversely, S1P interacts with S1PR1 to inhibit pro-inflammatory factors, exhibiting anti-atherosclerotic effects.<sup>76,77,115</sup> Additionally, inhibition of aSMase mediates the Nrf2 pathway, reducing macrophage infiltration and lipid deposition.<sup>87</sup>

The imbalance of sphingolipid metabolism is closely associated with the pathogenesis of hypertension. Relevant studies have shown that under hypertensive pathological conditions, the levels of Cer and Sph in endothelial cells are abnormally elevated.<sup>86</sup> In addition, the absence of SPHK1 and sphingosine kinase 2 (SPHK2) expression reduces arterial contractility, a phenomenon positively correlated with S1P levels. Meanwhile, activation of aSMase also elevates S1P levels, impairing endothelial cell function and contributing to elevated blood pressure. This process may involve S1P-induced oxidative stress mechanisms.<sup>88</sup> A study assessing the risk of hypertension found that risk scoring based on Cer concentration and plasma ratios could effectively predict disease progression and outcomes.<sup>116</sup>

In the pathological progression of acute coronary syndrome and myocardial infarction (MI), Cer and S1P exhibit opposing functional trends. In vivo experiments have confirmed that the levels of sphingolipid metabolites, such as dhCer, CER6, and Cer, significantly increase in the plasma of MI mice. However, this trend reverses during the MI recovery phase, and elevated sphingolipid levels are regarded as an important marker of cardiac dysfunction.<sup>117</sup> Further research has shown that activating CDases can accelerate the hydrolysis of Cer, thereby reducing cardiomyocyte apoptosis, improving overall cardiac function, and extending survival post-MI.<sup>30</sup> Additionally, S1P interacts with S1PR2 and S1PR3, playing a critical role in maintaining the normal conduction of action potentials in cardiomyocytes.<sup>118</sup> Furthermore, S1P mediates the mTOR signaling pathway, inducing autophagy in cardiomyocytes post-MI, effectively preventing adverse remodeling and demonstrating significant cardioprotective effects.<sup>119</sup>

## Sphingolipid Metabolism with HF

HF represents the endstage manifestation of all CVDs, resulting from abnormalities in cardiac function or structure.<sup>8</sup> The etiology of HF is complex, with pathological mechanisms encompassing endothelial injury, vascular dysfunction, inflammation, oxidative stress, myocardial fibrosis, and energy metabolism disturbances, among others.<sup>11–13</sup> Studies have shown that the sphingolipid metabolic pathway is disrupted during the progression of HF, resulting in altered levels of key enzymes and related metabolites.<sup>120</sup> In the plasma of HF patients, elevated levels of SPT, Cer, SM, Sph, and GSL have been observed, accompanied by decreased levels of S1P and C1P, along with an elevated Cer/S1P ratio.<sup>72,121</sup> Therefore, abnormal changes in sphingolipid levels serve as risk factors for assessing and predicting HF progression.<sup>122</sup> In recent years, increasing research on sphingolipid metabolism has identified key substances in this process as potential therapeutic targets for HF.<sup>120</sup> It is thus evident that sphingolipid metabolism is integral to the pathogenesis of HF (Figure 3).

## Mechanisms of Sphingolipid Metabolism in HF

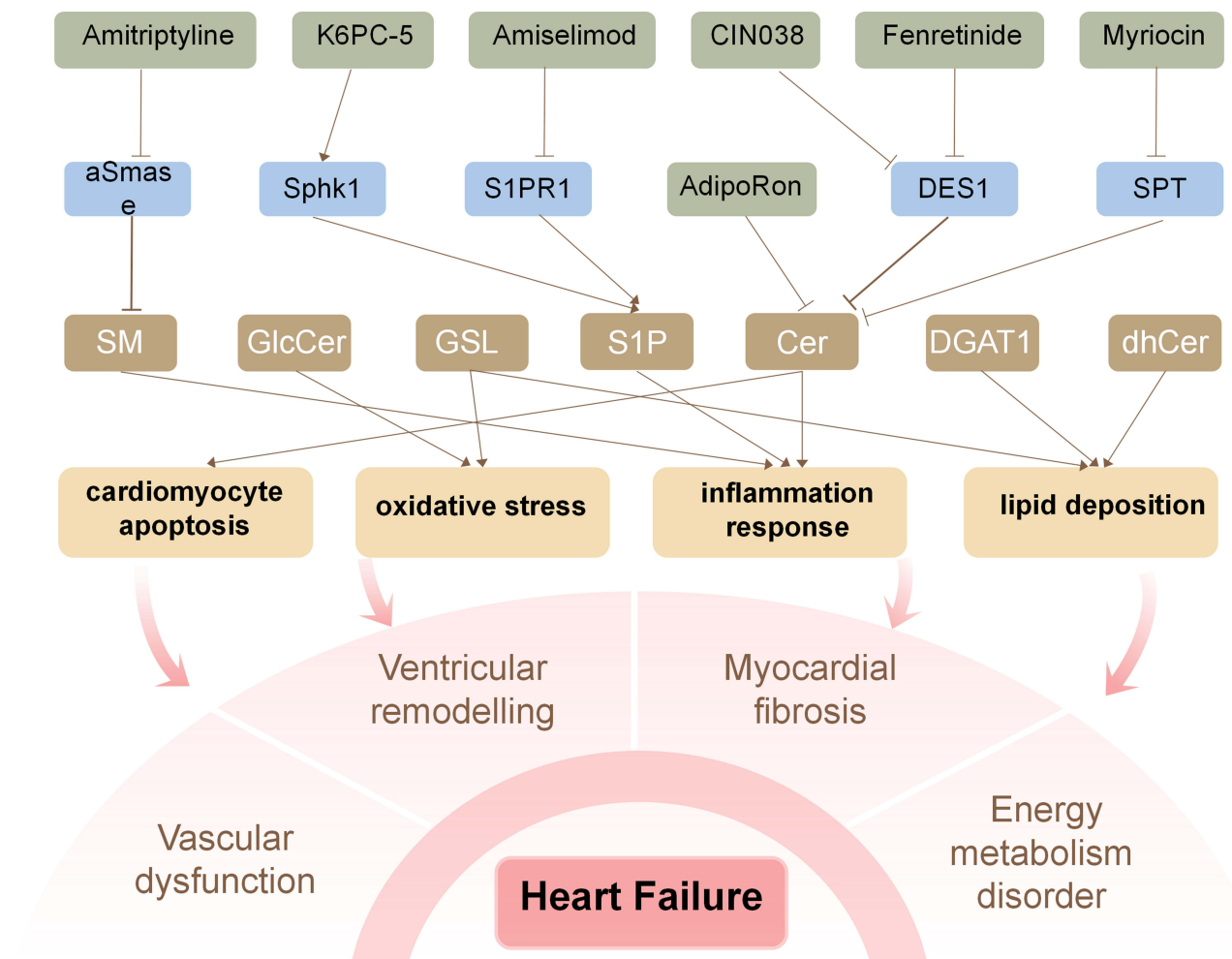
Although the American College of Cardiology (ACC)/American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines classify HF into three types based on left ventricular ejection fraction (LVEF)—HFpEF (LVEF  $\geq 50\%$ ), HFmrEF (LVEF 41–49%), and HFrEF (LVEF  $\leq 40\%$ )—HFmrEF is considered an intermediate stage and often progresses to either HFpEF or HFrEF.<sup>1,123</sup> Therefore, research has primarily focused on the two major types, HFrEF and HFpEF, when studying the effects of sphingolipid metabolism on HF.

### Sphingolipid Metabolism in the HFrEF

The main pathological features of HFrEF include ventricular dilatation, systolic dysfunction, and myocardial fibrosis, which are primarily linked to ischemic damage to the heart.<sup>124,125</sup> The sphingolipid metabolic pathway plays a key role in the pathological process of HFrEF by impairing cardiomyocyte function, promoting oxidative stress, and triggering inflammatory responses.<sup>97,98</sup>

Changes in sphingolipid metabolism directly affect the physiological state of cardiomyocytes. Studies have shown that Cer and dhSph levels are elevated, while SM levels are reduced, in the myocardial tissues of post-MI HF mouse models.<sup>126</sup> Abnormal elevation of Cer not only affects mitochondrial respiratory capacity and disrupts membrane structure but also increases mitochondrial permeability to cytochrome c, ultimately promoting cardiomyocyte apoptosis.<sup>127</sup> Increased levels of dhSph, a key substrate for Cer synthesis, serve as the raw material for Cer production,<sup>42</sup> while Cer may also be derived from the catabolism of SM. Inhibiting the expression of SPT isoforms SPTLC1 and SPTLC2 reduces myocardial Cer accumulation and alleviates contractile dysfunction.<sup>128</sup>

Oxidative stress plays a key role in the progression of myocardial fibrosis and cardiac hypertrophy. GSL generate reactive oxygen species (ROS) and activate ERK-1/p44 MAPK in cardiomyocytes, leading to myocardial hypertrophy and subsequent HF. Elevated levels of GlcCer have been observed in cardiac tissues of patients with HFrEF, with a similar trend observed in mouse models.<sup>89</sup> Further studies revealed that UGCG, the rate-limiting enzyme in GlcCer synthesis, was overexpressed in cardiomyocytes and promoted mitochondrial ROS production, driving cardiac hypertrophy and myocardial fibrosis.<sup>90</sup>



**Figure 3** The role of sphingolipid metabolism in heart failure, Mechanisms and Therapeutic Targets. In the pathological process of HF, abnormal elevation of Cer can directly induces cardiomyocyte apoptosis and triggers an inflammatory response; SM and S1P, as key regulators, can attenuate the cardiac inflammation; GSL and GlcCer promote oxidative stress in cardiomyocytes, contributing to myocardial hypertrophy; DGAT1 and dhCer not only promote the accumulation of Cer, but also, together with S1P, lead to lipid deposition. These pathological changes collectively result in vascular dysfunction, myocardial fibrosis, ventricular remodeling, and disturbances in energy metabolism, which form the pathological basis of HF. Myriocin, an SPT inhibitor, suppresses de novo sphingolipid synthesis, reduces Cer accumulation, and alleviates apoptosis; AdipoRon lowers Cer levels and improves myocardial injury; CIN038 and Fenretinide are able to inhibit the expression of DES1, which mediates the inflammatory response in the heart; Amiselimod, an S1P receptor 1 (S1PR1) agonist, modulates S1P levels, restores endothelial homeostasis, and enhances vascular function; K6PC-5, an activator of SPHK1, increases S1P levels and ameliorates myocardial injury; and Amitriptyline, an inhibitor of aSMase, reduces endothelial inflammation by potentially slowing SM degradation.

**Abbreviations:** SM, Sphingomyelin; GlcCer, Gluco-sylceramide; GSL, Glycosphingolipid; S1P, sphingosine-1-phosphate; S1PR1, S1P receptor 1; Cer, ceramide; DGAT1, diacylglycerol O-acyltransferase 1; dhCer, dihydroceramide; SPHK1, sphingosine kinase 1; aSMase, acid sphingomyelinase; SPT, serine palmitoyltransferase; DES1, dihydroceramide desaturase 1.

The levels of S1P and SM are significantly negatively correlated with the severity of HFpEF. As a key regulator, S1P mediates the pathological mechanisms of post-ischemic reperfusion injury and promotes cardiac remodeling.<sup>129</sup> By activating the SPHK1-S1P signaling pathway, S1P regulates reactive ROS levels via S1PR3, providing cardioprotective effects.<sup>130</sup> Additionally, the  $\beta$ 1-adrenergic receptor ( $\beta$ 1-AR) induces chronic inflammation at the site of myocardial damage in HF. The SPHK1/ S1P/ S1PR1 axis plays a critical role in regulating the  $\beta$ 1-AR-induced pro-inflammatory response. This axis helps modulate the inflammatory environment and can contribute to restoring normal myocardial function, potentially alleviating some of the pathological changes associated with HF.<sup>131</sup>

### Sphingolipid Metabolism in the HFpEF

HFpEF is strongly associated with disorders in cardiac energy metabolism, with metabolic diseases such as obesity and type 2 diabetes mellitus (T2DM) serving as major contributors to HFpEF pathophysiology.<sup>124,125</sup> Sphingolipid metabolism may directly or indirectly disrupt systemic lipid metabolism, leading to the deposition of circulating lipids in the

heart. This accumulation of lipids induces myocardial remodeling and vascular dysfunction, ultimately driving the progression of HFpEF.<sup>13,103</sup>

In a high-fat diet (HFD)-fed mouse model of HF, fatty acid oxidation in the heart is impaired, leading to the accumulation of Cer and resulting in cardiac lipotoxicity, which exacerbates systolic dysfunction in HF.<sup>120</sup> DGAT1, an important rate-limiting enzyme for the metabolism of Cer to acyl ceramides, also plays a key role in the conversion of DAG to triglycerides (TG). In the failing heart, a decrease in DGAT1 expression results in increased Cer and DAG specificity, further worsening cardiac dysfunction.<sup>91</sup> Excessive accumulation of GSL in cardiomyocytes induces LacCer-initiated intracellular oxidative stress and inflammatory pathways,<sup>72</sup> reduces the efficiency of energy metabolism, and impairs cardiac function. Thus, modulation of the GSL pathway is essential for restoring cardiac energy metabolism and alleviating myocardial injury in HFpEF.<sup>72,132</sup> Autophagy may represent a critical mechanism in the regulation of HFpEF associated with metabolic diseases. In an in vitro model of diabetes combined with HF, CERS5 and Cer induced autophagy by altering the localization or activity of membrane-resident proteins, thereby mediating cardiomyocyte hypertrophy.<sup>133</sup>

Furthermore, persistent hyperglycemia and insulin resistance in T2DM, recognized as risk factors for HFpEF, disrupt sphingolipid metabolism. These disturbances can lead to lipotoxicity, oxidative stress, and myocardial dysfunction. Elevated levels of dhCer and GlcCer, which disrupt energy metabolism, exacerbate insulin resistance, and increase cardiac lipotoxicity by inhibiting autophagy-related pathways, have been observed in the plasma of patients with T2DM.<sup>72,134</sup> Under conditions of cardiac lipotoxicity, Cer adaptation promotes fatty acid uptake and storage while reducing glucose utilization, leading to apoptosis and fibrosis, which further increase Cer levels.<sup>135</sup> Increasing CDase activity facilitates Cer reduction and activates the AMPK-PPAR $\alpha$ /PGC-1 $\alpha$  pathway and related downstream signaling to regulate oxidative stress, inflammation, and apoptosis, thereby improving cardiac lipid metabolism.<sup>136</sup> Additionally, in diabetic cardiomyopathy (DCM) mouse models, acid aSMase has been shown to trigger apoptosis by increasing reactive ROS production through the stimulation of NOX4 expression. Conversely, specific knockdown of aSMase in cardiomyocytes restored HFD-induced cardiac dysfunction, remodeling, and apoptosis, while NOX4 protein expression was downregulated.<sup>137</sup> Furthermore, plasma S1P has been identified as an independent predictor of CVD development in patients with T2DM. Elevated S1P levels have been shown to counteract insulin signaling dysfunction and promote cardiomyocyte survival.<sup>138</sup>

## Sphingolipid Metabolism as a Biomarker for HF

Currently, sphingolipid metabolites and key enzymes are widely utilized as potential biomarkers for cardiovascular risk assessment and prognosis in clinical settings.<sup>24,25,28,116</sup> They are valuable in evaluating disease progression, therapeutic response, and prognostic outcomes in HF. In lipidomic studies of CVD patients, several sphingolipids, including dhCer, Cer, and SM, have been identified that are heritable and linked to genetic characteristics of CVD. Most of these sphingolipids are positively correlated with low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) levels.<sup>139</sup> A meta-analysis exploring the association between different Cer isoforms and CVD revealed that major adverse cardiovascular events (MACE) are strongly linked to plasma concentrations of specific Cer isoforms, including Cer(d18:1/16:0), Cer(d18:1/18:0), and Cer(d18:1/24:1).<sup>140</sup> Similarly, Javaheri et al found that long-chain and ultra-long-chain Cer are strongly associated with MACE, with elevated long-chain Cer concentrations, independent of conventional risk factors, serving as a specific marker for diagnosing HFpEF.<sup>141</sup> Alterations in Cer ratios, such as Cer(d18:1/16:0)/Cer(d18:1/24:1), are also associated with mortality and hospitalization rates in HF patients.<sup>142</sup> Additionally, researchers have developed a comprehensive scoring system called the Ceramide Heart Failure Score (CHFS), which was created to evaluate myocardial injury, inflammation, and fluid retention. This scoring system helps stratify the risk of poor prognosis in HF patients and highlights the potential of Cer as a therapeutic target in HF drug development.<sup>143</sup>

In addition to Cer, SM and aSMase may serve as potential biomarkers for HF. In a recent cohort study from the Cardiovascular Health Study, which followed 4,612 participants over a 10-year period, elevated plasma levels of SM and Cer were associated with an increased risk of sudden cardiac death.<sup>144</sup> Similarly, a study on the etiology of HF reported that serum SM levels in HFpEF patients showed a decreasing trend compared to healthy individuals, potentially serving as a key indicator for HF identification.<sup>145</sup> Elevated aSMase activity was detected in the muscle of patients with HF and

was positively correlated with inflammation levels and HF disease markers. ASMase activation may represent a potential mechanism underlying HF-related functional impairment.<sup>146</sup> Valerie Samouillan analyzed lipid metabolism in cardiac tissues of post-MI patients using Fourier Transform Infrared Spectroscopy (FTIR). They found elevated SM levels at the infarction site, with a positive correlation between esterified lipids and adverse cardiac remodeling. FTIR lipid metrics could potentially serve as biomarkers of cardiac remodeling.<sup>147</sup>

S1P is not only regarded as a clinical marker of HF but also considered a potential therapeutic target. A study on sphingolipid metabolism-related genes revealed that levels of S1P and CERS1 were significantly elevated in the cardiac tissues of patients with advanced chronic HF. Notably, CERS1 was closely associated with the cardiac remodeling process, making the monitoring of S1P and CERS1 levels an important criterion for assessing HF severity.<sup>121</sup> Furthermore, the specific deletion of S1PR1 was shown to exacerbate cardiac remodeling after MI and may lead to cardiac insufficiency.<sup>148</sup> Therefore, activation of the S1P/S1PR1 signaling pathway during cardiac repair is regarded as an indicator of recovery of cardiac function after MI. Measuring S1P levels may also serve as an early diagnostic tool for HF.<sup>149</sup> Furthermore, plasma S1P levels in HF patients exhibited a U-shaped correlation with mortality. Notably, the prognostic value of abnormally elevated S1P levels for predicting death remained entirely independent of traditional risk factors and HF-related predictors. This highlights the importance of S1P for the long-term prognosis of HF.<sup>150</sup>

## Sphingolipid Metabolism as a Potential Therapeutic Target in HF

### Dietary Intervention

Sphingolipid metabolism is crucial for maintaining organismal health and influencing disease progression. Consequently, there is growing interest in the role of dietary supplementation in modulating sphingolipid metabolism as a potential strategy for preventing metabolic and CVDs.<sup>151,152</sup> Studies have shown that a Mediterranean diet (MedDiet) enriched with extra virgin olive oil or nuts directly modulates Cer biosynthesis, reducing plasma Cer concentrations and high-risk factors for CVD. This could positively contribute to the prevention of MACE.<sup>153</sup>

Meanwhile, the Nordic diet—which includes whole grains, fruits, vegetables, berries, vegetable oils, margarine, fish, low-fat dairy products, and low-fat meats—improves plasma concentrations of Cer, SM, and Sph, while modulating lipid and glucose metabolism in obesity and T2DM. It also reduces systemic inflammation.<sup>154</sup> In a study investigating the relationship between dairy consumption and plasma sphingolipidomics, dairy consumption was negatively correlated with plasma levels of dhCer, a marker of T2DM, suggesting that dairy intake may reduce the risk of T2DM. This finding has important implications for HFpEF prevention.<sup>155</sup> Furthermore, studies have shown that milk and dairy products are rich in SM, and supplementation with SM has been shown to inhibit intestinal lipid absorption. This process promotes brown-like transformation in white fat, which may prevent the development of AS and HF.<sup>156</sup> A preliminary study on sphingolipid metabolism in hypertriglyceridemic patients demonstrated that fish oil supplementation effectively reduced plasma TG levels, along with Cer and SM concentrations in lipoproteins. These changes were associated with a decreased risk of AS and an improved prognosis for CVD.<sup>157</sup> Furthermore, a dietary intervention study in overweight postmenopausal women with risk factors for CVD investigated changes in SM and Cer concentrations in fasting and postprandial plasma, as well as chylomicron particles. The study found that supplementing the diet with milk and increasing SM interaction with intestinal cholesterol reduced high-risk factors for CVD.<sup>158</sup>

### Exercise Intervention

Regular exercise and structured workouts play a crucial role in regulating sphingolipid metabolism and serve as powerful adjuncts in the prevention and treatment of cardiometabolic diseases.<sup>159</sup> An 8-week high-intensity interval training (HIIT) study demonstrated that HIIT is a safe and effective strategy for reducing Cer levels and improving health outcomes in patients with cardiometabolic diseases.<sup>160</sup> In dyslipidemic individuals, exercise has been shown to reduce dhCer and SM levels while mitigating insulin resistance-associated lipid accumulation, which is essential for preventing T2DM.<sup>161</sup> Research has demonstrated that exercise elevates S1P levels and its terminal breakdown products in the myocardium. This elevation facilitates muscle contraction, enhances mitochondrial fatty acid  $\beta$ -oxidation, and provides protection against cardiac I/R injury.<sup>162</sup>

Obesity-induced elevations in circulating free fatty acids further stimulate Cer synthesis, increasing the risk of CVD. In contrast, physical exercise reduces SM and Cer concentrations while increasing SIP levels, thereby promoting cardioprotective mechanisms and lowering CVD risk.<sup>163</sup> Furthermore, research indicates that weight loss achieved through exercise is associated with a reduction in circulating SM biosynthesis. The extent of this reduction correlates positively with decreased LDL-C levels, suggesting that exercise may enhance vascular function by modulating SM metabolism.<sup>164</sup> Regular training enhances energy efficiency, increases insulin sensitivity, and decreases Cer levels in skeletal muscle in patients with T2DM, a change that may be linked to improved mitochondrial oxidative capacity. The beneficial effects of exercise on reducing CVD risk have been particularly significant in patients with T2DM.<sup>165</sup>

## Drug Therapy

Although no therapeutic drugs currently target sphingolipid components specifically for HF, the role of sphingolipid metabolism in regulating cardiac function and HF has prompted the development and clinical application of various drugs targeting sphingolipid metabolism or its signaling pathways (Table 2). These drugs offer valuable insights for the clinical prevention and management of HF. Myriocin, an SPT inhibitor, has been shown to inhibit sphingolipid

**Table 2** Drugs Targeting Sphingolipid Metabolism and Their Effect on HF

Drug	Target	Efficacy	Duration of Treatment	Model Used	Rodent Strain	Clinical Study
Myriocin	SPT	Improves apoptosis, inflammatory response, and reduces lipid levels <sup>57,166,167</sup>	4–12 weeks	Atherosclerotic	C57BL/6 mice	No
Empagliflozin	Cer	Reduces cardiac inflammation <sup>168,169</sup>	4–6 weeks	Type 2 Diabetes Mellitus	Zucker diabetic rats	Yes
AdipoRon	Cer	Mitigates cardiomyocyte damage <sup>170,171</sup>	2–4 weeks	Hyperlipidemia-induced cardiomyocyte injury	C57BL/6 mice, H9c2 rat myocardial cell	No
CIN038	DES1	Reduces cardiomyocyte hypertrophy <sup>172</sup>	3 weeks	Cardiac myocytes hypertrophy	Sprague-Dawley rats	No
Fenretinide	DES1	Suppresses inflammatory response and lowers blood pressure <sup>173</sup>	1 week	Spontaneously hypertensive	Wistar-Kyoto rats	No
Fingolimod	SIP/SIPRI	Improves vascular injury and suppresses cardiomyocyte apoptosis <sup>174</sup>	4 weeks	Myocardial ischemia/reperfusion	C57BL/6 mice	No
Amiselimod	SIP/SIPRI	Improves cardiac function <sup>175</sup>	4 week	Healthy subjects	Human	Yes
SEW2871	SIP/SIPRI	Regulates endothelial homeostasis, lowers blood pressure, <sup>176</sup> and mitigates AS <sup>177</sup>	3 weeks	Atherosclerotic	C57BL/6 mice	No
PF543	SPHK1	Suppresses inflammation, reduces cardiomyocyte hypertrophy, <sup>178</sup> and promotes cardiac remodeling <sup>179</sup>	4 weeks	Myocardial infarction	Sprague-Dawley rats	No
K6PC-5	SPHK1	Improves myocardial injury <sup>180</sup>	3 h	Ischemic heart damage	H9c2 rat myocardiocytes	No
Amitriptyline	aSase	Improves endothelial function and protects cardiomyocytes <sup>181</sup>	4 weeks	Atherosclerotic	C57BL/6 mice	No

**Abbreviations:** CIN038, a selective Des1 inhibitor; SEW2871, an SIPRI-selective agonist; PF543, an SPHK1 inhibitor; K6PC-5, an activator of SPHK1; SPT, serine palmitoyltransferase; Cer, ceramide; DES1, dihy-droceramide desaturase I; SIP, sphingosine-1-phosphate; SIPRI, SIP receptor I; SPHK1, sphingosine kinase I; aSase, acid sphingomyelinase.

metabolism through the de novo synthesis pathway, reduce the accumulation of Cer. Additionally, myricetin modulates the expression of key regulatory factors, including caspase-3, interleukin-8 (IL-8), and interleukin-6 (IL-6), leading to the attenuation of apoptosis and the inflammatory response *in vivo*.<sup>166</sup> It also restores mitochondrial function,<sup>57</sup> abrogates plaques, and regulates lipid levels in AS mouse models.<sup>167</sup> Empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor commonly used to treat T2DM, has been shown to reduce Cer and SM levels in the rat heart<sup>168</sup> and inhibit the expression of pro-inflammatory factors. In the treatment of HF, empagliflozin improves clinical symptoms and lowers the risk of HF readmission in patients with the condition.<sup>169</sup> AdipoRon, an orally active lipocalin receptor agonist, reduces Cer levels in mouse tissues,<sup>170</sup> improves lipid metabolism, and mitigates Cer-induced lipotoxic myocardial injury and cardiac hypertrophy.<sup>171</sup> DES1 is the final key enzyme in Cer synthesis, and CIN038 specifically inhibits DES1 expression. This inhibition mediates sphingolipid imbalance, modulates NF- $\kappa$ B signaling, and regulates the expression of  $\beta$ -MHC, collagen type I, and TNF- $\alpha$  genes. Consequently, it attenuates the inflammatory response in the heart and alleviates cardiomyocyte hypertrophy in neonatal rats.<sup>172</sup> In addition, another DES1 inhibitor, Fenretinide, a retinoid, promotes the expression of PPAR $\gamma$  and inhibits the LPS-induced release of pro-inflammatory cytokines such as TNF- $\alpha$  and IL-6, thereby reducing blood pressure.<sup>173</sup>

In addition, there are targeted drugs against S1P and its receptor S1PR1, such as Fingolimod (FTY720), which acts as an S1P receptor agonist, directly targeting the site of ischemic injury. It promotes endothelial cell repair, improves vascular injury, inhibits cardiac apoptosis, and enhances cardiac function.<sup>174</sup> Amiselimod, another S1PR1 agonist, has demonstrated superior cardiac safety in clinical studies compared to FTY720.<sup>175</sup> SEW2871, another S1PR1 agonist, modulates endothelial homeostasis, improves vascular impairment, and regulates hypertension in rats.<sup>176</sup> Additionally, as an antagonist, SEW2871 disrupted S1PR1 ligand-dependent complexes within primary macrophages and AS plaques in mice. This suggests that SEW2871 can attenuate AS and provide cardiovascular protective effects.<sup>177</sup>

Several drugs that activate or inhibit key enzymes of sphingolipid metabolism have been investigated in experimental and clinical studies. For example, PF543, a selective inhibitor of SPHK1, suppresses the serum expression of pro-inflammatory cytokines, including IL-1 $\beta$ , IL-6, and TNF- $\alpha$ . This reduction in inflammatory signaling mitigates the cardiac inflammatory response following MI and contributes to improved cardiac function.<sup>178</sup> Consequently, these effects slow myocardial fibrosis progression, and promotes cardiac remodeling in HF.<sup>179</sup> The SPHK1 activator K6PC-5 increases S1P levels, which prevents oxygen-glucose deprivation (OGD)-induced cardiomyocyte death, ameliorates myocardial injury, and offers potential therapeutic benefits for ischemic heart disease.<sup>180</sup> Dysregulated of aSMase activity is associated with the development of AS and other CVD.<sup>182</sup> The aSMase inhibitor amitriptyline reduces TNF- $\alpha$ -induced endothelial inflammation, thereby improving vascular endothelial function, while also protecting cardiomyocytes from hypoxia/reoxygenation-induced injury.<sup>181</sup>

## Discussion

Despite increasing research into the risk factors and pathogenesis of HF, as well as significant progress in clinical prevention and treatment that has improved HF cure rates and reduced mortality,<sup>183</sup> HF remains a major challenge for the global healthcare system due to its high comorbidity rates, complex disease course, poor prognosis, and high readmission rates.<sup>8–11</sup> Therefore, further research is required to investigate the multifactorial pathways underlying HF pathogenesis and to develop more effective treatment strategies.

The sphingolipid metabolic pathway is a complex network of enzymes and metabolites under precise regulatory control. It is extensively involved in biological processes and plays a central role in regulating pathophysiological mechanisms, including apoptosis, inflammatory responses, immune responses, and oxidative stress.<sup>21–23</sup> Recent studies have elucidated the role of sphingolipid metabolism in CVD, with growing evidence highlighting its involvement in numerous CVD pathophysiological processes. Sphingolipid metabolism plays a critical role in regulating vascular function, improving cardiac structure, and restoring energy metabolism.<sup>25–27</sup>

In this review, we examine the role of sphingolipid metabolism in HF. In the pathological mechanisms of HF, sphingolipid metabolites such as Cer, SM, Sph, and S1P, along with key enzymes such as SPTLC1, SPHK1, and aSMase, play essential roles in processes such as endothelial injury,<sup>74</sup> vascular dysfunction,<sup>128</sup> myocardial fibrosis,<sup>90</sup> and cardiac hypertrophy.<sup>133</sup> Several studies have demonstrated that alterations in sphingolipid metabolic pathways are recognized as

potential biomarkers and are widely used in clinical research.<sup>141–144</sup> Certain drugs targeting sphingolipid metabolites and key enzymes, such as Myriocin, AdipoRon, Fenretinide, and Amitriptyline, have demonstrated cardioprotective effects through diverse mechanisms, improving clinical symptoms and enhancing survival rates in HF patients.<sup>166–168</sup> Additionally, dietary interventions may regulate sphingolipid metabolism,<sup>167</sup> thereby reducing the risk of CVD and offering preventive benefits.<sup>151,152</sup>

Existing studies provide substantial evidence supporting the role of sphingolipid metabolism in HF. However, significant challenges persist in leveraging sphingolipid metabolic pathways for clinical diagnostics and pharmacological applications, necessitating further research and development.

1. The specificity of sphingolipid assays remains undefined, leading to potential variability in results when assessing sphingolipid metabolism across different sample types. For instance, sphingolipid levels may vary between cardiac tissues and plasma or serum, the latter being more accessible for clinical collection and follow-up monitoring.<sup>184</sup> However, given that the heart is the primary organ affected in HF, alterations in sphingolipid metabolism within cardiac tissue may play a crucial role in mediating structural and functional changes in the heart.<sup>24</sup>
2. Sphingolipids can influence biological processes based on their molecular structure, including acyl chain length, the number and position of unsaturations, and their localization within membrane regions. Additionally, their effects are modulated by the specific lipid composition of the membranes in which they are embedded. However, research on the molecular structure of sphingolipids remains limited, highlighting the need for further investigation in this area.
3. Sphingolipid metabolism is a highly complex process involving a diverse range of metabolites and enzymes. However, current research has primarily focused on a limited subset, including Cer, S1P, Sph, SPT, and SphK1. In contrast, the roles of more complex sphingolipids and the regulatory factors influencing sphingolipid production—such as the activity and expression of enzymes involved in sphingolipid synthesis and metabolism—remain largely unexplored, highlighting the need for further investigation.
4. The drugs used in sphingolipid metabolism research often lack specificity and selectivity. Given that sphingolipids have diverse cellular functions and their metabolic pathways are highly intricate, designing drugs that can precisely regulate target sphingolipids and selectively produce therapeutic effects through relevant pathological pathways remains an urgent challenge.

## Future Research Direction

With advancements in lipidomics technology,<sup>185</sup> targeted analysis of sphingolipid metabolism has become increasingly prevalent in related research. In the future, more precise profiling of sphingolipid dynamics in patients with HF may facilitate the identification of novel therapeutic targets. The investigation of sphingolipid metabolism should extend beyond well-characterized components to explore lesser-known metabolites and their regulatory mechanisms at the molecular level. Additionally, the development of highly selective drugs that modulate sphingolipid metabolism while minimizing off-target effects is essential. Rigorous clinical trials assessing efficacy and safety will be crucial in advancing precision treatment for HF.

## Conclusion

In this review, we highlight the pivotal role of sphingolipid metabolism in the pathogenesis of HF. Dysregulation of sphingolipid metabolic pathways promotes cardiomyocyte apoptosis, oxidative stress, and inflammatory responses, leading to cardiac lipotoxicity in metabolic disorders. These processes, in turn, drive key pathological mechanisms of HF, including ventricular remodeling, myocardial fibrosis, vascular abnormalities, and cardiometabolic disturbances. Monitoring these metabolic alterations during disease progression may serve as a valuable marker for the clinical identification of HF. Targeted reduction of sphingolipid metabolic levels through dietary interventions, exercise, and pharmacological treatments may improve cardiac function and long-term prognosis in HF patients. These findings provide a systematic and comprehensive perspective on novel diagnostic and therapeutic strategies targeting

sphingolipids, addressing gaps in current knowledge. Future research should focus on sphingolipid metabolites and their regulatory mechanisms, employing advanced techniques to more precisely profile sphingolipid dynamics in HF patients. Additionally, the development of highly selective regulatory drugs with minimal off-target effects holds significant promise for the precise treatment of HF.

## Abbreviations

CVD, Cardiovascular disease; HF, Heart failure; ER, Endoplasmic reticulum; LVEF, Left ventricular ejection fraction; HFpEF, Heart failure with preserved ejection fraction; HfmrEF, Heart failure with mildly reduced ejection fraction; HFrEF, Heart failure with reduced ejection fraction; Cer, Ceramide; SM, Sphingomyelin; GSL, Glycosphingolipid; S1P, Sphingosine-1-phosphate; C1P, Ceramide-1-phosphate; MCS, membrane contact sites; dhCer, Dihydroceramide; GlcCer, Glucosylceramide; SPT, Serine palmitoyl transferase; 3KDS, 3-keto-dihydrosphingosine; KDSR, 3-keto-dihydrosphingosine reductase; CERs, Ceramide synthetases; dhSph, Dihydrosphingosine; DEGS1, Sphingolipid  $\Delta 4$ -desaturase DES1; CDases, Acidic ceramidases; Sph, Sphingosine; SPHKs, Sphingosine kinases; SGPPs, S1P phosphatases; PLPPs, Phosphate phosphatases; SGPL1, Sphingosine-1-phosphate lyase 1; TGN, Trans-Golgi network; CERT, Ceramide transfer protein; SMS1, Sphingomyelin synthase 1; DAG, Diacylglycerol; PKD, Protein kinase D; UGCG, UDP-glucose ceramide glycosyltransferase; aSMase, Acid sphingomyelinase; CERK, Ceramide kinase; DGATs, Diacylglycerol O-acyltransferases; JNK, c-Jun N-terminal kinase; PKC, Protein kinase C; SPHK1, Sphingosine kinase 1; SPHK2, Sphingosine kinase 2; ERK, Extracellular signal-regulated kinase; Evs, Extracellular vesicles; AS, Atherosclerosis; MI, Myocardial infarction; NADPH, Nicotinamide adenine dinucleotide phosphate; ROS, Reactive oxygen species; eNOS, Endothelial nitric oxide synthase; NO, Nitric oxide; CAPK, cAMP-dependent protein kinase; S1PRs, Sphingosine-1-phosphate receptors; PTEN, Phosphatase and tensin homolog; SPTLC1, Serine palmitoyltransferase 1; SPTLC2, serine palmitoyltransferase 2; T2DM, Type 2 diabetes mellitus.

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## Disclosure

The authors declare that they have no competing interests in this work.

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